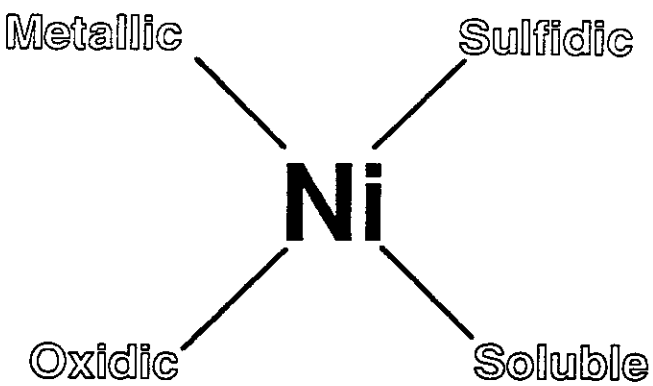
INITIAL STATEMENT OF REASONS FOR RULEMAKING

PROPOSED IDENTIFICATION
OF NICKEL
AS A TOXIC AIR CONTAMINANT



TECHNICAL SUPPORT DOCUMENT

Part C

Public Comments and ARB/DHS Staff Responses

State of California
Air Resources Board

June 1991

This report has been reviewed by the staffs of the California Air Resources Board and the Department of Health Services and approved for publication. Approval does not signify that the contents necessarily reflect the views and policicies of the Air Resources Board or the Department of Health Services, nor does mention of trade names of commercial products constitute endorsment or recommendation for use.

PART C - PUBLIC COMMENTS AND RESPONSES TO THE PRELIMINARY DRAFT PART A AND B NICKEL

Prepared by the Staffs of the Air Resources Board
and the Department of Health Services

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I.

Comment Letters Received on the Preliminary Draft Version of the Nickel Identification Report, Parts A and B

REGULATORY COMPLIANCE CONSULTANTS, INC.
600 Faye Lane
Redondo Beach, CA 90277
(213) 316-6653

August 9, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Att: Nickel
P.O. Box 2815
Sacramento, Ca. 95812

Subject: Proposed Identification of Nickel as a Toxic Air Contaminant - Technical Document June 1990.

A review of the literature search of Part A and Part B of the the above report raises more questions as to the conclusions of the findings than it does to substantiate the position that quote "all insoluble nickel compounds should be considered potentially carcinogenic to humans by inhalation".

It appears that only selected studies were used to arrive at the above conclusion and other studies listed in the report were rejected if they did not conform to the proposed above conclusions.

Section 8 Pg 116 (Part B) Stated. " Animal inhalation studies of nickel oxide were reviewed in section 7.1.1.3 . No studies found increased lung cancer incidence."

The reports listed in the study are not conclusive or even generally supportive to the findings that have been recommended.

The electroplating industry was listed as emitting 1.4 tons of nickel in 1984 by SCAQMD. This is an interesting statistic since nickel can only be electroplated in the soluble form. What is the basis and accuracy of this statistic?

EPA has limited its classification of Nickel as a hazardous material to a specific classification of "Nickel Dust".

The conclusions by The DHS based on this report appear to be stretched to arrive at some preconceived concept.

Before the conclusions of this report are adopted further definitive studies should be made to address the specific issue of all nickel compounds being carcinogenic to humans by inhalation.

Our society is currently faced with the problem of limited resources. To require regulatory agencies, industry, and the public to use our limited resources to address issues that are highly speculative in their conclusions and achievement is certainly not in the best interest of the public and its economic well being.

000001

Glenn Fitzgerald, President

AUTOMATIC PLATING & POLISHING
NICKEL, CHROME PLATING TO
AUTOMOTIVE SPECIFICATIONS

FOSS PLATING COMPANY INC.

213 945-3451

9140 SECURA WAY — SANTA FE SPRINGS, CALIFORNIA 90670

August 22, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources
Attn: Nickel
PO Box 2815
Sacramento, CA 95812

Reference: California Air Resources Board Technical Support Document "Proposed Identification of Nickel as a Toxic Air Contiminant"

Dear Ms. Shiroma:

We have received your subject report and make the following comments with particular emphasis on the inclusion of nickel chloride and nickel sulfate (soluble nickel), and nickel metal, which are the main nickel compounds we use. Comments were also submitted by our association with the help of Mr. Dean High. We fully concur with his comments.

Foss Plating Company has 35 employees and is engaged in nickel plating as our primary process prior to chrome plating. We have had in plant testing of our ambient air within our shop and have found that nickel is well below the threshold set by OSHA. Our only emissions to the outside air, if any, are roof fans. Emissions would be negligible because the efficiency of our plating solutions is near 100%. Also, our compounds are all water soluable.

We are concerned about our listing in the SCAQMD 1984 study. This material was given voluntarily and without the help of a technical expert. We used formulas that we have since found to be incorrect. We are in the process of recalculating our actual emissions using new information. Thus I feel that other companies like our own probably made similar errors. I feel that the SCAQMD 1984 study vastly overstates the contributions of nickel to the ambient air from our industry. It should be redone.

I also feel that the weight of evidence indicates that soluble nickel does not pose a major threat to the environment, and that reasonable thresholds should be considered. There is no evidence that it is a carcinogen and it should not be considered a TAC.

At the workshop on August 15, several industry sources indicated that assumptions were used in connection with the Ontario Cohort that can not be supported. In regards to the risk assessment all current evidence should be taken into account.

It is our feeling that soluble nickel and the nickel plating industry should be removed from consideration as a source of harmful emissions to the ambient air.

Consideration should also be made of the types of nickel in the ambient air. Soluble nickel should be segregated out in the risk assessment.

Respectfully submitted,

Larry D. Foss
Air Quality Chairman MFASC
Vice President-Finance

WSPA
Western States Petroleum Association

Michael D. Wang
Manager
Operating and Environmental Issues

August 21, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: Nickel
P.O. Box 2815
Sacramento, CA 95812

RE: WSPA COMMENTS ON THE JUNE 1990 PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT

Dear Ms. Shiroma:

The Western States Petroleum Association (WSPA) appreciates the opportunity to comment on the June 1990 preliminary draft report on nickel prepared by the Air Resources Board (ARB) and Department of Health Services (DHS).

In response to the health risk assessment prepared by the ARB/DHS, WSPA is submitting the attached comments. These comments were prepared by a WSPA consultant, and are intended to present more detailed and timely information necessary for ARB/DHS consideration prior to being able to accurately estimate the risk associated with nickel exposure.

In the Part A report, page A28, the CARB references 113.9 billion BTU's from crude oil firing in 1985. This number is in agreement with the total fuel oil usage in Kern County (according to KCAPCD's Annual Fuel Usage Survey). However, it is not representative of crude oil firing in the Oildale-Bakersfield area since it includes 49.1 billion BTU's from the Western Kern County oilfields. Central Kern County fuel oil usage in 1985 was reported at 64.8 billion BTU's. It is not clear from CARB's report which numbers were used in the calculations for nickel emissions supporting table 11-6 on page A29. The use of old or inaccurate BTU information in raising the issue of potential "hot spots" appears premature. The designation of a "hot spot" is better addressed by the AB-2588 process which insures the generation of high quality information for this purpose.

[illegible] Brand Blvd., Suite 1400 • Glendale, California 91203 • [illegible]

WSPA encourages consideration and incorporation of these comments in the final reports and looks forward to working with the ARB and DHS to insure that high quality information is used for determination of the most accurate estimation of risk posed by nickel exposure.

Please call Scott Folwarkow or me if you have any questions regarding these comments.

Very truly yours,

MDW/sf
Attachment

CALifornia TECHnical PLATING, INC.

11533 BRADLEY AVE.

SAN FERNANDO, CALIFORNIA 91340

365-8205

August 20, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources
Attn: Nickel
P.O. Box 2815
Sacramento, Ca. 95812

Reference: California Air Resources Board Technical Support Document
"Proposed Identification of Nickel as A Toxic Air Contaminant"

Dear Ms. Shiroma:

We have received the subject reports and offer comments on them as follows, with particular emphasis on the inclusion of nickel chloride and nickel sulfate (soluble nickel) which are essentially the only nickel compounds used in the electroplating process. We make these comments from the perspective of our own knowledge and experience: and also with the assistance of certain other experts in the field, most particularly, Mr. M. Dean High, Vice President of Pacific Environmental Services, Inc. Further, we will attempt not to be entirely repetitious of those comments made on behalf of the Metal Finishing Association of Southern California, but certainly want to wholeheartedly endorse those comments.

We believe the following issues must be clarified:

1. We strongly encourage CARB to make a greater distinction between "soluble" and "insoluble" nickel. As best as we can determine there is no data to support the inclusion of soluble nickel as a carcinogen. Therefore, since the electroplating process deals exclusively with soluble nickel, we believe the electroplating industry per se should not be identified as a potentially regulated industry.

2. CARB refers to an SCAQMD study indicating 1.4 tons of nickel emissions per year from electroplating sources. They do this, however, without citing the specific reference or the test methodology. We would like this information in order to better evaluate the unsupported 1.4 ton figure.

3. It seems questionable sampling procedure to use only nine samples to represent a potentially wide range of insoluble nickel in ambient air. Was the risk estimated of DHS based on only insoluble nickel concentration measured in California air? If the range was [illegible] to [illegible], what is the justification for using only one [illegible]?

4. Indoor exposure to Ni from wood burning or cigarette smoke is not properly or completely presented.

5. Can CARB clarify the way in which cigarette smoking was handled in the four occupational refinery studies.

6. Why would CARB not use all available data (2 years) to estimate long term exposures?

7. Nickel oxides are not quantified from various metal melting, production, and recovery operations. Such emissions could be insoluble Ni, and could be significant in total mass emissions. Nickel refinery dust most obviously comes to mind as an example.

8. The fuel oil source category shows a range of 10.5 - 345 t/y. The range seems too broad to prioritize the importance of this source.

9. Four cohort studies were referenced but three were discounted and only one was used to estimate cancer risk. Ni exposure concentrations were one million times higher than California air. How can anyone possible have any confidence in the science that could make that kind of extrapolation?

10. On page A2, the report states that "total nickel emissions from stationary sources are estimated to be 18-353 tons per year." Again the breadth of that estimated range begs questioning.

11. On page 4 of part B there is a statement that is apparently a disclaimer of sorts. We recognize that it is in reference to risk assessments, but to state that this report "represents plausible estimates" in any context in light of some of the rather questionable data, unsupported data, data where the ranges are so broad as to have little meaning, and extrapolations that are more a leap of faith rather than science, we believe is disingenuous at best.

Thank you for the opportunity to present our comments.

Yours very truly,

David Anzures
Vice President

SDGE San Diego Gas & Electric
P.O. BOX 1831 • SAN DIEGO, CA 92112 • (619) 696-2000

August 14, 1990

FILE NO

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant
Identification Branch
Stationary Source Division
Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

Attn: Nickel

SUBJECT: PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT

Dear Ms. Shiroma:

The San Diego Gas & Electric Company (SDG&E) would like to comment on the State of California Air Resources Board's (ARB) technical support document entitled "Proposed Identification of Nickel as a Toxic Air Contaminant". We believe that the document has been carefully prepared and would like to discuss on only a few specific conclusions as follows:

1. In Part A, Appendix V, page 1, the nickel content of residual fuel oil used in the continental U.S. is proposed to be 3 to 118 ppmw. California utilities are now required to burn low sulfur oil (normally less than 0.5% sulfur). Since the metals and sulfur content of an oil are typically closely linked, a low sulfur oil is also low in metals. For example the nickel content of our residual oil (maximum 0.5% sulfur) normally ranges from 6 to 16 ppmw.

   Thus an upper emission level of 118 ppmw is only a hypothetical value and does not represent actual California utility emissions.

2. In Part B, Table 7.12, exposure was assumed to be zero when the worker was not at the plant. This would appear to highly unlikely given the size of the community and the lack of public transpiration, i.e., one would expect the ambient level of nickel in the community to be very high with workers experiencing round the clock exposure during their entire working career at the plant.

In Part B, Section 8 concludes that based on the presently available data nickel subsulfide appears to be a carcinogen. Section 8 also concludes that nickel oxide is a carcinogen even though 1) no animal studies found an increase in lung cancer incidence and 2) the cancers found in nickel refinery workers was most likely due to exposure to nickel subsulfide.

It would seem more logical to conclude that the current data does not show that nickel oxide is a carcinogen. Certainly there is no reason to ascribe the same potency to nickel oxide and nickel subsulfide. Further, assuming that all nickel compounds are equally potent carcinogens seems analogous to classifying all carbon compounds as carcinogens because a few exhibit carcinogenistic properties.

Sincerely,

H. K. Bishop, PhD
Principal Environmental Analyst

HKB:sl

Calidria

A PRODUCT OF [illegible]

[illegible]
TEL (408) 385-5961
FAX (408) 385-[illegible]49

August 14, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: Nickel
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma:

Please excuse this belated response to Mr. Venturini's letter dated June 22, 1990 requesting comments on your draft report on nickel and announcement of a public meeting on the same subject. We are unable to attend the meeting on August 15 so I request that you accept these comments by FAX for the record.

KCAC mines and mills short fiber chrysotile asbestos from a deposit in San Benito County. Our mill is five miles south of King City in Monterey County. We have been in operation for 27 years and our products are marketed in the U.S. and around the world.

Our only concern with the Part A Report is the amount of estimated nickel emissions from asbestos mining and milling listed in the Stationary Sources Table (III-1) on page A41. The amount noted of 0.65 tons/year is based on old data and information and should not be considered as currently accurate.

KCAC is now the only miner and miller of asbestos in California: and, based on a 1986 report prepared at the request of the ARB, we estimate that our asbestos emissions are about 120 pounds per year. Using the ARB formula in Appendix V of the Part A Report, the estimated nickel emissions from chrysotile asbestos mining and milling would be 0.2 pounds/year, or 0.0001 tons/year.

The ARB emissions testing done at this location in 1988 confirmed that our chrysotile asbestos emissions are extremely low. Perhaps the amount of nickel in these samples could be determined and you would have a much more accurate estimate than using old EPA and ARB data.

Thank you for accepting these comments and please advise if you have any questions or require additional information.

[illegible] yours,

John L. Myers

John L. Myers
President

JLM/mbl

Sent via FAX to 916-327-7212
at 11 am on 8/14/90.

METAL FINISHING ASSOCIATION OF SOUTHERN CALIFORNIA INC.

August 6, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant
Identification Branch
Air Resources Board
1102 Q. Street
P. O. Box 2815
Sacramento, CA 95812

Ref.: Draft Technical Support Document "Proposed Identification of Nickel As a Toxic Air Contaminant" Part A and Part B

Dear Ms. Shiroma:

We have reviewed the subject reports and offer comments primarily on the use and impacts of nickel chloride and nickel sulfate which are utilized in electroplating tanks for nickel plating. We have identified our comments for either the Part A or Part B Reports. Mr. M. Dean High, Vice President of Pacific Environmental Services, Inc., assisted the Metal Finishing Association of Southern California with a review of the documents and the preparation of these comments.

Since the objective of the study was to consider the carcinogenic potential of nickel over a 70 year exposure, we suggest using all 16 months of available data (Part A Report page A7) rather than the maximum 12 months selected.

In the Part B Report, page 6, the report states that the available data from animal studies was four orders of magnitude (10000 times) greater than measured ambient air levels. Available data for human studies were 6 to 7 orders of magnitude (1 to 10 million times) greater than measured ambient air levels in California. The conclusion on page 6 is that "the range of risks from nickel is from 1.3 to 7 lung cancer deaths per million. In view of the dynamic extrapolation required to relate known risks to the measured ambient nickel levels and the relatively acceptable projected cancer risk of about one per million, we recommend that the Scientific Review Panel postpone a decision on the "proposed identification of nickel as a toxic air contaminant" until more relevant and specific data can be generated to support such a decision.

[illegible] Sepulveda Boulevard Suite 410 • Sherman Oaks, California 91403 • 818 986-7388

If nickel is to be identified as a toxic air contaminant our industry offers the following comments. In the Part A report, page A41, electroplating emissions of nickel compounds are shown as 1.4 tons/year. These emissions would primarily be water soluble nickel sulfate or nickel chloride droplets or mist since these are the two compounds which are used in nickel plating baths. The mist is generated by hydrogen or oxygen bubbles breaking the surface of the plating solution.

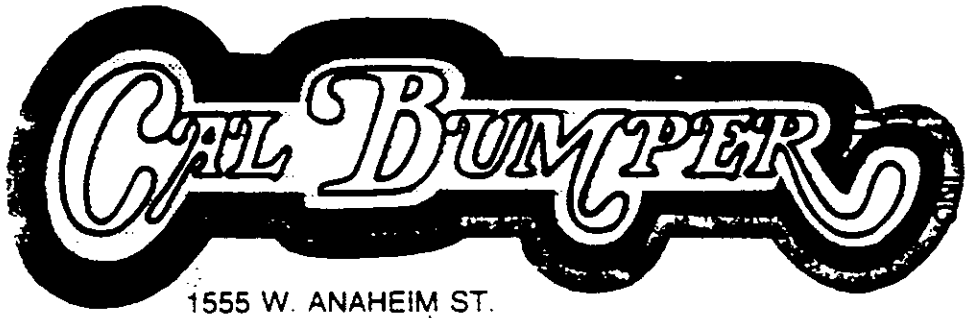
In the Part B Report, page 117, concerning soluble nickel salts the report states: "...even if soluble nickel salts were carcinogenic by inhalation, their potency would likely be lower than for the insoluble nickel compounds. This follows from the fact that soluble nickel salts would not remain in the lungs as do nickel subsulfide and nickel oxide." "Thus, DHS staff conclude that all insoluble nickel compounds should be considered potentially carcinogenic to humans by inhalation."

Since the DHS, at least at this time, considers only insoluble nickel compounds to be potentially carcinogenic to humans by inhalation, we request that the electroplating industry be deleted from the table (page A41) as a stationary source. At a minimum, the table should show nickel sulfate and nickel chloride rather than nickel metal. Electroplating in a water based solution can not and does not liberate nickel metal to the atmosphere. Finally, the table shows 1.4 tons/year of nickel metal emissions in the SCAQMD for 1984. We note the secondary reference, SCAQMD's "Emissions of Potentially Toxic/Hazardous Air Contaminants In The South Coast Air Basin - 1984 Update." If the electroplating category is not deleted, and if SCAQMD's 1984 estimate of nickel emissions was based on source tests, the part A Report should identify the specific reports, the testing methods utilized and the form of the measured nickel compounds: soluble nickel, sulfidic nickel, metallic nickel, or oxidic nickel. If it was not based on source test data, the basis for the estimate should be clearly explained in the Part A Report.

The text on P-A46 of the Part A Report describes electroplating but includes grinding, polishing and cutting in the same section. We recommend that grinding, polishing and cutting of a nickel parts be discussed separately and emissions be estimated separately on P-A41.

Very Truly Yours,

Larry Foss, Chairman
Air Quality Committee
Metal Finishing Association
Of Southern California



1555 W. ANAHEIM ST.
LONG BEACH, CALIF. 90813
(213) 436-1203 OR 979-2313
(714) 891-5391

August 15, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: Nickel
P.O. Box 2815
Sacramento, CA 95812

Re: California Air Resources Board Technical Support Document "Proposed Identification Of Nickel As A Toxic Air Contaminant"

Dear Ms. Shiroma:

The purpose of this letter is to state our comments on the draft report that was prepared by the staffs of the Air Resources Board and the Department of Health Services. This company is in the business of chrome plating automobile parts and as such is vitally interested in this report and any legislation based upon it. We are familiar with the comments of Mr. M. Dean High of Pacific Environmental Services, a recognized expert in the field of plating issues, and of the Metal Finishing Association of Southern California of which we are a member. We support their comments and conclusions and wish to dispute the conclusions contained in the referenced draft report.

Our position is that the referenced document and supporting reports are flawed, inaccurate and incomplete. Intitially we must state that we do not have trained statisticians as employees but that those employees who have taken basic college statistics courses find the reports to lack basic parameters sufficient to produce meaningful results. The sample groups and definitions thereof are unclear or undefined. For example, we cite the conclusion of SCAQMD that nickel emissions are 1.4 tons per year. There is no distinction mentioned between soluble versus insoluble nickel which in our opinion is very important.

The report seems to rely on only 9 samples to reach the conclusion that there is a potentially wide range of insoluble nickel in ambient air. Again, the sample number is too low to meet good statistical criteria and the conclusion does not distinguish between soluble and insoluble nickel which is of major interest to our industry. The reason we feel the distinction is necessary is because our industry uses nickel chloride and nickel sulfate which are both soluble nickel. We also wish to question the use of only the highest possible result, 90% insoluble nickel concentration, by the Department of Health Services.

We have real concerns about the possible statistical consequences that follow if there is no distinction drawn relative to wood burning, cigarette smoke or metal melting, production and recovery operations. If there is the possibility of regulation of our industry, then any studies relative to the alleged negative results of our operations should be based on exposure therefrom.

Are we reading the fuel oil category incorrectly? The report indicates a range of a low of 10.5 tons per year to a high of 345.0 tons per year. This range is far too large from our perspective. We also reach this conclusion when we review the estimates of total nickel emissions from stationary sources. A range from 18 tons per year to 353 tons is just too large. More studies must be completed before valid conclusions as to emissions can be reached.

The subject document creates more issues than it resolves with respect to claims of cancer risk. It seems that every time that government wants to regulate or eliminate an industry it raises the risk of cancer. In this case there is reference to four studies but only one was used for the purposes of this document. What was wrong with the other reports? Did they come to the "wrong" conclusion? We believe that a conclusion based upon a

concentration which is one million times higher than that found in California air is without validity.

Based upon all of the above, we question all of the stated and implied results of this document. We question whether the report "represents plausible estimates" of contaminants, emissions, results or risks. We believe that the statistical studies are flawed to the point of error. To make any decisions based upon the subject document would be a mistake of significant proportions.

Very truly yours,

CAL BUMPER COMPANY, INC.

M.E. Lovelle
President

shiroma/cb/tb

ENGELHARD

ENGELHARD CORPORATION
[illegible] MERCANTILE ROAD
[illegible]

August 6, 1990

Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
P. O. Box 2815
Sacramento, California 95812

RE: NICKEL

Attn.: Ms. Genevieve Shiroma, Chief

Dear Ms. Shiroma:

The following are our comments regarding the preliminary draft report on nickel as prepared by the staffs of the ARB and DHS labeled as Part A and Part B dated June 1990.

It is our intention to restrict our comments to the issues of nickel emission statistics, speciation of nickel compounds, and the toxicity attributed to nickel and its various compounds.

Our interest lies in the electroplating field and therefore in the chemicals utilized in this industry. Among those used for the electroplating of nickel are nickel metal as anode material, nickel chloride, nickel sulfate, and nickel sulfamate. The chemistry of these plating processes is exclusively aqueous based. Therefore all chemicals which are used in this industry are water soluble.

Comment is made that the staff of the DHS concludes that "it is unlikely that noncancer adverse health effects would be caused by the levels of nickel compounds currently found in the ambient air". With this in mind it is pertinent to reconsider the contribution of the electroplating industry to the nickel air emissions inventory.

The source data of 1.4 tons of nickel emissions from electroplating as shown on page A46 is drawn from SCAQMD data published in 1985 and gathered at some earlier date. Several points need to be made about subsequent events:

a) There has been a sharp nationwide decline in nickel electroplating. From 1988 to 1989 usage dropped 18% per a recent INCO study. Declines have been occurring most years since this report was done due to the changes in automotive design (fewer nickel/chrome bumpers, grills, and bright trim), the advent of powder and electrophoretic coatings, and the general shift of chemical processing offshore and to Mexico.

b) In California there has been improved enforcement of OSHA standards on chemical processing which reduces emissions. Also many general plating plants have closed or stopped nickel plating due to the efforts of CARB to eliminate hexavalent chromium (emissions) which frequently follows nickel electroplating.

c) The shrinkage of the printed circuit board manufacturing industry in California is well-known as are the stories about how this has moved offshore or to Mexico. Most PCB manufacturing includes nickel plating.

It would appear that the contribution from the electroplating industry to the nickel air emissions inventory is declining and as such current emission statistics should be evaluated by the DHS prior to any further action to establish standards for this industry.

Comment is made at page A46, Part A Report, that the efficiency of a bath contributes to the aerosol formed; while true, nickel baths operate at efficiencies approaching 100% eliminating the formation of aerosols. The air emissions typically found in an electroplating shop would be composed exclusively of water soluble nickel compounds generated as a result of mechanical splashing and too rigorous air agitation. An exception would be a shop which mechanically polishes plated nickel.

In the Summary section of the Part B Report and throughout this Part reference is made to the toxicity of nickel metal, presumably as dust, and insoluble nickel compounds. Since nickel plating is an aqueous based technique and by virtue of that solubility in water the use of water soluble nickel compounds in that industry poses a much lower threat to health upon exposure both in-plant and as as result of expected air emissions.

Throughout the Part B Report reference is made to health effect studies, mainly animal, which point to increases in illnesses due to exposure to insoluble nickel compounds through various exposure routes. Work was also done using specific compounds such as nickel oxide, nickel dust, nickel carbonyl, and nickel subsulfide. Results presented identify these compounds as the predominantly dangerous forms of nickel. We would not argue the conclusions drawn from this body of work.

However, much of the work reported on the aqueous compounds of nickel utilized routes of entry to the body which are not particularly pertinent to environmental exposure to air emissions. These included ingestion, intratracheal, and injection (subcutaneous and intravenous) forms of exposure. Further, the conclusion drawn at page 88 that the "results of the dietary rat study appear adequate to detect the carcinogenic potential of nickel sulfate in rats.." is somewhat unusual after the lengthy prior discussion of the Schroeder studies. Prior comment at page 85 stated that the results of these studies was essentially inconclusive with respect to the carcinogenic potential of soluble nickel salts in drinking water of rats and mice.

If we are to agree with the tenous conclusion of the DHS staff that "based on the findings of nickel-induced carcinogenesis in humans and animals ..... nickel is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness ....", then we must also strongly support the conclusion that insoluble nickel compounds instead of total nickel compounds should be used as the exposure index. It would follow, therefore, that the air emission standard would be established for specific insoluble nickel compounds rather than all nickel compounds.

We urge that before considering the regulation of nickel electroplating emissions that the CARB review inclusive and accurate current information on:

1. Accurate and reasonably current statistics on nickel emissions throughout the geographic area of intended regulation.

2. Clinical or epidemiological evidence that the soluble nickel compound emissions of the type ordinarily used in electroplating are carcinogenic when inhaled.

3. A finding from the DHS that air pollution from nickel plating 'does' cause an increase in mortality, serious illness, or 'does' pose a present hazard to human health.

We are looking forward to a review of the comments from other affected individuals and your response to those comments.

Sincerely,

Dennis R. Masarik
Director, R & D

/ph

GENE'S
PLATING WORKS
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Nickel-Chrome Plating
on Steel
on Aluminum
on Brass
on Die-cast

August 7, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources
Attn: Nickel
P.O. Box 2815
Sacramento, CA 95812

Reference: California Air Resources Board Technical Support Document
"Proposed Identification of Nickel As A Toxic Air Contaminant"

Dear Ms. Shiroma:

We have received the subject reports and offer comments on them as follows, with particular emphasis on the inclusion of nickel chloride and nickel sulfate (soluble nickel) which are essentially the only nickel compounds used in the electroplating process. We make these comments from the perspective of our own knowledge and experience; and also with the assistance of certain other experts in the field, most particularly, Mr. M. Dean High, Vice President of Pacific Environmental Services, Inc. Further, we will attempt not to be entirely repetitious of those comments made on behalf of the Metal Finishing Association of Southern California, but certainly want to wholeheartedly endorse those comments.

We believe the following issues must be clarified:

1. We strongly encourage CARB to make a greater distinction between "soluble" and "insoluble" nickel. As best as we can determine there is no data to support the inclusion of soluble nickel as a carcinogen. Therefore, since the electroplating process deals exclusively with soluble nickel, we believe the electroplating industry per se should not be identified as a potentially regulated industry.

2. CARB refers to an SCAQMD study indicating 1.4 tons of nickel emissions per year from elctroplating sources. They do this, however, without citing the specific reference or the test methodology. We would like this information in order to better evaluate the unsupported 1.4 ton figure.

3. It seems questionable sampling procedure to use only nine samples to represent a potentially wide range of insoluble nickel in ambient air. Was the risk estimates of DHS based on only insoluble nickel concentration measured in California air? If the range was 5% to 90%, what is the justification for using only the 90%?

4. Indoor exposure to Ni from wood burning or cigarette smoke is not properly or completely presented.

5. Can CARB clarify the way in which cigarette smoking was handled in the four occupational refinery studies.

6. Why would CARB not use all available data (2 years) to estimate long term exposures?

7. Nickel oxides are not quantified from various metal melting, production, and recovery operations. Such emissions could be insoluble Ni, and could be significant in total mass emissions. Nickel refinery dust most obviously comes to mind as an example.

8. The fuel oil source category shows a range of 10.5 - 345 t/y. The range seems too broad to prioritize the importance of this source.

9. Four cohort studies were referenced but three were discounted and only one was used to estimate cancer risk. Ni exposure concentrations were one million times higher than California air. How can anyone possibly have any confidence in the science that could make that kind of extrapolation?

10. On page A2, the report states that "total nickel emissions from stationary sources are estimated to be 18-353 tons per year." Again the breadth of that estimated range begs questioning.

11. On page 4 of part B there is a statement that is apparently a disclaimer of sorts. We recognize that it is in reference to risk assessments, but to state that this report "represents plausible estimates" in any context in light of some of the rather questionable data, unsupported data, data where the ranges are so broad as to have little meaning, and extrapolations that are more a leap of faith rather than science, we believe is disingenuous at best.

Thank you for the opportunity to present our comments.

Yours very truly,

Harry W. Levy

Harry W. Levy

HWL:jl

MODERN PLATING COMPANY

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AUGUST 9, 1990

MS. GENEVIEVE SHIROMA, CHIEF
TOXIC AIR CONTAMINANT IDENTIFICATION BRANCH
STATIONARY SOURCE DIVISION
AIR RESOURCES
ATTN: NICKEL
P.O. BOX 2815
SACRAMENTO, CA 95812

REFERENCE: CALIFORNIA AIR RESOURCES BOARD TECHNICAL SUPPORT DOCUMENT "PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT"

DEAR MS. SHIROMA:

WE HAVE RECEIVED THE SUBJECT REPORTS AND OFFER COMMENTS ON THEM AS FOLLOWS, WITH PARTICULAR EMPHASIS ON THE INCLUSION OF NICKEL CHLORIDE AND NICKEL SULFATE (SOLUBLE NICKEL) WHICH ARE ESSENTIALLY THE ONLY NICKEL COMPOUNDS USED IN THE ELECTROPLATING PROCESS. WE MAKE THESE COMMENTS FROM THE PERSPECTIVE OF OUR OWN KNOWLEDGE AND EXPERIENCE; AND ALSO WITH THE ASSISTANCE OF CERTAIN OTHER EXPERTS IN THE FIELD, MOST PARTICULARY, MR. M. DEAN HIGH, VICE PRESIDENT OF PACIFIC ENVIRONMENTAL SERVICES, INC. FURTHER, WE WILL ATTEMPT NOT TO BE ENTIRELY REPETITIOUS OF THOSE COMMENTS MADE ON BEHALF OF THE METAL FINISHING ASSOCIATION OF SOUTHERN CALIFORNIA, BUT CERTAINLY WANT TO WHOLEHEARTEDLY ENDORSE THOSE COMMENTS.

WE BELIEVE THE FOLLOWING ISSUES MUST BE CLARIFIED:

1. GREATER DISTINCTION BETWEEN "SOLUBLE" AND "INSOLUBLE" NICKEL.

   WE STRONGLY ENCOURAGE CARB TO MAKE A GREATER DISTINCTION BETWEEN THESE TWO NICKELS. AS BEST AS WE CAN DETERMINE THERE IS NO DATA TO SUPPORT THE INCLUSION OF SOLUBLE NICKEL AS A CARCINOGEN. THE ELECTROPLATING PROCESS DEALS EXCLUSIVELY WITH SOLUBLE NICKEL, WE BELIEVE THE ELECTROPLATING INDUSTRY PER SE SHOULD NOT BE IDENTIFIED AS A POTENTIALLY REGULATED INDUSTRY.

2. SCAQMD STUDY OF NICKEL EMISSIONS

   IN REFERENCE BY CARB TO SCAQMD STUDY INDICATING 1.4 TONS OF NICKEL EMISSIONS PER YEAR FROM ELECTROPLATING SOURCES. HOWEVER, THEY DO THIS WITHOUT CITING THE SPECIFIC REFERENCE OF THE TEST METHODOLOGY. IN ORDER TO BETTER EVALUATE THE UNSUPPORTED 1.4 TON FIGURE, WE WOULD LIKE THIS INFORMATION.

3. SAMPLING PROCEDURE

TO USE ONLY NINE SAMPLES TO REPRESENT A POTENTIALLY WIDE RANGE OF INSOLUBLE NICKEL IN AMBIENT AIR, SEEMS QUESTIONABLE. WAS THE RISK ESTIMATES OF DHS BASED ON ONLY INSOLUBLE NICKEL CONCENTRATION MEASURED IN CALIFORNIA AIR? WHAT IS THE JUSTIFICATION FOR USING ONLY THE 90%, IF THE RANGE WAS 55% TO 90%?

4. NICKEL FROM WOOD BURNING OR CIGARETTE SMOKE

INDOOR EXPOSURE IS NOT PROPERLY OR COMPLETELY PRESENTED OF NICKEL FROM WOOD BURNING OR CIGARETTE SMOKE.

5. CARB CLARIFICATION OF OCCUPATIONAL REFINERY STUDIES

WE WOULD LIKE CARB TO CLARIFY THE WAY IN WHICH CIGARETTE SMOKING WAS HANDLING IN THE FOUR OCCUPATIONAL REFINERY STUDIES.

6. AVAILABLE DATA FOR ESTIMATE LONG TERM EXPOSURES

WAY WAS ALL AVAILABLE DATE (2 YEARS) TO ESTIMATE LONG TERM EXPOSURES NOT USE BY CARB?

7. INSOLUBLE NICKEL SIGNIFICANT IN TOTAL MASS EMISSIONS

NICKEL OXIDES ARE NOT QUANTIFIED FROM VARIOUS METAL MELTING, PRODUCTION, AND RECOVERY OPERATIONS. SUCH EMISSIONS COULD BE INSOLUBLE NICKEL, AND COULD BE SIGNIFICANT IN TOTAL MASS EMISSIONS. NICKEL REFINERY DUST MOST OBVIOUSLY COMES TO MIND AS AN EXAMPLE.

8. FUEL OIL SOURCE CATEGORY

THE FUEL OIL SOURCE CATEGORY SHOWS A RANGE OF 10.5 - 345 t/y. THE RANGE SEEMS TOO BROAD TO PRIORITIZE THE IMPORTANCE OF THIS SOURCE.

9. CONFIDENCE IN STUDIES

FOUR COHORT STUDIES WERE REFERENCED BUT THREE WERE DISCOUNTED AND ONLY ONE WAS USED TO ESTIMATE CANCER RISK. NICKEL EXPOSURE CONCENTRATIONS WERE ONE MILLION TIMES HIGHER THAN CALIFORNIA AIR. HOW CAN ANYONE POSSIBLE HAVE ANY CONFIDENCE IN THE SCIENCE THAT COULD MAKE THAT KIND OF EXTRAPOLATION?

10. ESTIMATED RANGE BEGS QUESTIONING

ON PAGE A2, THE REPORT STATES THAT "TOTAL NICKEL EMISSIONS FROM STATIONARY SOURCES ARE ESTIMATED TO BE 18-353 TONS PER YEAR." AGAIN THE BREADTH OF THAT ESTIMATED RANGE BEGS QUESTIONING.

11. REPORT "REPRESENTS PLAUSIBLE ESTIMATES"

ON PAGE 4 OF PART "B" THERE IS A STATEMENT THAT IS APPARENTLY A DISCLAIMER OF SORTS. WE RECOGNIZE THAT IT IS IN REFERENCE TO RISK ASSESSMENTS, BUT TO STATE THAT THIS REPORT "REPRESENTS PLAUSIBLE ESTIMATES" IN ANY CONTEXT IN LIGHT OF SOME OF THE RATHER QUESTIONABLE DATA, UNSUPPORTED DATA, DATE WHERE THE RANGES ARE SO BROAD AS TO HAVE LITTLE MEANING, AND EXTRAPOLATIONS THAT ARE MORE A LEAP OF FAITH RATHER THAN SCIENCE, WE BELIEVE IS DISINGENUOUS AT BEST.

THANK YOU FOR THE OPPORTUNITY TO PRESENT OUR COMMENTS.

VERY TRULY YOURS,

JOHN BOHACIK

JB:vmh

Department of Water and Power the City of Los Angeles

TOM BRADLEY
Mayor

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DUANE L. GEORGESON, *Assistant General Manager - Water*
DANIEL W. WATERS, *Assistant General Manager - External Affairs*
NORMAN J. POWERS, *Chief Financial Officer*

August 20, 1990

Ms. Genevieve Shiroma
Chief, Toxic Air Contaminant
Identification Branch
California Air Resources Board
1102 Q Street
P.O. Box 2815
Sacramento, California 95812

Dear Ms. Shiroma:

Department of Water and Power Comments
Technical Support Document on Proposed Identification
of Nickel as a Toxic Air Contaminant

This letter is to submit the comments of the Los Angeles Department of Water and Power (Department) with respect to the Technical Support Document (TSD) for the Proposed Identification of Nickel as a Toxic Air Contaminant. We appreciate the opportunity to provide these comments and hope that they are received with ample time for consideration by the Scientific Review Panel.

Comments on TSD, Part A

This part of the TSD is clearly presented and accurately conveys staff's estimates of nickel (Ni) sources, emissions, and exposures. Our comments on this part pertain to the treatment of utility residual oil usage.

In Part A, the amount of Ni emissions from utility residual oil combustion is stated at between 2.9 and 112 tons Ni per year. This is based on Ni concentrations of 3 to 118 parts per million (ppm) in the fuel. [Appendix V, Page 3] Two pages before these calculations, though, staff cites Southern California Edison's fuel oil testing results which average 4.71 ppm. Staff dismisses this concentration estimate because

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"these oils are foreign oils with relatively low sulfur and ash content." We contend that, due to local air quality regulations, this type of fuel is representative of what is used in the South Coast Air Basin and most of California, and that these Ni concentrations are accurate. Furthermore, the concentration estimates used by staff are doubtful. Staff states on Appendix V, Page 1, that these values, from Chansky, et al, "were measured before 1974 and may not represent the current fuel oil characteristics." This indicates that staff should reinvestigate the appropriateness of the estimated fuel Ni concentrations used for emission calculations, especially as such estimates apply to utility residual oil usage. We suggest that the Ni concentration proposed by Southern California Edison be used as it is more appropriate for California utility emissions than the Chansky Ni concentration.

On page A44, California Energy Commission fuel oil use forecasts from 1986 and 1987 are cited as reasons that utility fuel oil use will increase 250 percent by 1997. At this time, though, the South Coast Air Quality Management District (District) has adopted or is considering new rules which will restrict the use of residual fuel oil in such a way that the increase described above will be highly improbable. The District's intent, under these new rules, is to eliminate the use of residual fuel oil in instances where it is not otherwise possible to sufficiently reduce pollutant emissions. The effect of these and other local residual fuel use restrictions need to be considered when projecting future residual fuel oil usage. Staff should reassess projected fuel oil use accounting for these additional restrictions.

Comments on TSD, Part B

This part presents staff's summary of Ni health studies done to date and assesses the effects of exposure to various Ni compounds. Our comments on this part pertain to the treatment of different Ni compounds in establishing health risks due to Ni exposure.

The discussion of health risks in this part goes to great lengths to differentiate between the effects of different Ni compounds. For example, in section 7.1.4, evidence for carcinogenic potential through inhalation is described as conclusive for nickel subsulfide, less conclusive for nickel carbonyl, and inconclusive for nickel oxide. Furthermore, staff states in this section that "insoluble nickel compounds appear more likely to be carcinogenic" than soluble compounds. Also, the results of non-carcinogenic effects studies discussed were dependent on the particular Ni compound to which the subjects were exposed. These facts support the notion that different Ni compounds should be treated differently with respect to health impacts of exposure.

Instead, staff has opted for a simpler approach to developing numerical guidelines for exposure to Ni. They establish non-carcinogenic observed effect levels for animals as a function of exposure to "nickel", not as a function of exposure to the particular Ni compound which produced the harmful effects. This assumes that all Ni compounds are as toxicologically potent as the most potent compound. The research results presented and summarized in the TSD imply otherwise. Also, with respect to carcinogenic effects, a unit risk factor is established for all Ni compounds of 230 to 290 per million per ng/l based on nickel carbonyl exposure. This is contrary to staff's statements that certain Ni compounds, particularly soluble Ni compounds, are less carcinogenic than others. Unit risk factors, when appropriate, should be established for each Ni compound due to the differing carcinogenic risks posed by each compound.

In establishing the exposure levels at which thresholds are apparent, staff relies on studies which use atmospheric Ni loading in excess of 50 ng/l and frequently use Ni loading in excess of 500 ng/l. However, 50 ng/l is the one-hour California standard for PM10 exposure. Staff should address the possibility that the observed effects are attributable not only to exposure to Ni compounds, but also to exposure to particulate levels in excess of established ambient standards.

The conclusions regarding carcinogenic effects are based on the Ontario cohort study. We understand that one of the assumptions of this study is that exposure to Ni compounds occurred only during the work shift. This is likely to be in error due to the fact that the workers probably lived in the vicinity of the emitting facility, and that a lack of efficient emission controls on the facility probably led to high ambient Ni concentrations in the vicinity of the facility. This would imply that the stated levels of cancer could have resulted from a greater than estimated Ni exposure. Staff should investigate this possibility as it would affect the resultant unit risk factor.

Staff calculates a unit risk of 230 to 290 per million per ng/l. Using the same cohort study, EPA calculated average unit risks of 89 per million per ng/l. Staff should address the possible reasons as to why its calculated risk is a factor of three greater than the EPA's when both agencies used the same data.

Pacific Gas and Electric Company

August 22, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attn: Nickel
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma:

PG&E Comments on ARB/DHS June 1990 Draft
Identification of Nickel as a Toxic Air Contaminant

Pacific Gas and Electric Company (PG&E) appreciates this opportunity to comment on the draft nickel exposure (Part A) and risk (Part B) assessments. To assist us in reviewing your document, we retained Risk Focus, a division of Versar, Inc., to review Part B. Their comments are detailed in the attached report, summarized in our "Comments on Part B", and further summarized below:

1. **DHS should only identify Insoluble Nickel Compounds as Toxic Air Contaminants at this time.**

2. **The unit risk derived from sinter-plant subcohorts of the Ontario cohort should only be applied to nickel subsulfide and nickel refinery dust. Preferably insoluble nickel should be speciated between nickel subsulfide and other nickel compounds, and a separate, non-sinter worker cohort should be used for estimating risks from exposures to other insoluble nickel compounds. If subsulfide is not separately speciated, the unit risk derived from the 47,980 non-sinter worker Ontario cohort should be used for unspeciated insoluble nickel. Using the non-sinter cohort, rather than the sinter-plant subcohort, would reduce the estimated unit risk by a factor of approximately 5.7.**

3. **The unit risk should not be artificially increased by a factor of 1.33 to account for workers whose vital status could not be established. An adjustment factor of 1.05 would adequately account for normal life spans, and would reduce the estimated unit risk by a factor of 1.27.**

4. **The unit risk should not based upon the presumption of no historical non-occupational exposure but continuous ambient air exposure. It is adequate to assume that individuals will not be exposed to current ambient air concentrations more than twice as much as they were exposed to historical occupational concentrations. Instead of artificially increasing risks by a factor of 4.6, the DHS should increase risks by a factor no greater than 2. This would reduce the unit risk by a factor of 2.3.**

5. The proposed unspeciated insoluble nickel unit risk factor should be reduced by a factor of 10 or more.

6. Page 118 should clearly state that nickel sulfate is not expected to be carcinogenic by ingestion, and that ingestion of insoluble nickel is expected to be far less carcinogenic than inhalation.

In addition, PG&E offers the following comments on Part A, some of which may also require corresponding changes to Part B:

1. Table III-1 should subdivide the residual oil category into low sulfur and high sulfur categories, using 0.5% sulfur as the dividing point. Corresponding revisions should be made in Appendix V.

2. In Table III-1, the emission numbers shown for oil combustion should be that expected to be emitted as insoluble nickel oxides, not that expected to be emitted as soluble nickel sulfates or total nickel.

3. Table II-5 should be revised to more clearly show that projected total body exposures from ingestion far exceed projected total body exposures from inhalation. This information should then be prominently incorporated into the Part A executive summary, and the significance of this information should be addressed in Part B, and in the combined summary.

4. The claim on page A1 that 55 to 90 percent of total nickel is insoluble should be restated as a preliminary result of limited and potentially non-representative testing -- not as a definitive conclusion for all of California.

Please call me, or Ted Holcombe of my staff at (415) 972-6910, if you have any questions about these comments, or if the Department of Health Services or the Scientific Review Panel Toxic Air Contaminants would like us to arrange for one of our consultants to speak with you on these comments, or to be available to answer questions at the Scientific Review Panel meeting on nickel.

Sincerely,

Attachments

1. Table III-1 should subdivide the residual oil category into low sulfur and high sulfur categories, using 0.5% sulfur as the dividing point. Corresponding revisions should be made to Appendix V.

   Table III-1 on page A41 lists "residual oil" combustion as being responsible for 37 to 95% of the total nickel emissions identified. Such a significant category deserves subdivision. Since the nickel content of oils is generally proportional to the sulfur content, high sulfur oils generally lead to greater nickel compound emissions. Oil field steam generators in the San Joaquin Valley may have burned relatively high sulfur oil during the period in which the ambient air data was collected, while most utility power plants are required to burn relatively low sulfur oil. Furthermore, we understand that oil field emissions are being reduced and are unlikely to ever return to their prior levels.

   To enable the readers to evaluate emission trends, it is important to separate high sulfur residual oil combustion from low sulfur residual oil combustion. We suggest 0.5% Sulfur as the most logical dividing line, because that is the lowest international crude oil standard, and the standard applicable to most of PG&E's power plants.

   In Appendix V, the references addressing the range of nickel observed in combustion oil should be tied to the corresponding sulfur content. For example, the report notes that nickel concentration were up to 118 ppm, but did not exceed 90 ppm at U.S. power plants. What the report fails to note is that some U.S. power plants burn very high sulfur (and high nickel oil). For example, the 1985 National Acid Precipitation Assessment Program Emissions Inventory lists numerous eastern power plants with <u>average</u> sulfur oxide emissions approaching 3 lbs/million BTU, while the corresponding <u>maximum</u> for a low sulfur power plant is 0.528 lbs/million BTU. It should not be surprising that higher nickel concentrations have been observed in power plants burning higher sulfur oil.

   It is inappropriate to use nickel concentrations measured in high sulfur oil when estimating power plant emissions, and also inappropriate to use nickel concentrations measured in low sulfur Indonesian crude for oil field steam generators burning higher sulfur California crude oil. In 1984, PG&E tested oil in 11 fuel tanks at 6 different power plants. The Nickel concentration in the oil ranged from 8.4 to 23.2 ppm, with an average of 16.0. In 1990 PG&E did an additional three tests of at three different power plants, one of which (Humboldt Bay) is authorized to burn higher sulfur oil. That testing showed 23 ppm in the lower sulfur units, and 28 ppm in the higher sulfur unit. Combining both groups of tests, the average for the low sulfur units was 17.1 ppm nickel.

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2. **In Table III-1, the emission numbers shown for oil combustion should be that expected to be emitted as insoluble nickel oxides, not that expected to be emitted as soluble nickel sulfates or total nickel.**

   In Table III-1 on page A41, the species listed as being emitted as a result of residual oil combustion is identified as "nickel sulfate", but the amount shown is that estimated for total nickel. According to the Environmental Protection Agency's September 1986 "Health Assessment Document for Nickel and Nickel Compounds" [EPA/600/8-83/012FF], pp. 3-18 through 3-19:

   a. In fly ash samples collected from five oil-fired utility boilers (in 1980), the nickel components were found to be 60 to 100 percent water soluble;

   b. In the analysis of the leachate from the solubility test, sulfate anion was the only anion present at more than trace levels;

   c. In the insoluble fraction of the fly ash samples from oil-fired boilers, nickel was determined by XRD to potentially exist as nickel oxide; however, it is frequently difficult to distinguish between pure nickel oxide and complex metal oxides involving nickel;

   d. In similar testing in 1983, the portion of the total amount of nickel present in the fly ash samples that was water soluble averaged 54%.

   On page 90 of Part B of this assessment, DHS indicates that nickel sulfate has been adequately evaluated, and has shown no evidence of carcinogenic potential by oral exposure. On page 117 DHS states that soluble nickel salts would not remain in the lungs as do nickel subsulfide and nickel oxide. DHS goes on to conclude that only <u>insoluble</u> nickel compounds should be identified as toxic air contaminants. Therefore it is more appropriate to estimate the amount of nickel oxides emitted from oil combustion, rather than the amount of nickel sulfate or total nickel. Table III-1 should be revised accordingly.

3. **Table II-5 should be revised to more clearly show that projected total body exposures from ingestion far exceed projected total body exposures from inhalation. This information should then be prominently incorporated into the Part A executive summary, and the significance of this information should be addressed in Part B, and in the combined A&B executive summary.**

On page A24, it is estimated that dietary exposures are on the order of 62 to 500 ug/day. On page A27 it is estimated that the average concentration in California drinking water is 10 ug/l, or 20 ug/day. By comparison, the average inhalation exposure is only 0.0074 ug/m^3 or 0.03 ug/day. Although Table II-5 address indoor exposures, it does not compare average ambient with average ingestion exposures. That comparison needs to be highlighted and mentioned in the Part A executive summary, the Part B executive summary, and the combined executive summary.

This is an important factor, because airborne exposures are insignificant unless they are far more risky than ingestion exposures, in which case the fraction of the airborne dust which falls to the ground causes insignificant effects. Part A and Part B need to address this relative significance/insignificance issue.

4. **The claim on page A1 that 55 to 90 percent of total nickel is insoluble should be restated as a preliminary result of limited and potentially non-representative testing -- not as a definitive conclusion for all of California.**

   If 61 to 95% of total California nickel emissions come from oil combustion (as suggested by Table III-1), and an average of 54-60% % of oil combustion emissions are soluble (as suggested by EPA, see comment A(2) above), it is not logical to expect 55-90% of total exposures to be insoluble. Either the inventory under-estimates emissions from such insoluble nickel sources, or the data was collected at points more strongly affected by insoluble nickel emission sources.

   Possible confounding factors that should be considered include:

   a. Relative proximity to insoluble nickel sources (such as electroplating, waste incineration, foundries etc) versus soluble nickel sources (such as oil combustion);

   b. The possible use of scrubbers on oil combustion sources in Kern County which may have preferrentially removed soluble nickel;

   c. The possible contribution of wind blown dust. Most of the samples were taken in relatively dry or rural areas where wind blown dust might be expected to be more significant, and where the limited rainfall might preferrentially remove soluble nickel to underground water tables while leaving insoluble nickel on the surface. Note that Figure IV-2 on page A57, lists wind blown dust as the second largest source of nickel on a global basis.

Appendix II does not claim that the nine samples taken at the six sites definitively characterized emissions from all sources in all areas of California. That is appropriate since none of the samples were taken near operating power plants or refineries in the San Francisco Bay Area or along the coast of California (PG&E's Kern Power Plant Units 1 & 2, near Bakersfield, are relatively small units, and only operated at 4.3% and 8.0% of capacity, respectively, in 1984, and even less thereafter). However, the last sentence on page A1, implies that the results of this sampling "showed that insoluble nickel in California's ambient air accounts for 55 to 90 percent of total nickel". Either the representativeness of those nine samples needs to be better explained in Appendix II, or the the statement on page A1 should be reworded, or both. PG&E suggests the following rewording of the last two sentences on page A1:

> Since the DHS has indicated that inhalation of the insoluble form of nickel as is the only known carcinogenic fraction, the ARB conducted research to determine the percentage of insoluble nickel in the ambient air. ~~The result~~ Limited testing of nine samples at six sites showed that insoluble nickel in California's ambient air ~~accounts~~ might account for as much as 55 to 90 percent of total nickel. However, other testing has shown that oil combustion, the largest identified source of nickel emissions in California, results in predominately soluble nickel emissions. This will be studied further before controls are proposed.

PG&E COMMENTS ON PART B of the Nickel Assessment -- August 22, 1990

1. **DHS should only identify Insoluble Nickel Compounds as Toxic Air Contaminants at this time.**

   The weight of evidence suggests that insoluble nickel compounds are retained in the lung longer and are more carcinogenic than soluble nickel compounds. The limited epidemiological data regarding nickel sulfates include significant confounding insoluble nickel exposures. In addition, it has not been established whether the form of nickel sulfate found in those occupational exposures is similar to that found in ambient exposures resulting from oil combustion. For example, occupational sulfates can be anhydrous, while oil combustion sulfates tend to be already hydrated when emitted. For these reasons, PG&E and Risk Focus strongly support the Department of Health Services (DHS) decision to only identify insoluble nickel compounds (including nickel sulfates emitted from power plants) as Toxic Air Contaminants at this time, pending completion of the National Toxicology Program Inhalation Cancer Bioassay.

2. **The unit risk derived from sinter-plant subcohorts of the Ontario cohort should only be applied to nickel subsulfide and nickel refinery dust. Preferably insoluble nickel should be speciated between nickel subsulfide and other nickel compounds, and a separate, non-sinter worker cohort should be used for estimating risks from exposures to other insoluble nickel compounds. If subsulfide is not separately speciated, the unit risk derived from the 47,980 non-sinter worker Ontario cohort should be used for unspeciated insoluble nickel. Using the non-sinter cohort, rather than the sinter-plant subcohort, would reduce the estimated unit risk by a factor of approximately 5.7.**

   The insoluble nickel to which sinter workers were exposed in Ontario is known to contain a relatively high proportion of nickel subsulfide. On the other hand, oil combustion, currently estimated in Part A of this report to contribute 61 to 98% of all airborne nickel emissions in California, is not believed to produce any nickel subsulfide. The exposures of the non-sinter Ontario subcohort are therefore more representative of the expected California exposures.

   Epidemiological studies of insoluble nickel exposures consistently show lower risks for non-sinter plant worker exposures (subjected to a lower percentage of nickel subsulfides and a higher percentage of other insoluble nickel) than sinter worker studies (subjected to a higher percentage of nickel subsulfides and a lower percentage of other insoluble nickel). Basing all California insoluble nickel risks on the sinter worker subcohort with the highest Standardized Mortality Ratio (SMR) is therefore unjustifiably conservative -- at least for the vast majority of California exposures.

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PG&E and Risk Focus therefore recommend that if exposures are not speciated between nickel subsulfide and other insoluble nickel, that the non-sinter cohort be used to estimate risks (from unspeciated insoluble nickel). Using the non-sinter cohort, rather than the sinter-plant subcohort, would reduce the estimated unit risk by a factor of roughly 5.7 (see Section III.6.3 of the attached Versar report).

The preferred and recommended course of action would be to propose separate unit risks for nickel subsulfide and for other insoluble nickel compounds. In this case, a sinter plant cohort should be used to estimate nickel subsulide risks, and a non-sinter plant cohort should be used to estimate risks from other insoluble nickel compounds. In choosing these cohorts, we recommend that the largest possible cohort or combination of cohorts be used to generate the best estimate of risks.

3. **The unit risk should not be increased by a factor of 1.33 to account for workers whose vital status could not be established. An adjustment factor of 1.05 would adequately account for normal life spans, and would reduce the estimated unit risk by a factor of 1.27.**

   The draft unit risk estimate excludes that fraction of the cohort lacking "vital status". Because every attempt was made to locate and identify known cancer cases, and the Canadians maintain an excellent death registry, the investigators are believed to have found most of the deaths, and those for which information is lacking are believed to be in the healthy fraction. What is uncertain is whether they lived a normal life span, a longer than normal life span, or a shorter than normal life span after the most recent data collection. Excluding this fraction artificially increases the unit risk. The only adjustment that might be warranted is one assuming a normal life span rather than a "still living" status. A "normal life span" adjustment would reduce risks by about 5%. Multiplying the unit risk by an adjustment factor of 1.05 rather than by the factor of 1.33 used by DHS would decrease the estimated risk by a factor of 1.27.

4. **The unit risk should not based upon the presumption of no historical non-occupational exposure but continuous ambient air exposure. It is adequate to assume that individuals will not be exposed to current ambient air concentrations more than twice as much as they were exposed to historical occupational concentrations. Instead of** increasing risks by a factor of 4.6, the DHS should increase risks by a factor no greater than 2. This would reduce the unit risk by a factor of 2.3.

DHS assumes that 1 ng/m^3 of insoluble nickel will cause 4.6 times more risks in California's ambient air than it is presumed to have caused in the Ontario "historic worker" cohort. This "equivalent lifetime exposure per year" adjustment factor is based upon the assumption that the "public" will be exposed to the ambient air 24 hours per day, 7 days per week, 52 weeks per year of exposure; while the "historic worker" was only exposed 8 hours per day, 5 days per week, 48 weeks per year of exposure.

However, the amount of time the average person in California spends outdoors is only 13%. This is actually about 1.7 times less than the 22% of time the average "historic worker" was assumed to spend at the workplace. Furthermore, an historic worker's exposures to nickel did not necessarily end when he left work. Nickel associated dusts may have been carried home on clothing; and dusts at Copper Cliffs were removed by roof fans which may have contributed to elevated concentrations in the vicinity of the plant.

PG&E notes that it is the finer particles which tend to be captured by the lung, the organ of concern in the current DHS assessment, and that these same particles would be most readily removed by the roof fans and most widely distributed in the ambient air outside the plant. While exposures were undoubtedly higher at work than outside of work, the question is:

> What is the difference between the ratio of historic "work" to "after work" exposures; versus the ratio of modern particulate exposures in the ambient air to the contribution that ambient air particulate concentrations currently make toward indoor particulate concentrations?

Given the poor corolation between ambient and indoor exposures, and the ever increasing use of filters, drapes, rugs, vacuums, and more air tight, more energy efficient, cars, homes and offices, the ratios might not be all that different.

These considerations suggest that the differences in exposure frequency and duration between the historical work place and the ambient air may be far less than the factor of (24/8)*(7/5)*(52/48) assumed by DHS. Risk Focus suggests that it would be adequately health protective to use a factor of 2. Using a factor of 2 rather than a factor of 4.6 would reduce the estimated unit risk by a factor of 2.3, and would provide for those individuals who spend more than a third of their time outdoors.

5. The proposed unspeciated insoluble nickel unit risk factor should be reduced by a factor of 10 or more.

Using the entire cohort, rather than the sinter-plant subcohort, would reduce the estimated unit risk by a factor of roughly 5.7.

Using a 5% normal life span adjustment rather than the exclusion of those lacking complete vital status would reduce the estimated unit risk by a factor of roughly 1.27.

Using a factor of 2 rather than a factor of 4.6 to correct for differences between the duration of occupational and ambient exposures during a year of exposure would reduce risks by a factor of 2.3.

Combining the effects of these three recommended adjustments only would suggest that the unit risk for the non-sinter cohort should be a factor of 16 lower than that proposed for the sinter plant cohort.

PG&E notes that the last two adjustments would be in addition to the average age adjustment factor of 3.3 proposed by Donna J. Sivulka of Nipera at the August 15, 1990 consultation meeting. Combining the "age", "vital status" and "equivalent lifetime exposure per year" adjustments would reduce the unit risk based upon the sinter plant cohort, which we suggest be considered as representative of nickel subsulfide dominated insoluble nickel compound exposures, by a factor of 1.27*2.3*3.3 = 9.6 or almost 10.

Assuming that the non-sinter plant subcohort would qualify for a similar age adjustment, the combined adjustments could reduce risks by a factor of more than 50. This suggests that the risks for the non-sinter plant cohort, which we suggest be considered as representative of nickel oxide dominated insoluble nickel compound exposures, could be on the order of 4.8×10^{-6}.

6. **Page 118 should clearly state that nickel sulfate is not expected to be carcinogenic by ingestion, and that ingestion of insoluble nickel is expected to be far less carcinogenic than inhalation.**

On page 90, DHS indicates that nickel sulfate has been adequately evaluated, and has shown no evidence of carcinogenic potential by oral exposure, and that insoluble nickel compounds have not been adequately evaluated. The last two sentences on page 118 should therefore be corrected so as not to suggest that the carcinogenic potential for oral ingestion of nickel sulfate needs further study.

Since this risk assessment focuses on insoluble nickel, we suggest at the minimum the word "insoluble" should be inserted before the word "nickel" in the last two sentences.

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Also, since soluble nickel has no known carcinogenic effect, and insoluble nickel compounds would be less likely to be absorbed when ingested, it would not be unreasonable to conclude, pending further study to the contrary, that ingestion of nickel compounds would probably create lower cancer risks than inhalation of a similar amount of insoluble nickel. PG&E therefore suggests revising the last two sentences to read:

> In the absence of greater supportive evidence, it is not possible to make conclusions regarding the carcinogenicity following ingestion of insoluble nickel compounds. However, it is ~~clear~~ likely that further studies ~~are necessary to ascertain~~ would show that the carcinogenic potential of insoluble nickel compounds from exposure by the oral route is significantly lower than that for exposure by the inhalation route. Until better data is available, it would not be unreasonable to assume that the risks from ingestion of nickel would to be insignificant.

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ASSESSMENT OF THE HEALTH RISKS OF INHALING NICKEL COMPOUNDS PRESENT IN AMBIENT AIR

Prepared for
PACIFIC GAS AND ELECTRIC COMPANY
San Francisco, California

Prepared by

RiskFocus®
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Springfield, Virginia

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Foreword

This report was prepared under the management and supervision of VERSAR's **RiskFocus** Division located in the Washington, D.C. metropolitan area. **RiskFocus** provides comprehensive *stewardship* for product integrity and registration, worker safety, waste disposal, regulatory interpretation and compliance, and risk communication.

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ASSESSMENT OF THE HEALTH RISKS OF INHALING NICKEL COMPOUNDS PRESENT IN AMBIENT AIR

I. Introduction

In response to the State of California's proposal to regulate nickel in ambient air and the State's preliminary technical support document regarding the "*Proposed Identification of Nickel as a Toxic Air Contaminant*," **RiskFocus** was retained by the Pacific Gas & Electric Company (PG&E) to review of the State's technical support document (State of California, 1990a; State of California, 1990b) with respect to it's scientific accuracy and consistency with historical and current scientific knowledge, and to perform an independent risk assessment of the relative risk of nickel subsulfide versus those nickel compounds associated with the generation of electric power. Comments regarding Part B of the State's technical support document, "*Health Risk Assessment for Nickel*" (State of California. 1990b) are incorporated throughout the risk assessment presented herein.

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The framework used to conduct risk assessments was developed in 1983 by the National Research Council[2]. Although cancer is the form of toxic injury of predominant concern, the framework is well suited to address other forms of toxic injury systematically and objectively, whether from single ("acute") or repeated and prolonged ("chronic") dosing. Additional methods that focus on noncancer toxicity have been published by the World Health Organization. **RiskFocus** uses these methodological tools, and other authoritative texts, such as *Toxic Substances and Human Risks*[3], in performing multi-chemical, multipathway risk assessments. The four major steps contained in a comprehensive risk assessment, as delineated by the National Research Council, are summarized in Appendix A.

Section II of this report discusses potential human exposure to nickel compounds in California, particularly with respect to the types of nickel compounds present in the ambient environment versus the occupational setting used as a basis for estimating risks. A discussion of the hazards associated with exposure to different examples of nickel compounds and the available dose-response data for these compounds is presented in Section III. Section III also provides a discussion of critical issues associated with quantitative risk analyses for nickel compounds. Section IV characterizes the risk associated with potential exposure to nickel compounds in ambient air by integrating information presented in Sections II and III. Finally, Section V summarizes recommendations based on the risk assessment presented in this report.

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[2]National Research Council. 1983. *Risk Assessment in the Federal Government: Managing the Process.* Washington, DC: National Academy Press. 191 pp.

[3]R.G.Tardiff and J.V.Rodricks, editors. New York: Plenum Publishing Co., 1988.

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II. *Exposure Assessment for Nickel Compounds in Ambient Air*

Human ambient exposures to nickel compounds largely result from ingestion of both food and water, followed by inhalation of ambient air [to which the unit cancer risk proposed in the State of California, Department of Health Services' (DHS) risk assessment (1990b) would be applied] which typically constitutes a relatively small percentage of total body exposure (NAS, 1975; EPA, 1986; EPA, 1985). In contrast, occupational exposures to nickel compounds (used as the basis for the proposed unit cancer risk), largely result from inhalation and dermal exposures (NAS, 1975; State of California, 1990b; Bernacki *et al.*, 1978; Chovil *et al.*, 1981; Cox *et al.*, 1981; Enterline and Marsh, 1982; Godbold and Tompkins, 1979; Kaldor *et al.*, 1986; Langer *et al.*, 1980; Lessard *et al.*, 1978; Torjussen, 1985; Magnus *et al.*, 1982; Polednak, 1981; Shannon *et al.*, 1984; Olse and Sabroe, 1984; and Mastromatteo, 1986.). Furthermore, ambient inhalation exposures are likely to include forms of nickel, such as nickel sulfate or oxides, while occupational exposures have historically included, in addition to these compounds, significant exposures to nickel subsulfide, or in some settings, primarily nickel carbonyl[4].

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[4] Nickel carbonyl is relatively unstable in ambient air as evidenced by a half-life of approximately [illegible] seconds (EPA 1986). Thus, it is relatively insignificant with respect to ambient air exposure.

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Nickel compounds are generally present in natural waters and in practically all soils and foods. The available evidence indicates that the natural concentrations of nickel in waters, soils and foods do not constitute a biological hazard (NAS, 1975, EPA, 1986). Indeed, nickel may be an essential trace element for the nutritional requirements of man and animals (NAS, 1975; EPA, 1986). Humans normally ingest nickel in food and water at an estimated 300 to 600 μg/day (NAS, 1975)[5]. Although it is not clearly explained, the State of California's human exposure assessment for environmentally occurring nickel compounds in California (1990a) focuses on the inhalation route of exposure, presumably because it is of toxicological significance (see Section III), because toxicity data on other routes of exposure are not adequate for quantitative analyses, and because the assessment is prepared for an agency charged with the regulation of air quality, rather than the quality of water or food.

With respect to inhalation exposure in California, the State (1990a) measured ambient nickel concentrations from their 20-station network, which collected 24-hour samples on teflon filters during January 1985 through February 1987. As cited in the State's report (1990a) the estimated mean, total nickel concentrations ranged from 2.8 ng/m^3 at Citrus Heights to 21.8 ng/m^3 at Bakersfield. Site specific standard deviations ranged from 40 to 85 percent of the estimated mean concentrations indicating a significant degree of variability in the data. The mean statewide population-weighted exposure for November 1985 through October 1986 estimated by the State is 7.4 ng/m^3 with a lower bound of 6.0 ng/m^3 and an upper bound of 8.3 ng/m^3. These concentrations may not necessarily reflect actual personal exposure concentrations, because (1) indoor air's contribution to total exposure is not included; and (2) mean air concentrations for each of the six air basins included in the State's

[5]By comparison, if the mean statewide population-weighted mean concentration of total nickel associated with ambient air particles in California (i.e., 7.4 ng/m³ State of California 1990a), is applied to an inhalation rate of 20 m³ per day, the resultant dose (assuming 100 percent absorption) would be approximately 96 ng/day. This daily inhalation dose represents only 0.1 to 0.3 percent of the estimated daily ingestion intake.

monitoring program assume that all the people in those areas were exposed to the single mean value estimated for that air basin over their entire lifetime.

The State (1990a) also measured the proportion of insoluble nickel in total nickel associated with respirable ambient air particles in California. The State reported that 55 to 90 percent of total nickel is composed of insoluble nickel. Using this proportion of insoluble nickel, the State estimated that 20,339,250 people in California are exposed to an average of 4.1 (7.4 ng/m^3 x 0.55) to 6.7 ng/m^3 (i.e., 7.4 ng/m^3 x 0.90) insoluble nickel in the ambient air. However, the State did not determine the specific soluble and insoluble nickel species present and their relative concentrations.

With respect to the nickel species which occur in ambient air associated with particles, evidence suggests that nickel sulfates and nickel oxides represent the primary components (EPA, 1986; Schroeder *et al.*, 1987). Oxidation of nickel species present as aerosols may result from interaction with various atmospheric oxidants, such as molecular oxygen, ozone, or hydrogen peroxide (Schroeder *et al.*, 1987). The concentrations of total elemental nickel associated with particulate matter in the atmosphere has ranged from 0.01 to 60 ng/m^3 in remote locations, from 0.6 to 78 ng/m^3 in rural locations, and from 1 to 371 ng/m^3 in urban areas with in the U.S. (Schroeder, 1987). However, the relative proportion of insoluble, soluble, or specific nickel compounds were not determined.

It is useful to assess the nickel speciation of fly ash from combustion sources to obtain an estimate of the relative proportion of different nickel species in ambient air. This is because fly ash, particularly from fuel oil combustion, has been estimated to comprise up to 81 percent of total nickel present in the South Coast Air Basin of California (Cass and McRae, 1983) and 61 to 98 percent of the total California nickel inventory (State of California, 1990a). Further, national atmospheric nickel emissions

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from oil combustion have been estimated to account for 60 to 98 percent of the total nickel present (Krishnan and Hellwig, 1982, Baig *et al.*, 1981).

Analyses of fly ash from oil-fired boilers found that the nickel component was 60 to 100 percent water soluble. This led to the hypothesis that the predominant form of nickel present was nickel sulfate, which was confirmed by analysis using Fourier transform infrared spectroscopy (Gendreau *et al.*, 1980). Further, the insoluble nickel fraction of fly ash samples from oil-fired boilers was determined to exist potentially as nickel oxide and/or complex metal oxides involving nickel (Henry and Knapp, 1980). Dietz and Wieser (1983) have reported nickel oxide to be present in oil combustion fly ash. Similarly, analyses of coal fly ash (EPA, 1986) from coal-fired boilers have suggested that the soluble fraction of nickel (20 to 80 percent of total nickel) exists primarily as nickel sulfate and the insoluble fraction contains nickel as a nickel oxide or a component of complex metal oxides. There is no evidence that nickel subsulfide is present in oil or coal fly ash emissions or is associated with ambient air particles (EPA, 1986). As mentioned above, data collected by the State of California (1990a) suggest that nickel associated with ambient air particulate matter in California is comprised of approximately 55 to 90 percent insoluble nickel species and by inference, 10 to 45 percent soluble nickel species.

The evidence for nickel sulfate and nickel oxide being the predominant forms of nickel associated with fly ash and, therefore, with ambient air particles is supported by the estimated nickel and nickel compound emissions in California (1990a). According to the State of California, the species of nickel emitted from various stationary and mobile sources in California include nickel sulfate, nickel oxide, complex oxides of nickel, nickel magnesium silicate, nickel metal, and nickel carbonyl (State of California, 1990a). Atmospheric transport and fate (e.g., chemical transformations, deposition) of these compounds has not been fully elucidated. However, environmental fate data are available for nickel carbonyl: this compound is relatively unstable in ambient air as evidenced by a half-life of approximately 100

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seconds (EPA, 1986) and would be expected to dissipate rapidly. In summary, the weight-of-evidence suggests that atmospheric nickel is largely in the form of soluble nickel sulfate (EPA, 1986) and, as with many other metallic elements of anthropogenic origin, insoluble oxides, particularly, nickel oxide (EPA, 1986, Schroeder *et al.*, 1987).

In contrast to inhalation exposures to these nickel compounds in ambient air, occupational inhalation exposures, particularly associated with nickel refining processes, have included nickel subsulfide. Table 1 illustrates an example composition of flue-dust for a nickel refinery (Gilman, 1962).

TABLE 1. Analysis of Flue Dust from an Ontario Nickel Refinery

COMPOUND	FRACTION (percentage)
Nickel subsulfide, Ni_3S_2	57.0
Nickel sulfate, $NiSO_4 * 6H_2O$	20.0
Moisture	7.3
Nickel oxide, NiO	6.3
Cupric oxide, CuO	3.4
Miscellaneous	2.0
Ferric oxide, Fe_2O_3	1.8
Silicon dioxide, SiO_2	1.2
Cobalt oxide, CoO	1.0

It is not know whether this analysis is representative of flue dusts from other nickel refineries (NAS, 1985). However, significant exposures to nickel subsulfide would be expected for all nickel refineries using a sulfuric acid leaching step during nickel matte processing. Varying degrees of nickel oxide exposure also generally occurred as a component of the refinery dust in the very dusty calcining and sintering areas of

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pyrometallurgical sulfide nickel matte refineries. With respect to nickel sulfate exposures in the occupational environment, electrolysis workers in Norway and Canada were exposed to high concentrations of nickel chloride and nickel sulfate, however, heavy exposures to other less soluble nickel compounds were also reported to occur in these same workers (EPA, 1986; ICNCM, 1990). Of particular importance are the levels of exposure to nickel compounds experienced by various occupational cohorts (EPA, 1986; ICNCM, 1990). Air levels of total nickel in the workplace have been reported to range from 0.01 to 5.0 mg/m^3 in the West Virginia cohort to as high as 400 mg/m^3 in the Ontario cohort (EPA, 1986). It is important to note that these exposures levels were four to eight orders of magnitude higher than exposures potentially experienced by residents of California (i.e., statewide population-weighted mean concentration of 0.0000074 mg/m^3). Section III, which follows, discusses the toxicological and epidemiological data for nickel subsulfide, nickel oxide, and nickel sulfate and the use of human dose-response data for quantitative risk analysis for nickel compounds.

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III. Hazard Identification and Dose-Response Assessment of Nickel Compounds in Ambient Air

Although small amounts of nickel have been shown to be essential to some species of animals, including humans (NAS, 1975), high levels of inhalation exposure to nickel and nickel compounds have been reported to cause pulmonary effects such as asthma (NAS, 1975). In addition, very high inhalation exposure to nickel refinery dust, which contains nickel subsulfide, has been associated with an increased risk of nasal, laryngeal, and lung cancer (EPA, 1986).

Assessing hazards associated with ambient exposures in California to nickel compounds should focus on potential *carcinogenic* effects and the relevant route of exposure for this effect, i.e., *inhalation*, because the levels of nickel associated with respirable particles in California are not likely to exceed levels associated with other adverse effects in either humans or animals. This argument has been documented in the State's risk assessment (State of California, 1990b), and is discussed further in this section.

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The following section is based on a critical examination of the scientific literature regarding the hazardous properties of nickel compounds and their behavior (i.e., dose-response) in biological systems. This section includes a review of the scientific merits of the State of California's, June 1990, *Health Risk Assessment for Nickel* (State of California, 1990b), and focuses on the toxicological evaluation of nickel compounds of particular relevance to the electric utility industry, i.e., nickel oxide, sulfate, which have been associated with trace emissions from fuel combustion facilities. These two compounds and nickel subsulfide, are the focus of the toxicological review of nickel compounds presented in the State of California's risk assessment (State of California, 1990b); largely because of the availability of toxicological data on these compounds and because of their occurrence, albeit in varying degrees, in occupational and ambient settings which have been documented in epidemiological investigations and ambient air monitoring studies (Cass and McRae, 1983; Schroeder *et al.*, 1987; EPA, 1986; ICNCM, 1990).

In addition, an evaluation was conducted concerning the quantitative risk modeling based on epidemiological data (i.e., the occupational cohort from the Sudbury, Ontario sintering plant) performed by the State to arrive at an estimate of "lifetime added risk" resulting from ambient exposure to nickel compounds. An extensive review of the substantial database of epidemiological studies of nickel compounds raises important issues regarding the State of California's use of the Ontario "subcohort" of sinter plant workers to estimate the dose-response relationship of nickel compounds in humans and the carcinogenic potency of the mixture of nickel compounds to which these workers were exposed. The uncertainties, limitations, and appropriate methods regarding the use of this occupational epidemiology study for assessing excess cancer risk among persons exposed to environmentally occurring nickel associated with ambient air particles are discussed in section III-C.

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A. Review of Key Toxicological Studies

This section reviews key pharmacokinetic and toxicological studies for nickel oxide, nickel sulfate, and nickel subsulfide, and focuses on the inhalation route of exposure. Of particular importance in assessing human health risks associated with exposure to nickel compounds in ambient air is the observation that a significant source of uncertainty exists because of the lack of knowledge regarding the composition of specific nickel compounds occurring in ambient air of California. Lack of quantitative speciation of the concentrations of the various nickel compounds which are associated with respirable ambient air particles prohibits the use of compound-specific pharmacokinetic and toxicity data in a quantitative manner, where adequate data exist.

1. Pharmacokinetics of Nickel Compounds.

As mentioned in Section II, there are four potential routes of entry of nickel compounds into the human body: oral (e.g., food and drinking water which may contain nickel derived from cooking, beverages, and eating utensils), inhalation (e.g., from natural and anthropogenic sources of atmospheric nickel compounds), percutaneous absorption (which is restricted to the passage of nickel through the outermost layers of the epidermis, such that binding with apoantigenic factors may occur, hence, the clinical importance of nickel dermatitis), and parenteral administration (e.g., metallic implants and prostheses). The route-specific pharmacokinetics and target organ toxicity of a number key nickel compounds (e.g., nickel oxide, nickel subsulfide, and nickel sulfate) has been substantially characterized for humans and animal exposures. The pharmacokinetic behavior of nickel compounds appear to be similar for humans and animals, although the studies identifying similar hazardous effects (e.g., contact dermatitis, hepatic and reproductive effects) in animals and humans are limited.

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As noted by the State of California (1990b), inhalation absorption and target tissue dose of nickel compounds is largely dependent upon the physicochemical properties (e.g., solubility) of each nickel compound as well as the pulmonary dynamics of the exposed animal species. This process has been documented by pulmonary clearance and deposition studies (Torjussen *et al.*, 1978; Torjussen and Anderson, 1979; Tanaka *et al.*, 1985; Valentine and Fisher, 1984; Carvalho and Ziemer, 1982; and Dunnick *et al.*, 1989). These and other studies suggest that insoluble, particulate-associated nickel compounds, e.g., nickel oxide and subsulfide, are deposited and cleared from the lung as a function of particle size, physicochemical properties (e.g., water solubility), and species-specific compartmentalization of the pulmonary tract. Absorption and clearance of insoluble nickel compounds is a very slow process, and is accompanied by accumulation in the lung tissue (EPA, 1986; Dunnick *et al.*, 1989). Thus, the subcellular, target tissue dose present over time is a dynamic function of pulmonary deposition and clearance, which depends on compound-specific characteristics.

For example, the clearance half-life of nickel compounds as a mixture, from the nasal mucosa of exposed workers was reported to be approximately 3.5 years (Torjussen and Anderson, 1979). Whereas, the clearance half-life of nickel oxide has been reported to range from 11.5 to 21 months, for 1.2 and 4.0 μm diameter particle sizes, respectively (Tanaka *et al.*, 1985). Further, the target tissue dose of nickel oxide has been shown to depend on the deposition rate (which is dependent upon particle size distribution), and is relatively independent of the length of exposure (Kodama *et al.*, 1985).

As acknowledged by the State (1990b), the only tissue exhibiting age-dependent accumulation appears to be the lungs (Mushak, 1980). This accumulation is believed to be associated with inhalation of insoluble nickel compounds (EPA, 1986). Although the State of California has recognized the importance of pulmonary pharmacokinetics in assessing the internal doses of nickel compounds particularly insoluble nickel

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compounds which California has reported to comprise 55 to 90 percent of total nickel associated with respirable ambient air particulate) it was not included in the quantitative risk assessment. In the interest of including state-of-the-art scientific methods and supporting data, which yield the most accurate estimation of target tissue dose for assessing health risks, the State should consider the usefulness of pulmonary deposition data for nickel compounds.

Another issue of particular relevance to the pulmonary pharmacokinetics of nickel compounds is their subcellular bioavailability as it relates to the proposed mechanisms of nickel carcinogenicity. A complete understanding of the biological effects of nickel is dependent on knowledge of nickel binding sites within the human cell. Because relatively little is known about the molecular sites attacked by nickel within the cells, it is of interest to consider reactions of nickel ions with molecules that have been isolated from the cell. Nickel binding to biologically important substances has usually been studied in the context of the binding of metal ions in general. Nickel in its common oxidation state, i.e., 2+, is unusual in its potentialities, in that it is capable of being interconverted among three geometric structures - square planar, octahedral, and tetrahedral (NAS, 1975). As acknowledged in the State's risk assessment (State of California, 1990b), the morphological transformation of mammalian cells by nickel appears to vary greatly between nickel compounds (Costa, 1981; Costa *et al.*, 1982; Costa and Heck, 1984). The rate of cellular uptake and intracellular bioavailability of nickel 2+ from various nickel compounds appears to account, in part, for their respective carcinogenic potencies (Sunderman, 1989; IARC, 1987; Costa, 1981; Costa and Heck, 1984). Further, *in vitro* morphological transformation of human cells by nickel compounds generally do not appear to be as susceptible as other mammalian cell cultures (Sunderman, 1989). Use of compound-specific bioavailability data is also contingent upon knowledge of the composition of nickel compounds in ambient and occupational settings.

Finally, the State of California, did not discuss data regarding the distribution of nickel compounds in biological fluids in humans. The National Academy of Sciences (1975) provided a summary of studies which quantified concentrations of nickel in human serum, plasma, whole blood, and urine. Tables 2 and 3 summarize nickel concentrations in human serum and plasma, and whole blood, respectively. The significance of these data is their support of the use of biomonitoring as an index of ambient exposure to nickel (McNeely *et al.*, 1972). It must be emphasized that there is not yet any evidence that ambient exposures of the general public to nickel, even at Sudbury, Ontario, the site of the largest open-pit nickel mines in North America, are associated with adverse effects in man or animals (NAS, 1975). In relating body burden to occupational exposure levels, serum and urine are the most studied. Grandjean (1986) has reviewed exposure and biomonitoring data from a number of epidemiological studies. This review demonstrated a general positive relationship between air nickel levels and urinary levels. Although biological monitoring in the occupational setting has not been used to support quantitative estimation exposure levels, it is indicative of whether or not absorbed doses are at concentrations below those associated with systemic effects.

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TABLE 3. Nickel Concentrations in Human Serum and Plasma

Author[a]	Method	Area	No. of Subjects	Serum (S) or Plasma (P)	Nickel Concentration µg/100 ml Mean	Range
Cluett and Yoe	Spectrophotometry	Virginia	1	P	1.2	1.0 - 8.5
Koch *et al.*	Emission spectrography	New York	?	P	3.0	1.0 - 6.0
Monaco lli *et al.*	Emission spectrography	Virginia	12	P	4.0	0.0 - 18
Paixao and Yoe	Emission spectrography	Virginia	39	P	2.3	0.0 - 27
Herring *et al.*	Emission spectrography	Virginia	109	P	6.0	0.0 - 18
Butt *et al.*	Emission spectrography	California	48	S	5.3 - 6.2[b]	—
Zhernakhova	Emission spectrography	Russia	154	S	5.5 ± 2.8 (male)	0.1 - 7.3
Sunderman	Spectrophotometry	Florida	23	S	2.2	0.1 - 7.3
Schaller *et al.*	Atomic absorption	Germany	26	P	2.1	0.6 - 3.7
Mertz *et al.*	Emission spectrography	Germany	59[b]	S	0.78	0.06 - 4.60
Howard (personal communication)	Emission spectrography	England	50	S	2.1	0.1 - 5.0
Nomoto and Sunderman	Atomic absorption	Connecticut	40	S	0.26	0.11 - 0.46
Niedermeier *et al.*	Emission spectrography	Alabama	105[d]	S	4.0	1 - 25
McNeely *et al.*	Atomic absorption	Connecticut Canada[e]	26 25	S S	0.26 0.46	0.08 - 0.52 0.20 - 0.73
Pekarek and Hauer	Atomic absorption	Washington, DC	20	S	1.5 ± 0.5	—
Nomoto	Atomic absorption	Japan	23	S	0.21 ± 0.11	—

[a] References are found in NAS (1975).
[b] Confidence limits of mean value; nickel not detected in 18 serum samples.
[c] Includes 25 healthy subjects and 34 patients.
[d] Nickel not detected in 57 percent of serum samples.
[e] Sudbury, Ontario.

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TABLE 6. Nickel Concentrations in Human Whole Blood

Author[a]	Method	Area	Number of Subject	Nickel Concentration µg/100 ml Mean	Range
Cluett and Yoe	Spectrophotometry	Virginia	8	4.1	2.5 - 6.7
Paixao and Yoe	Emission spectrography	Virginia	40	3.6[b]	—
Imbus *et al.*	Emission spectrography	[c]	153	4.2	0.9 - 9.8[d]
Butt *et al.*	Emission spectrography	California	47	32.7	—
Schaller *et al.*	Atomic absorption	Germany	63	2.7	0.6 - 7.0
Szadkowski *et al.*	Atomic absorption	Germany	20	2.3 ± 0.7	—
Nomoto and	Atomic absorption	Connecticut	17	0.48	0.29 - 0.70
Delves *et al.*	Atomic absorption	England	76[e]	2.2	—

[a] References are found in NAS (1975).
[b] Calculated from values for plasma and red cells.
[c] Industrial workers from Ohio, New York, Florida, Colorado, and Oregon.
[d] 2.5 - 97.5 percentile.
[e] Children

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2. Nickel Speciation and Noncancer Effects

The lung is the target organ of nickel toxicity in humans. Inhalation exposure to varying mixtures of nickel compounds have been associated with lung pathology, including cancer, asthma, and increased susceptibility to pulmonary infections, probably due to secondary effects of nickel on the immune system (EPA, 1986; NAS, 1975; IARC, 1987). Similar effects have been demonstrated in experimental animal studies (Adkins *et al.*, 1979; Ambrose *et al.*, 1976; Benson *et al.*, 1987; Bingham *et al.*, 1972; EPA, 1983; Hueper, 1958; Johansson *et al.*, 1983; Langer *et al.*, 1980; Lu *et al.*, 1979; Machado *et al.*, 1982; Port *et al.*, 1975; Stoner *et al.*, 1976; Sundermann *et al.*, 1976; Sundermann *et al.*, 1978; Wehmer and Craig, 1972; Wehner *et al.*, 1979; Wehner *et al.*, 1981; Weischer *et al.*, 1980; Yarita and Nettesheim, 1978; and Ottolenghi *et al.*, 1974). The adverse noncancer health effects of nickel compounds are not anticipated to occur given the measured ambient air concentrations in California (i.e., 0.000001 mg to 0.00002 mg Nickel/m^3; State of California, 1990a) compared to the No-Observed-Effects-Levels (NOELs) and Lowest-Observed-Effects-Levels (LOELs) observed in humans and animals (which are presented below). However, comparison of the toxic potency of various nickel compounds with respect to their noncancer effects observed in humans or animals provides additional evidence regarding the need for understanding the relative concentrations of each nickel species associated with respirable particulate matter in California's ambient air.

Specific dose-response data for the systemic, noncarcinogenic effects resulting from repeated and prolonged exposure to nickel compounds in humans is not available. However, the effects of various nickel compounds on the lungs of rabbits, rats, mice, and hamsters have been observed in inhalation studies of short,

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intermediate, and long-term duration. The State of California summarized the noncancer health effects levels data (i.e., NOELs and LOELs) for inhalation of nickel as follows (State of California, 1990b, p. 52):

Short-term repeated exposure (up to 1 month):

Humans: insufficient data

Animals: NOEL = 0.04 mg nickel compounds/m^3; LOEL = 0.08 mg nickel compounds/m^3 (Spiegelberg *et al.*, 1984)

Subchronic exposure (2 - 4 months):

Humans: insufficient data

Animals: insufficient data; lowest dose tested to date, 0.02 mg nickel/m^3 which resulted in alterations in alveolar macrophage populations (Spiegelberg *et al.*, 1984)

Chronic exposure: (greater than 4 months):

Humans: insufficient data; occupational asthma reported in production plant where air concentration of nickel compounds ranged from 0.013 to 0.067 mg nickel/m^3 (Davies, 1986)

Animals: LOEL is assumed to be approximately 0.025 mg nickel/m^3 based on effects to the immune system (Rittmann *et al.*, 1981).

Although these NOELs and LOELs are consistent with our own independent review of the available toxicological data for nickel compounds, additional comparative potency data are available for discussion. Of particular importance is the study conducted by Dunnick *et al.* (1989) which evaluated lung toxicity after 13-week inhalation exposure to nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate in F344 rats and B6C3F_1 mice. The significance of this study is that it related nickel toxicity to the amount of nickel in the lungs and compound solubility. Nickel sulfate

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(22.3 percent nickel) was tested at aerosol concentrations of 0.0, 0.02, 0.05, 0.1, 0.2, and 0.4 mg/m^3; nickel subsulfide (73.3 percent nickel) was tested at aerosol concentrations of 0.0, 0.11, 0.2, 0.4, 0.9, and 1.8 mg/m^3; and nickel oxide (78.6 percent nickel) was tested at aerosol concentrations of 0.0, 0.4, 0.9, 2.0, 3.9, and 7.9 mg/m^3 [6]. No exposure-related mortality was observed in rats or mice. The only treated animals which demonstrated a decrease in final body weight relative to the control animals were male rats in the 0.2, 0.4, and 1.8 mg/m^3 nickel subsulfide exposure groups. There were also no exposure-related changes in organ weights (i.e., thymus, liver, kidney, brain, or testis); and no exposure-related effects were seen in sperm number, sperm motility, sperm morphology, or in the length of the estrous cycle. Inflammatory changes were observed in the lung, nasal cavity, and bronchial lymph node after exposure to each of the nickel compounds tested. The toxic potency to the lung and nasal cavity for noncarcinogenic effects, measured as increases in alveolar macrophage hyperplasia, inflammation, and fibrosis, was as follows: nickel sulfate > nickel subsulfide > nickel oxide. It is important to note that adverse effects were only observed by exposing the laboratory animals to concentrations of these nickel compounds which were four orders of magnitude greater than the California ambient air concentrations of nickel reported by the State (State of California, 1990a).

Further, NOELs for lung lesions was observed in male and female mice at a dose level of 0.25 mg nickel sulfate/m^3 (0.02 mg Ni/m^3) and 0.15 mg nickel subsulfide/m^3 (0.1 mg Ni/m^3), both of which are well above the ambient air concentrations of total and insoluble nickel reported by the State (State of California, 1990a). At the lowest tested dose of nickel oxide, i.e., 0.6 mg nickel oxide/m^3 (0.4 mg Ni/m^3), alveolar macrophage hyperplasia was observed in male and female mice and rats. Again, this tested dose is well above ambient air concentrations of total and insoluble nickel. Concentrations of Ni in the lungs of rats and mice increased with

[6]These exposure concentrations were based on a previously performed 12-day range-finding study [illegible] which determined concentrations at which body weight effects and or lung lesions occurred in the experimental animals (Dunnick et al. 1988).

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exposure concentration. Male and female animals had similar lung burdens of Ni. Equilibrium levels of nickel were reached by 13 weeks in the lungs after nickel sulfate and subsulfide exposures. However, the levels of nickel oxide in the lung continued to increase. Although the lung burden of nickel oxide was the highest, the lung lesions resulting from nickel oxide exposure were the least severe. These results are in agreement with other studies which demonstrate that soluble nickel compounds are cleared from the rat lung, while insoluble compounds accumulate (Menzel *et al.*, 1987; Tanaka *et al.*, 1985). Further, the noncancer toxicity of nickel compounds correlates with the solubility of each compound, rather than the amount of nickel in the lung.

In addition, the State of California (1990b) cited a LOEL for reproductive and development effects based on the study of Schroeder and Mitchener (1971) and dietary/dosing estimates provided by the same authors (Schroeder *et al.*, 1974). The LOEL was based on an oral drinking water study using five pairs of Long-Evan rats which were fed approximately 5 ppm nickel in the form of a soluble salt (the specific salt was not specified). The study was terminated when three generations had been weaned. The LOEL, based on increased number of runts and decreased litter size, was observed at a dose level of 400 μg nickel salts/kg body weight/day in the rat. Then using very conservative assumptions regarding route-to-route extrapolation, the State's report estimates that the maximally exposed human could have a daily absorbed dose as high as 0.007 μg/kg/day which is over four orders of magnitude below the LOEL in the rat. The actual margin of safety with respect to potential reproductive effects for most individuals in California is likely to be substantially larger, given the conservative exposure assumptions used, for example: exposure at the maximum concentration reported by the Air Resources Board (State of California, 1990a), breathing rate of 20 m^3 of air per day at this concentration, and 100 percent pulmonary retention and absorption for humans, and 100 percent absorption by the gastrointestinal tract in the rat. However, the conclusion that ambient exposures to nickel would not be expected to be associated with any reproductive effect or

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developmental effect is consistent with the available data for such effects in animals exposed to nickel compounds. These data also suggest that the most sensitive target organs for nickel effects via inhalation are the lungs and the immune system, and not the reproductive system.

3. Nickel Speciation and Carcinogenic Effects

With respect to the relative *carcinogenic* potencies of different nickel species, as acknowledged by the State of California (1990b), to date, injection administration is the only route of exposure for which data are available for direct comparison of the respective carcinogenic potencies of the different nickel compounds. In a study by Sunderman (1984), 18 nickel compounds were tested for carcinogenicity in 414 Fischer rats by a single intramuscular injection at equivalent doses (i.e., 14 mg Ni per rat). Animals were then observed for a two-year period. The relative potency's of each compound tested as determined by the incidence of sarcomas. The results have been summarized and discussed elsewhere (EPA, 1986; State of California, 1990b). Nickel subsulfide injections resulted in a 100 percent incidence of sarcomas; whereas, nickel oxide resulted in a 93 percent incidence. The State of California (1990b) indicates that nickel subsulfide and nickel oxide "possess approximately equal potency" following injection administration; however, there are variables which suggest otherwise. For example, the latency period for sarcomas in rats was 30 weeks and 49 weeks for nickel subsulfide and nickel oxide, respectively. The median survival period was 39 weeks for nickel subsulfide versus 58 weeks for nickel oxide, and the incidence representing the number of rats with metastases per number with sarcomas was 56 percent for nickel subsulfide and 29 percent for nickel oxide. It is important to note that this study has no relevance with respect to the evaluation of the carcinogenic potential of nickel compounds by any route of ambient exposure which may be experienced by humans (e.g., inhalation, ingestion).

Of particular relevance to assess potential lung cancer risks associated with ambient nickel exposure is the adequacy of the toxicological database for animals

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exposed by this route. Evidence of carcinogenicity following inhalation exposure in experimental animals has been demonstrated for nickel subsulfide (IARC, 1987; NAS, 1975; EPA, 1986), and suggested for nickel carbonyl. However, the evidence for nickel oxide is negative or inconclusive (EPA, 1986). Although nickel sulfate has not yet been assessed with respect to carcinogenic activity via the inhalation route, evidence of carcinogenicity in experimental is negative based on the results of an ingestion study (Ambrose *et al.*, 1976). As summarized in Table 4, data for the evaluation of

TABLE 4. Summary of the results of carcinogenesis bioassays in experimental animals for nickel subsulfide, nickel oxide, and nickel sulfate.

STUDY	RESULTS
Nickel Subsulfide (inhalation)	
Ottolenghi et al., (1974)	Positive
Fisher et al., (1986)	Negative
Nickel Oxide (inhalation)	
Wehner et al. (1975)	Negative
Tanaka et al., (1985)	Negative
Horie et al., (1985)	Equivocal
Nickel Sulfate (ingestion)	
Ambrose et al. (1976)	Negative

potential carcinogenic effects of nickel compounds by the inhalation route in humans is based on animal studies using insoluble compounds (i.e., nickel subsulfide and nickel oxide), whereas, evidence regarding the ingestion route is based on soluble compounds (i.e., nickel sulfate).

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As mentioned previously, inhalation exposures of the general population to nickel compounds is believed to be largely due to nickel associated with suspended, respirable particles which have originated from various anthropogenic and natural sources. Source assignments for nickel made on the basis of emissions data and inferences from air quality measurements suggest than key anthropogenic source of trace nickel emissions is associated with fine particles results from combustion sources, including coal and oil burning units in utility, industrial, commercial, and residential use (EPA, 1986; Cass and McRae, 1983). Fuel oil fly ash, which is similar to coal fly ash with respect to nickel composition, is composed of approximately 2 percent elemental nickel; further, the nickel species present are largely nickel sulfates and smaller amounts of nickel oxides and complex metallic oxides (EPA, 1986). Therefore, of particular interest in evaluating the potential carcinogenicity of nickel compounds associated with ambient air particulate is the assessment of the chronic toxicity of inhaled fly ash.

Wehner *et al.* (1981) conducted a 20-month inhalation study using hamsters (102 animals per group) which were exposed to 70 mg/m^3 respirable nickel-enriched fly ash (NEFA) aerosol, 17 mg/m^3 NEFA, 70 mg/m^3 fly ash (FA), or sham exposures. The NEFA particles of respirable size contained approximately 6.0 percent nickel, compared to approximately 0.3 percent for FA[7]. Fly ash was enriched with nickel by adding nickel acetate to pulverized coal before combustion.

The animals were exposed 6 hours per day, 5 days per week. From each of the four groups of 102 hamsters, 5 were randomly selected and sacrificed after 4, 8, 12, and 16 months of exposure; all surviving animals were sacrificed after 20 months of exposure. An additional 5 animals were withdrawn from exposure at the same time intervals for lifelong observations. Exposures to NEFA were observed to have no

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[7] The fly ash was generated from iron-rich Ohio coal from the Pittsburgh No. 8 seam. The coal was fired in a multifuel furnace and the resulting fly ash emissions were collected in a baghouse.

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significant effect on body weight or life span of the animals, although deposition of NEFA in the lungs was observed. Dust was deposited (anthracosis) in the lungs of all experimental animals groups. Further, the incidence and severity of interstitial reaction and bronchiolization were significantly higher in the dust-exposed groups than in the sham-exposed controls. The severity of anthracosis, interstitial reaction and bronchiolization was significantly lower in the low-NEFA group than in the high-NEFA group. No statistically significant increase in tumor incidence was observed. The authors concluded that addition of nickel to fly ash did not significantly enhance pathogenicity, including carcinogenicity, of fly ash in their animal model. Further, the quantity of dust, rather than its nickel content, appears to be the major factor in determining tissue response.

B. Review of Key Epidemiological Studies

1. Introduction

It is well documented in a number of epidemiological studies that occupational exposure to nickel refinery dust and nickel subsulfide is associated with increased risk of respiratory tract cancer, involving target organ sites including nasal, laryngeal, and lung tissues (ATSDR, 1988). However, no epidemiological studies were found in the literature which demonstrate an association between exposure to ambient forms of nickel and increased cancer risk in the general population. Furthermore, as noted previously, occupationally-exposed individuals may come into contact with numerous potentially hazardous substances that are characteristic of the workplace, which complicates the dosimetry for the risk assessment, and may lead to overestimation of risk for the single chemical of interest.

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2. General Features of Occupational Cohort Studies

The results of epidemiological studies are often expressed in terms of the Standardized Mortality Ratio, or SMR[8]. While applied here to occupational epidemiology studies, SMRs can be calculated for any other defined subgroups of a population. Occupational cohort studies generally require a large sample size for meaningfulness, and a long follow-up period, suggesting that SMRs calculated prior to the death of all members of the study population will change as time elapses. Some of the general limitations of cohort studies are (1) the need to adjust for the "healthy worker" effect; (2) the use of sometimes inappropriate exposure classification schemes; (3) incomplete ascertainment of the members of the study cohort; and (4) the frequent lack of information on confounding factors such as smoking habits, the latter of which would lead to an overestimation of risk (Blair and Spirtas, 1980).

The "power" or ability to measure an effect in a statistically significant way, is limited at least partly by cohort size, length of follow-up, and the accepted level of error. For example, assuming a 25-year follow-up and an error rate of 5 and 10 percent, respectively, for Type I and Type II errors[9], the cohort size necessary to detect a 50 percent excess risk (SMR = 150) for lung cancer would be approximately 5,000 individuals. Importantly, for shorter follow-up periods, the number of individuals required for a cohort is substantially larger (Blair and Spirtas, 1980). Other examples are shown in Table 5.

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[8]The SMR is the number of deaths, either total or cause-specific (e.g., due to lung cancer), observed in a given study population multiplied by one-hundred and divided by the number of deaths that would have been expected if the age- and sex-specific death rates due to that same cause in a "standard" population are applied.

[9]A type I error occurs when one rejects the null hypothesis (concludes that the SMR is greater than 100) when the null hypothesis is true. In the statistical literature, the probability of this kind of error is denoted by the Greek letter, α. A type II error occurs when one accepts the null hypothesis (concludes that the SMR is not greater than 100) when the alternate hypothesis (that the SMR is greater than 100) is true. In the statistical literature, the probability of this kind of error is denoted by the Greek letter, β.

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TABLE 5. Minimum Sample Sizes for Occupational Cohort Studies[a]

SMR	Mortality Rate Per 100,000			
	40 (*e.g.*, Lung Cancer)	20 (*e.g.*, Colon Cancer)	10 (*e.g.*, Pancreatic Cancer)	5 (*e.g.*, Liver Cancer)
400	228	456	911	1,821
200	1,426	2,851	5,701	11,402
150	4,993	9,986	19,963	39,923
120	28,341	56,667	113,320	226,626

[a] Assumptions are as follows: Alpha-level = 5%, Beta-level = 10%, Allocation ratio = 1,000, Mean follow-up = 25 years.

Occupational cohort studies should include a comparison worker population that is similar in all aspects to the study group for all disease-related factors (e.g., age distribution, race, sex, ethnicity, tobacco and alcohol use, and socioeconomic status), except that they lack the exposure of interest (Blair and Spirtas, 1980). The practical limitations of expense and/or inability to locate such a comparison population typically forces investigators to resort to using national mortality rates for the general population to estimate the expected number of cases. As a result, the "healthy worker" effect is introduced because a typical population of active workers has a mortality rate that is typically 10 to 40 percent lower than that of the general population, which contains high risk subpopulations such as infants and the elderly.

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When weak associations are observed (i.e., SMR's from >100 to 120), five criteria should be applied to determine if the apparent association between an exposure and disease is real (Wynder, 1982):

- Consistency, i.e., whether the association can be demonstrated repeatedly from different studies, and for different subgroups within the same study.

- Strength, i.e., whether the effect appears to be dose-dependent

- Specificity, i.e. whether the apparent association links a clearly-defined exposure to a specific disease.

- Temporal sequence, i.e., whether the exposure precede the disease, and for carcinogens, whether a reasonable time-to-tumor observed.

- Coherence, i.e., whether the apparent association is consistent with known or postulated biological and pharmacokinetic mechanisms for the chemical of interest, bearing in mind what is known concerning the dose, exposure route, duration of contact, metabolism, and absorption-excretion rates for the chemical.

Furthermore, an occupational cohort study must correctly define the duration of exposure for each cohort member. Person-year allocation to exposure categories must be time-dependent, e.g., the duration of exposure in the high dose category should begin only when the worker enters that work category, regardless of other positions held, unless in the same exposure category at a similar facility (Blair and Spirtas, 1980).

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3. Summary of Key Epidemiological Studies On Nickel

Epidemiological studies of populations of workers in nickel refineries in different countries demonstrate association between nickel exposures and excess incidences of cancers of the respiratory tract, including the nasal cavity, lung, and possibly the larnyx (IARC, 1987). Unfortunately, none of the individual studies that have been performed to date have been able to conclusively associate these increased risks with a specific form of nickel (IARC, 1987). Furthermore, no epidemiological studies have been reported that would associate exposure to nickel as found in ambient air with increased cancer risks.

A number of key epidemiological studies regarding occupational exposure to nickel have been reported in roughly the last decade. Enterline and Marsh (1982) studied the health risks to three groups of workers (total of 266) in a nickel processing plant based on length of employment. Nickel exposures were reported as 5 mg/m^3 for workers in the nickel processing area, and 0.01 to 0.75 mg Ni $/m^3$ for workers at the facility in non-processing job categories. The results showed an excess of nasal sinus cancer deaths in nickel refinery workers (SMR = 2443), although an overall excess of lung cancer was not detected. This SMR was calculated using age and calendar-specific national and local mortality rates.

Doll *et al.* (1977) conducted a study of mortality in 937 nickel refinery workers who worked at the Clydach, Wales facility for at least 5 years. In this cohort, a total of 145 lung cancer cases and 56 nasal cancer cases were identified. Highly elevated SMRs for nasal cancer (9,900 to 64,900) and less elevated, but significantly increased, risks for lung cancer (SMRs = 570 to 1005) were observed for workers who started worked at the facility for at least 5 years prior to 1925. Virtually no cases of nasal sinus cancer were reported in workers at the facility who began their employment in 1925 or later; however, a slightly elevated lung cancer risk was noted (SMR = 250) in workers who began employment between 1925 and 1929. These SMRs were calculated using age-specific and time-specific mortality rates for England and Wales.

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The meaningfulness of these SMRs in quantitative terms is limited by the small size of the study cohort.

Chovill *et al.* (1981) studied a small cohort of 495 workers at the Copper Cliff nickel sinter plant near Sudbury, Ontario exposed to nickel refinery dust between the years 1948 and 1962. This study reported 37 lung cancer deaths in the cohort versus 4.25 expected (SMR = 870). The meaningfulnesss of this SMR in quantitative terms is limited by failure to use the entire cohort that was available for evaluation, as noted in the study below.

In perhaps the most rigorous study to date, the mortality of approximately 54,000 male workers employed in all aspects of extraction and refining of nickel within the Canadian province of Ontario was evaluated by Roberts *et al.* (1983). This included workers at the Copper Cliff, Coniston, and Port Colborne nickel refineries, all of which contained sintering operations. The SMR for lung cancer and the SMR for nasal cancer were reported to increase linearly with increasing duration of exposure in sinter plant workers. Mortality was ascertained for each job category during a 27-year follow-up period between 1950 and 1976. All SMRs were calculated using age-specific, calendar-time-specific and cause-specific mortality rates for Ontario males rather than the national population. Out of this cohort, men without sinter plant experience had an SMR of 104 for all four cancer sites evaluated combined (lung, larnyx, nasal, and kidney) versus statistically significant excesses ($p < 0.001$) in cancer deaths among the Copper Cliff and Coniston sinter plant workers (the combined Sudbury cohort), yielding an SMR of 463, with all cases reflected as nasal or lung cancer. In addition 2 deaths from nasal cancer in sinter plant workers were found which represents a 21-fold increase in risk from this rare cancer (SMR = 2100); even though this represents a small number of cases, this difference was statistically significant ($p < 0.001$). For men involved in the leaching, calcining, and sintering process in the Port Colborne nickel refinery, nasal cancer deaths start to appear after 15 years after the first exposure, when the SMR increases to approximately 4,000.

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The trend of these data, taken together (see Table 6) support use of a 15-year follow-up period since first exposure for calculation of SMRs for this cohort. When SMR data are plotted against duration of exposure, the weighted least-squares slope estimates indicate that the lung cancer SMR increases by 90 percent per year of exposure for sinter workers at the Copper Cliff facility and by 21 percent per year of exposure for leaching, calcining, and sinter workers at Port Colborne.

Roberts *et al.* (1989a,b) reported a follow-up to their earlier study which describes the observed and expected mortality from cancers of the lung, larnyx, nasal cavities, and kidney in the same Ontario cohort (54,000 nickel workers) with a follow-up of 35 years. Similar results as in the earlier study are reported, i.e., for the Copper Cliff cohort, the SMR for non-sinter workers exposed to nickel is 111 versus 311 for sinter plant workers exposed to nickel refinery dust beyond 15 years since first exposed. These differences between observed and expected lung cancer mortalities are statistically significant ($p<0.006$ and $p<1 \times 10^{-7}$, respectively). While small, the bulk of the nonsinter worker lung cancer excess, appears to be associated with mining and welding activities. The Coniston sinter worker cohort had virtually an identical excess lung cancer risk for sinter workers (SMR = 298, $p<0.0016$). In this study neither sinter-plant workers from Copper Cliff, Coniston, or Port Colborne displayed a significant increase in kidney cancer.

Warner (1985) has attempted to reconstruct occupational exposure levels to nickel at the Copper Cliff sinter plant from limited historical monitoring data and from samples taken after closing of the facility. Limited speciation data suggest that the sinter plant dust contained primarily nickel oxide and nickel subsulfide, with very little nickel sulfate being present (Warner 1985). A single 40-hour sample of dusty air on the operating floor from 1960 yielded a total nickel concentration of 46.4 mg/m^3 (Warner, 1985). Roof monitoring data, which are probably underestimates due to dilution of the floor-level dust with clean air from windows located above the operating floor, yielded levels of approximately 60 to 875 $mg\ m^{-3}$ (medians of 140 to

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230 mg/m^3) for the years 1948 to 1951 and levels ranging from 20 to 250 mg/m^3 (medians of 50 to 180 mg/m^3) from 1954 to 1961 (Warner, 1985). This information is reported elsewhere as airborne levels of nickel of 400 mg/m^3 in 1950, falling to 100 mg/m^3 in 1958 (Roberts *et al.*, 1983). These data are presented in Figure 1.

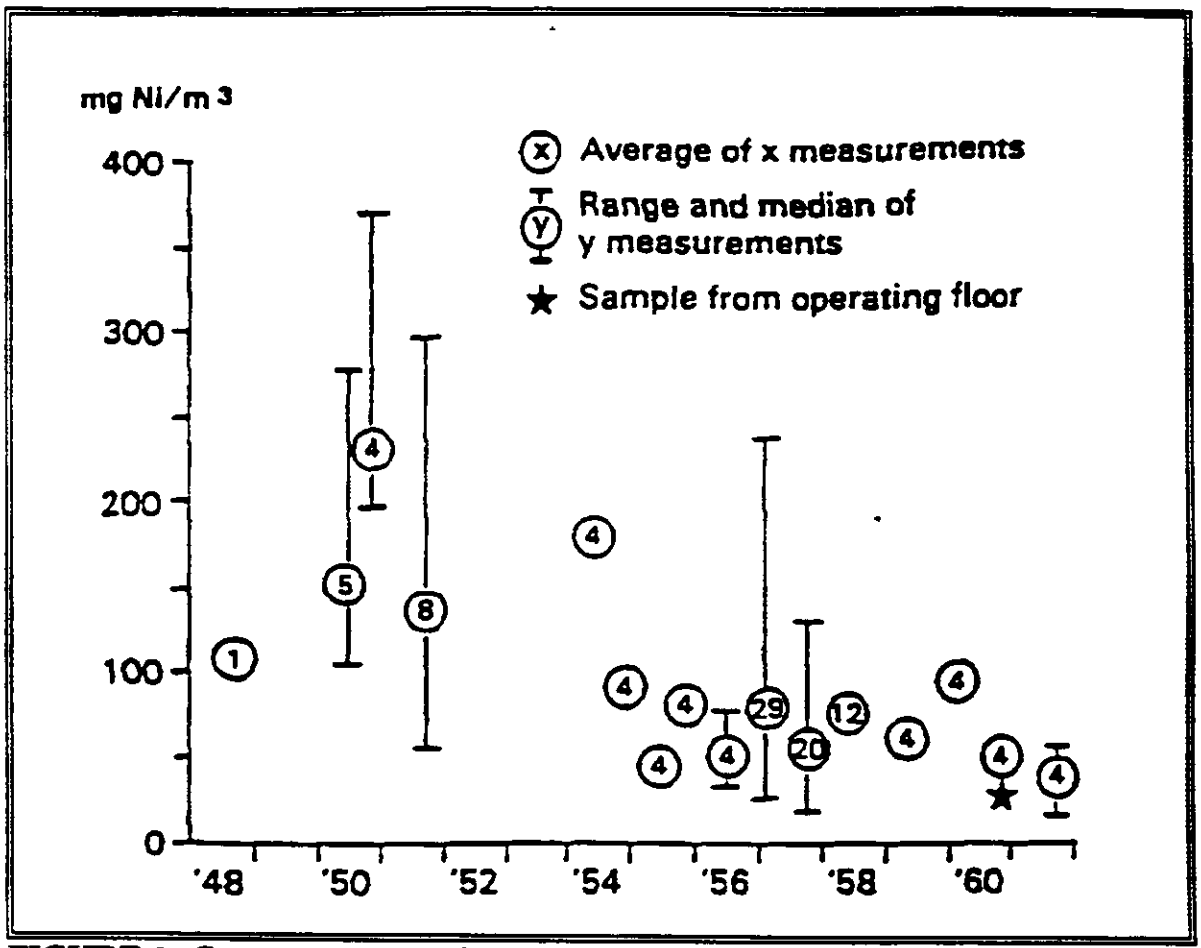

FIGURE 1. Concentrations of nickel in dusty air leaving the roof monitors of the Copper Cliff Sinter Plant (Brown and Sunderman 1985).

Magnus *et al.* (1982) studied a cohort of 2247 nickel refinery workers at a nickel refinery in Norway who had been employed for at least 3 years beginning before 1966. Risks of nasal cancer were increased in all job categories, with the highest SMR (SMR = 4,000) for workers involved in nickel roasting/smelting, followed next by electrolysis workers (SMR = 2600). An excess risk of laryngeal cancer was observed in roasting/smelting process workers (SMR = 670) and in other related process

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workers (SMR = 330). Lung cancer was increased in all worker categories, with the highest excess observed for electrolysis workers (SMR = 550), followed by other process workers (SMR = 390) and roasting/smelting workers (SMR = 360). Expected cancer death rates were estimated from age-specific national mortality rates. An assessment of the effect of smoking on excess cancer risks for this cohort suggested that the effects of smoking and nickel exposure are additive rather than multiplicative.

C. Review of Quantitative Risk Assessment

1. General Comments

The State of California quantitative cancer risk calculations (1990b) are based on the Ontario refinery epidemiology study (see Section II-C). In the State's analysis, exposures were based on measurements of nickel dust, without determination of the form(s) of nickel present in the dust. Thus, the risk estimates apply to whatever combination of carcinogenic nickel species to which refinery workers were exposed. The forms of nickel likely to predominate worker exposures were nickel subsulfide and nickel oxide. Of particular interest is that the carcinogenic potency estimate derived by the State based on the Ontario cohort (i.e., 2.92×10^{-4} per $\mu g/m^3$) is about 14 times lower than the potency estimate derived based on a nickel subsulfide animal inhalation cancer bioassay (i.e., 4.16×10^{-3} per $\mu g/m^3$). This comparison would suggest that nickel subsulfide is more potent than the mixture containing nickel subsulfide at the refinery. As acknowledged by the State, other factors such as differences in species sensitivity and uncertainties in low-dose extrapolation may account for some of this observed difference.

However, the State incorrectly assumes that "all insoluble nickel compounds should be considered potentially carcinogenic to humans by inhalation" and that the unit cancer risk based on the mixture of nickel species experienced by the Ontario

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sinter plant "subcohort" is representative of the cancer potency of the mixture of nickel species associated with respirable ambient air particles in California. These assumptions are not justifiable for nickel species associated with ambient air exposures for the following reasons:

- Although exposure of humans to nickel in the workplace has been associated with an increased incidence of cancer in the lung and nasal cavity, the exact causative agent(s) or chemical form(s) of nickel responsible for the toxic effects has not been determined (IARC, 1976, 1982, 1987; Doll, 1977; EPA 1986);

- Insoluble nickel compounds in ambient air vary in their contribution to total nickel associated with respirable particulate (e.g., 55 to 90 percent of total nickel is insoluble), and nickel subsulfide (which is the only insoluble compound with adequate data describing its potential carcinogenicity by the inhalation route in both animals and humans), is not the predominant form of insoluble nickel in ambient air; in contrast, nickel sulfate and nickel oxide, which have not been demonstrated to be carcinogenic in animals and which have not been clearly identified as human respiratory carcinogens, in the absence of confounding exposures to nickel subsulfide, are likely to be the most common forms of nickel associated with ambient air particulate (State of California, 1990a; Schroeder *et al.*, 1987); and

- The dose levels experienced by workers, and the observed dose-response relationships for respiratory cancers are four to eight orders of magnitude higher than levels of total nickel present in the ambient air in California.

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2. Review of the Report of the International Committee on Nickel Carcinogenesis in Man

Speciation of nickel compounds for quantitative risk assessment requires additional information regarding the composition and relative concentration of particle-associated nickel compounds in ambient air versus occupational settings, as well as demonstration of compound-specific carcinogenic activity, if any, and corresponding toxic potency. There are two ongoing research efforts, each of which has particular relevance towards answering these questions. The National Toxicology Program (NTP) is sponsoring inhalation carcinogenicity and subchronic toxicity studies of nickel oxide, nickel subsulfide, and nickel sulfate in rats and mice (Dunnick *et al.*, 1988, 1989[10]). The exposure phase of the cancer bioassays will be completed between April and November 1990. However, the comprehensive gross and histological examinations of all organ systems will not be completed until sometime in 1992[11]. These studies hopefully will offer considerable insight into the carcinogenic activity and potency of these compounds. In addition, Sir Richard Doll, at Oxford University is conducting a re-evaluation of nickel epidemiological studies[12]. The objective of these analyses is to clarify the exposure profiles of individual workers to specific nickel compounds. In view of the potential significance of this epidemiological re-evaluation, RiskFocus obtained a copy of the final report [International Committee on Nickel Carcinogenesis in Man (ICNCM, 1989, 1990)], which describes the results of the re-evaluation and undertook a critical examination

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[10]Dr. June Dunnick is coordinating inhalation cancer bioassays in rats and mice using aerosolized nickel oxide, nickel sulfate hexahydrate, and nickel subsulfide as part of the National Institute for Environmental Health Science's National Toxicology Program.

[11]Personal communication (7/11/90) with Dr. June Dunnick, National Institute of Environmental Health Science, Research Triangle Park, NC. (919) 541-4811.

[12]Sir Richard Doll is conducting a re-evaluation of epidemiological studies to assess the relative contribution of different nickel species to worker exposure and subsequent mortality statistics; the study hopes to clarify exposure of individual workers to specific nickel compounds; the study is a cooperative effort between Oxford University, U.S. EPA, the Ontario Ministry of Labour, National Health and Welfare Canada, Energy, Mines and Resources Canada, the Nickel Producers Environmental Research Association, and the Commission of European Communities.

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of the report's conclusions and recommendations. This review was supplemented by an interview with Lindsey Morgan of the International Nickel Company (INCO), who, in collaboration with other INCO scientists, i.e., Dr. Stuart Warner, have provided considerable insight into the reconstruction of historical occupational exposures to nickel compounds (Warner, 1985).

One of the conclusions presented by the ICNCM (1990), which has particular relevance in resolving the public health significance of exposure to nickel in ambient air, is that although the investigation did not provide dose-specific estimates of risk for individual nickel species, it was possible to comment on the cancer risks associated with the level of airborne nickel to which the general population is exposed. The evidence from the Committee's study suggests that respiratory cancer risks are associated with exposure to nickel compounds at concentrations in excess of 1 mg/m^3. This conclusion is corroborated by animal inhalation data, in addition to human epidemiological evidence. For example, the Ottolenghi *et al.* (1974) study observed neoplastic effects only at very high concentrations (i.e., 970 mg/m^3) when compared to the ambient air levels of nickel to which humans may be exposed. The ICNCM makes the important observation that, based upon a comprehensive examination of groups of men exposed to a variety of nickel species, no definitive evidence of increased cancer risk was associated with exposure to metal nickel, nickel oxide, soluble nickel (e.g., nickel sulfate, nickel chloride), or nickel subsulfide at concentrations less than 1 mg/m^3. Given the measured ambient air concentrations in California (see Section II), this review of the human epidemiological data would indicate that a significant margin of safety (i.e., greater than 10^5), irrespective of nickel species, exists for exposure to the general population. The State of California uses the Ontario "subcohort" of sinter plant workers to quantify cancer risk and notes that the average exposure level was 75 mg/m^3. Again, this is an extremely large dose compared to non-occupational, ambient exposures.

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With respect to ICNCM's review of the epidemiological data associated with exposure to specific nickel compounds, the committee found that exposure to large concentrations of nickel oxide, in the absence of nickel subsulfide, was associated with an increased lung and nasal cancer risk. This statement is contrasted to the EPA's previous suggestion that this association did not exist (EPA, 1986). However, the committee's statement is made in the setting of very high worker exposure levels, which are likely to have included exposure to other species of nickel. This is evidenced by the committee's review of two cohorts: Kristiansand and Clydach. The Kristiansand workers were thought to have been exposed primarily to oxides of nickel and/or soluble nickel compounds and were said to show "some evidence of increased lung cancer" (ICNCM, 1990). However, the magnitude of the excess and the association between duration of exposure and risk was not strong for nickel oxide. The Clydach data, which ICNCM also cites as supportive of the tumorigenicity of nickel oxide, observed cancer risks in the setting of extremely high doses (i.e., in excess of 50 mg/m^3). The ICNCM (1989, 1990) stresses that the exposures at Clydach were likely to be mixed, containing not only oxides, but also nickel subsulfides and soluble nickel compounds.

With respect to nickel subsulfide exposure, the ICNCM found an inconsistency in the apparent increases in lung cancer risk in the Coniston and Falconridge sinter plants. These operations were almost identical facilities that were believed to have had much lower concentrations of nickel subsulfide (i.e., 1 to 5 mg/m^3) than other work places. Yet these workplaces were associated with increased lung and nasal cancer risks. The approximately doubled lung cancer risk in men who worked in these two operations does not seem to be consistent with risks observed in men with similar exposures elsewhere. Of particular significance is that there were no nasal cancers in men who worked either at Coniston or Falconbridge. The absence of nasal cancers in both Coniston and Falconbridge workers makes attribution of the observed lung cancer risk to the reported low levels of nickel subsulfide, somewhat questionable, given the occurrence of both excess lung and nasal cancers in other

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refinery workers. Arsenic in the ore, which was released into the workplace by sintering, is one possible explanation suggested by the ICNCM for the increased lung cancer risk in the absence of nasal cancers. In addition to arsenic, the role of SO_2 should not be ignored with respect to its potential to produce severe pulmonary irritation and thereby potentiate pulmonary neoplasia. This idea does indeed have support based on the studies of Laskin and Kuschner (1969).

With respect to nickel sulfate exposure, the interview with Lindsey Morgan, INCO, revealed that the increased risk of respiratory cancer observed in plating (electrolysis) situations could more likely be due to chromium and not nickel. Further, nickel sulfate exposures in plating situations included confounding exposures to nickel subsulfide and nickel oxide (ICNCM, 1990) which create uncertainty as to the significance of soluble nickel exposure and increased respiratory cancer risk. In addition, an INCO chemist, present at the interview, expressed the idea that even if soluble nickel compounds (including nickel sulfate) were found to be associated with increases in respiratory cancer risk in occupational cohorts, the sulfate in the atmosphere, to which the general population is exposed, would likely be a different chemical form. That is, the ambient sulfate, derived largely from the pyrolysis of fossil fuels, is probably anhydrous (NiO_x-SO_2-O_2); this would not be likely to hydrate quickly under "routine" conditions. Thus, the sulfate found in the occupational settings is likely to be a hydrated salt and possibly more soluble than the form seen in the ambient setting. Further, it is not only important to determine the specific chemical form of nickel sulfate found in ambient air, but its relative concentration as well. Finally, there are no animal data regarding the potential carcinogenicity of soluble nickel (e.g., nickel sulfate) resulting from chronic inhalation exposure.

In summary, the ICNCM report (1989, 1990) concludes that based upon their examination of ten cohorts, it appears that more than one form of nickel gives rise to lung and nasal cancer in humans. However, the evidence of respiratory cancers in occupationally exposed individuals is attributed to the presence of nickel compounds

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at very high concentrations (e.g., up to 400 mg/m^3 at the Ontario plant). Further, potential confounding factors in the general epidemiological database include:

- the significant incidence of tuberculosis and chronic bronchitis during the 1910 to 1930 period (the attendant focal and/or diffuse pulmonary fibrosis consequent upon progression of these diseases may have increased the susceptibility to neoplasia); and

- possible concurrent exposures of nickel industry workers to asbestos; for example, many of the pipes in the Clydach plant were previously lagged with crocidolite (a form of asbestos).

As stated above, the ICNCM found that the cumulative evidence suggests that respiratory cancer risks are associated with exposures to nickel species at concentrations in excess of 1 mg/m^3. Thus, excess risks were confined to extremely high exposure levels with the absence of any evidence of hazard from metallic nickel (ICNCM, 1990).

3. Derivation of a Cancer Potency Estimate Based on the Ontario Cohort

The State of California's quantitative risk assessment (1990b) was based on the use of a portion of the Ontario cohort (495 sinter plant workers), without adequate explanation, rather than the larger non-sinter cohort that was exposed to mixed nickel species. That is, the State considered only a subset of 495 sinter-plant workers who showed an SMR of 871 for lung cancer (relative risk of 8.71). The study by Roberts *et al.* (1989), which examined in part a sinter-plant cohort of 1744 workers (which included the cohort used by the State), was examined by RiskFocus for comparison. If only the time period of more than 15 years since the first exposure is considered, which results in the highest effect observed in this study, a value of 311 is obtained for the SMR for lung cancer, with an upper bound of 398. That is, the SMR estimate

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from the State's selected cohort is more than twice the upper bound of the Roberts *et al.* (1989) study (i.e., 871/398 = 2.18).

Roberts, *et al.* (1989) studied a cohort of 54,000 nickel workers, which included the Copper Cliff cohort used by the State. The overall lung cancer SMR was found to be 111 for the 47,980 non-sinter plant workers, with an upper bound of 119. This result does not suggest that a significant, "clear-cut" cancer risk from nickel exposure exists for lung cancer among non-sinter plant workers exposed to nickel compounds. The USEPA (1986) and ICNCM (1990) also examined other cohorts with varying degrees of exposure to different nickel compounds, and excess lung cancer risks were not consistently observed (nasal cancers were particularly high in sinter workers in some studies; however, nasal cancer is infrequently observed in humans and the increases observed would not substantially influence the overall respiratory cancer rate or total cancer rate.) If cohorts from many different studies were combined in the form of a meta analysis and included the large body of negative studies (those with an SMR which does not differ significantly from 100), it is certain that the projected increase in cancer risk for the general population would be reduced by at least a factor of 2 compared to that shown for nickel sinter workers (i.e., 311/119 = 2.61). One can only conclude that there is something unique about sinter plant workers that make their risks unique relative to other workers exposed to nickel. This factor is likely to be exposure to a greater portion of nickel subsulfide, the only form of nickel observed to be carcinogenic by inhalation in studies with laboratory animals (see Section II), rather than exposure to nickel oxide and nickel sulfate. Accordingly, it is the view of **RiskFocus** that this subset of sinter workers from the Copper Cliff cohort selected by State is a poor choice for defining risk to the nickel compounds which appear to occur in the ambient air from non-sinter sources.

The State also used a peculiar way to look at follow-up. Because vital status could not be ascertained for 25 percent of the cohort, they increased artificially the risk coefficient up by 1, 0.75 or 1.33. The investigators in the Chovril *et al.* (1981)

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study did exhaustive searches for death certificates, resulting in a high degree of confidence that most dead workers were identified. The investigators also assumed that not-found-dead cohort members were alive. This is an appropriate assumption if only a few persons migrate out of the country, which appeared to be the case here. Further mortality is easier to identify than vital statistics (persons who are alive), because of the availability of death certificates. Thus, the investigators found most of the deaths, but did not conclusively establish vital status for all workers. This situation can inflate person years and reduce deaths. Scientifically, it may be justified to increase the risk coefficient by perhaps as much as 5 percent (i.e., a factor of 1.05) to reflect this situation; however, the State's use of a 33 percent adjustment (i.e., a factor of 1.33) is not justified. The State's error renders the risk coefficient approximately 27 percent too high [i.e., a factor of 1.27 (1.33/1.05 = 1.27)].

In addition, the State inflated the general populations lifetime exposure to nickel compounds. Worker "equivalent lifetime exposure levels" (8/24 hours, 5/7 days per week, 48/52 weeks per year) were assumed by the State to be approximately 4.55-fold lower than corresponding public exposure's frequency and duration. However, persons in the general population are not exposed continuously for their entire lifetime. Human activity patterns and indoor, outdoor, and personal air monitoring surveys indicate a variety of reasons for intermittent exposure time periods and changing exposure durations and concentrations (e.g., vacations, residence changes, indoor versus outdoor activities and corresponding inhalation rates, changing ambient and indoor exposure concentrations throughout the day reflecting a person's microenvironment) (Wallace *et al.*, 1988).

Further, epidemiological studies which do not account for "total worker exposure" (i.e., occupational and non-occupational exposures to the same compounds) may artificially inflate the estimated SMR associated with occupation exposures only. Worker exposure to nickel compounds may have continued at home or at other locations. For example, nickel-associated dusts were likely to be carried home on

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worker's clothing. The significance of household exposures has been exemplified by the documentation of mesothelioma excess in the spouses of asbestos workers (Anderson *et al.*, 1979; Anderson *et al.*, 1976). In addition, workers who lived in close proximity to plant emissions (e.g., dusts at Copper Cliffs were removed by roof fans) may have experienced ambient exposures much higher than the statewide ambient air concentrations measured by the State of California (1990a). Other sources of nickel inhalation exposure are also known to occur (e.g., cigarette smoke).

In view of considering measures to control exposure, and thereby reduce risks associated with toxic air contaminants by reducing ambient emission sources, it is important to recognize the importance of data which suggest that ambient concentrations of compounds over time do not correlate well with time-corresponding indoor concentrations of the same compounds (Wallace *et al.*, 1988). This phenomenon is related to numerous factors including environmental deposition, air filtration, and indoor emission sources of the compounds. Therefore, when estimating "lifetime equivalent" exposures for persons exposed to nickel in the ambient air from those exposed occupationally, it is important to compare the assumed 22 percent of sinter plant worker's time spent indoors at work (i.e., 8 hr/day, 5 days/wk, 48 wks/yr) to the amount of time that the "average" person in California spends outdoors, i.e., 13 percent (Wiley *et al.*, 1990), where they may be potentially exposed to nickel associated with ambient air particles. This comparison reveals that the adjustment to "equivalent" exposure from occupational to ambient, is approximately a factor of 1.0 (i.e., 13/22 = 0.59, which is rounded to 1.0).

In contrast, the State's adjustment to account for "equivalent lifetime exposure" in the ambient versus occupational environments, involves increasing the unit cancer risk by a factor of 4.55 = (24 hr/day)/(8 hrs/day) x (7 days/wk)/(5 days/wk) x (52 wks/yr)/(48 wks/yr). This factor does not account for the indoor/outdoor activity profiles of "average" Californians (i.e., 13 percent of time spent outdoors versus 87 percent of time spent indoors (Wiley *et al.*, 1990)), nor does it adjust for potential

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"non-occupational" exposure to workers. Conservatively, this adjustment factor, i.e., 4.55, should be no greater than 2.0, which would include those persons spending up to approximately one-third of their time outdoors. Therefore, the proposed unit cancer risk estimate is high by a factor of approximately 2.28 (i.e., 4.55/2.0 = 2.28).

In summary, the following considerations result in a more appropriate derivation of the maximum likelihood cancer potency estimate based on the Ontario cohort:

- The selection of the particular nickel sinter worker "subcohort" used by the state unjustifiably elevates risk by a factor of 2.18, relative to the complete nickel sinter cohort; moreover, the failure to include non-sinter cohorts improperly elevates risk by a factor of 2.61. This results in a deflation factor of 5.69 which can reasonably be applied to the SMR of 871 (i.e., 871/569 = 153) or to the unit cancer risk which is proportionate to the SMR. The resulting SMR and therefore, unit cancer risk (the unit cancer risk will be correspondingly reduced by a factor of 5.69), is consistent with the epidemiological data for non-sinter nickel cohorts which show upper bound lung cancer SMR's of less than 200 (see p. 52, Table 49, ICNCM, 1990).

- The manner in which the state treated followup in the Ontario cohort inappropriately inflates risk by a factor of 1.27.

- The continuous exposure assumptions for the general population and confounding exposures for workers further inflates risk by a factor 2.28.

Overall, these factors result in a scientifically rigorous cancer potency factor which is at least an order of magnitude less (i.e., a deflation factor of 16) than that estimated by the State (1990b). Thus, based on our considerations of the most

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appropriate calculation of "lifetime added risk" for exposure at 1 mg/m^3 of the insoluble nickel compound mixture in the Ontario "subcohort", the lifetime maximum likelihood cancer potency estimate should be 2.4×10^{-2} per mg insoluble Ni/m^3 or 2.4×10^{-5} per μg insoluble Ni/m^3. This estimate indicates that the risk of cancer from continuous daily inhalation of a hypothetical concentration of 1 μg insoluble Ni/m^3 of ambient air would be no greater than 2.4 per 100,000 individuals exposed. For lower exposure levels, the risk is reduced proportionately.

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IV. Risk Characterization

The following section provides risk estimates regarding the probability of excess respiratory cancer deaths occurring in the general population in California as a result of lifetime inhalation exposure to nickel compounds associated with respirable ambient air particles. These estimates are considered to be consistent with methodology appropriate for establishing accurate and scientifically defensible risk assessments for use in regulatory decision-making.

As part of the Technical Support Document (California, 1990a, 1990b) for consideration of the weight-of-evidence as to whether or not nickel should be listed as an air toxic, the State of California conducted an assessment of the risk posed by ambient atmospheric levels of nickel in California. The risk assessment was conducted using a portion of the Ontario cohort of nickel refinery workers, which was selected as appropriate by the State. Applying a relative risk model for linear extrapolation to lifetime exposure at lower doses, the State determined that the excess risk for lifetime exposure to 1 mg insoluble Ni/m^3 was 2.9×10^{-1}, or 2.9×10^{-4} per ug insoluble Ni/m^3. The risk to Californians from inhalation of atmospheric nickel was estimated by multiplying this unit risk by the nickel concentration range

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in ambient air in California of 0.0011 to 0.0236 $\mu g/m^3$, yielding an excess cancer risk of from 0.3 to 7 lung cancer deaths per million (0.3 to 7×10^{-6}).

In characterizing excess cancer risk resulting from exposure to nickel compounds associated with respirable ambient air particles, the State of California assumes that the Ontario "subcohort's" (sinter plant workers) inhalation exposures to nickel compounds were similar to those potentially experienced by persons in California. This assumption results in a substantial over-estimate of excess cancer deaths potentially experienced by residents in California. If one were to base the quantitative estimate of risk from such exposures on the non-sinter Ontario cohort (i.e., 47,980 non-sinter plant workers whose overall lung cancer SMR was 111, with an upper-bound of 119) the risk estimates would have greater relevancy to the nickel species present in ambient air and the total nickel levels measured therein. However, even if one were to use the "subcohort" chosen by the State, the cancer potency estimate should be appreciably lower than that derived by the State (see Section III-C).

If one were to use the cancer potency estimate derived by **RiskFocus**, the following calculations one would still likely arrive at over-estimates of excess mortality due to respiratory cancer. This is due to the extremely low overall level of exposure to nickel compounds experienced by the general population in California, as well as the virtual lack of exposure to nickel subsulfide associated with inhalation of ambient air particles [nickel subsulfide contributed significantly to the carcinogenic potency of the nickel dust to which the Ontario sinter cohort was exposed (EPA, 1986; ICNCM 1990)]. Nonetheless, using the maximum likelihood cancer potency estimate as derived in Section III-C of this report, which is based on the Ontario "subcohort's" SMR, i.e., 2.4×10^{-5} per μg insoluble Ni/m^3, and the California mean statewide population-weighted ambient air concentrations of insoluble nickel (i.e., 0.0047 to 0.0067 $\mu g/m^3$), the resulting estimates of excess lung cancer deaths per million person exposed over an entire lifetime range from 0.1 to 0.2. Even if one were to assume all

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nickel compounds were carcinogenic and use the mean statewide population-weighted concentration of total nickel, i.e., 0.0074 $\mu g/m^3$, the resulting estimate of excess lung cancer deaths per million would be 0.2, which is also below the "action level" sometimes viewed as acceptable, 1×10^{-6} or 1 excess cancer death per million per lifetime. If 1×10^{-5} or 1 excess cancer death per ten thousand is used as a level of acceptability, this estimate (i.e., 0.2 excess cancer deaths per million) is even twenty times below this action level. Further, even if one were to conservatively use the range of total (rather that insoluble) nickel concentrations cited in the State's risk assessment (1990b) of 0.0011 to 0.0236 $\mu g/m^3$, this results in estimates of 0.03 to 0.7 lung cancer deaths per million. The lower figure is derived from the maximum likelihood estimate of unit risk (2.4×10^{-5} per $\mu g/m^3$), and the higher figure is derived from a 95 percent upper bound (2.9×10^{-5} per $\mu g/m^3$).

In summary, estimated lung cancer deaths from lifetime, continuous exposure to nickel compounds in the ambient air of California do not exceed one excess death per million persons exposed over a lifetime. It is likely that the above estimates overstate risk related to ambient air exposures of nickel, given the lack of speciation information and relative potency for each species identified, and most importantly, the extremely low inhalation doses of nickel compounds which residents of California experience, i.e., four to eight orders of magnitude below those documented in human epidemiological studies. This conclusion is corroborated by the results of the re-analysis of ten cohorts conducted by the ICNCM (1990) which found that exposures of the general population to nickel compounds below 1 mg/m^3, should pose no likely significant risk of respiratory cancer.

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V. *Recommendations*

Recommendations are presented below for consideration by the State of California in assessing the human health risks associated with ambient inhalation exposure to nickel compounds and in their subsequent decision-making as to whether or not nickel should be identified as a toxic air contaminant. The recommendations are as follows:

- The State should use an alternative cohort, such as the non-sinter plant workers of the Ontario cohort (Roberts *et al.*, 1989), as the basis for derivation of a cancer potency estimate for estimating excess respiratory cancer mortality at the extremely low inhalation doses of nickel compounds likely to be experienced by residents of California. This recommendation is made as a result of consideration of the nickel species most likely to be associated with respirable ambient air particulate matter, which is thought not to include significant amounts of nickel subsulfide (high concentrations of nickel subsulfide were associated with sinter plant worker respiratory cancer incidence). Thus, the unit risk derived from the 495 sinter-plant subcohort of the Ontario cohort should only be applied to nickel subsulfide and nickel refinery dust. Preferably, insoluble nickel should be speciated and a separate, non-sinter worker cohort with relevant exposure profiles should be used for estimating

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risks from ambient inhalation exposures to nickel compounds which are associated with ambient air particles. This alternative is substantiated by evidence that the insoluble nickel to which sinter workers were exposed in Ontario is known to contain a relatively high proportion of nickel subsulfide; whereas oil combustion, currently the largest known source of airborne insoluble nickel emissions in California, is not believed to produce any nickel subsulfide. Since epidemiological studies of non-sinter workers consistently show lower risks than sinter worker studies, basing all California insoluble nickel risks on a sinter worker subcohort is unjustifiably conservative. The current California emission source data suggest that most exposures will not involve significant amounts of subsulfide, and that use of the non-sinter cohort data (see p. 52, Table 49 and p. 57, Table 59, ICNCM, 1990) would yield a unit risk more reflective of typical California exposures.

- The State should review the results of the International Committee on Nickel Carcinogenesis in Man (ICNCM, 1990) in their risk assessment for nickel compounds. This study provides critical insight into the adequacy of the epidemiological database for nickel mixtures and specific nickel species and should facilitate selection of the most appropriate cohort and occupational exposure data for quantitative risk analyses relevant to ambient inhalation exposures to nickel compounds.

- If an alternative cohort is not used for estimating a "lifetime added risk" for risk assessment analyses associated with inhalation exposures to insoluble nickel compounds occuring in ambient air, the currently proposed unspeciated, insoluble nickel unit risk factor (i.e., 2.4×10^{-4} per μg insoluble Ni/m^3 of air) should be reduced by an order of magnitude (i.e., 2.4×10^{-5} per μg insoluble Ni/m^3 of air) to incorporate the following adjustment factors:

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1) The selection of the particular nickel sinter worker "subcohort" used by the state unjustifiably elevates risk by a factor of 2.18, relative to the complete nickel sinter cohort; moreover, the failure to use the non-sinter cohorts improperly elevates risk by at least another factor of 2.61. This results in a deflation factor of 5.69 which can reasonably be applied to the SMR of 871 (and correspondingly, to the State's proposed unit risk factor). This is still conservative, in that non-sinter nickel cohorts show upper bound lung cancer SMR's of less than 200;

2) The manner in which the state treated follow-up in the Ontario cohort inappropriately inflates risk by a factor of 1.27. The unit risk should not be artificially increased by one-third to account for workers whose vital status could not be established. The adjustment factor should be closer to 5 percent. The draft unit risk estimate excludes that fraction of the cohort lacking "vital status." Because every attempt was made to locate and identify known cancer cases, the investigators are believed to have found most of the deaths, and those for which information is lacking, are believed to be in the health fraction. What is uncertain is whether they lived a normal life span, a longer than normal life span, or a shorter than normal life span after the initial data collection. Excluding this fraction artificially increases the unit risk. The only adjustment that might be warranted is one assuming a normal life span rather than a "still living" status. A "normal life span" adjustment would reduce risks by about 5 percent. Thus, using a 5 percent adjustment, rather than the exclusion of those lacking complete vital status, would reduce the estimated unit risk by a factor of 1.27; and

3) The continuous exposure assumptions for the general population and confounding exposures for workers further inflates risk by a factor 2.28. The unit risk should not be artificially increased based upon presumptions of continuous ambient inhalation exposure of Californians, and no historical non-occupational exposure. The proposed unit risk estimate assumes that exposures to ambient California concentrations of nickel compounds will be continuous, and that the historical cohort exposures were only for eight hours per day, five days a week, 48 weeks per year. These assumptions are unjustifiably conservative. Human activity pattern data and indoor, outdoor, and personal monitoring surveys indicate a variety of reasons for intermittent inhalation exposure durations and concentrations for compounds occurring in ambient air. Further, it has been reported that the "average" Californian spends 13 percent of their time outdoors, where potential exposure to ambient sources of insoluble nickel may occur. In contrast, the State has assumed that sinter plant workers spent approximately 22 percent of their time at work, where their exposure to nickel compounds occurred. In addition, epidemiological studies which do not account for non-occupational exposures (e.g., inhalation exposure from dusts carried home on a worker's clothing, living in close proximity to nickel emissions from a plant, environmental tobacco smoke), may artificially inflate the estimated SMR associated with occupational exposures only. Thus, the State's assumptions regarding continuous "equivalent lifetime exposure" and the lack of accounting for potential "non-occupational" exposure to workers result in a risk estimate which is high by a factor of 2.28.

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- Consideration should be given to the development of quantitative data regarding the relative concentrations of different nickel compounds in indoor air environments versus ambient air, so that, the relative significance of ambient concentrations can be better understood. This may be possible as an extension of the ongoing pilot study planned for the Riverside, California area, as part of the proposed "Particle - Total Exposure Assessment Methodology Study" being conducted as a cooperative research program by the U.S. EPA and the California Air Resources Board (Zelon *et al.*, 1990). As acknowledged by the State of California (June 1990a), ambient (environmental) exposure to nickel may occur as a result of inhaling nickel associated with respirable particles in ambient or indoor air, as well as through skin, iatrogenic sources (e.g., leaching of nickel from implanted medical devices), and ingestion of food and water containing nickel compounds. For purposes of effectively setting priorities and establishing regulatory actions that achieve a significant reduction of the risks associated with a given adverse health effect, route-specific exposure to all environmental media must be considered. As illustrated by the State of California's technical support document for identification of nickel as a toxic air contaminant, risk assessments used for environmental decision-making, often involve the assumption that ambient concentrations can be used to estimate human exposure levels. The accuracy of this critical assumption needs to be investigated by the concurrent examination of outdoor, indoor, and personal monitoring data. The results of such comparisons and relative frequency distributions provide critical insight into future environmental regulatory and research strategies. State and local governments need to consider the feasibility of control technologies and to assess their relative contribution to minimizing human exposure. If the control measures being considered affect primarily outdoor concentrations, an estimate of the proportion of human exposure contributed by outdoor versus indoor

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sources is required. For example, if outdoor concentrations contribute only 50 percent of exposure, a reduction of 50 percent in the emissions from outdoor sources would result in only a 25 percent reduction in total exposure.

- Consideration should be given to the potentially great usefulness of scientific information to be presented at the EUROMETEAUX conference on September 17, 18 and 19, 1990 in Brussels, Belgium regarding exposure assessment, hazard identification, risk assessment, and risk management of metals, including nickel.

- Based on our analyses, exposure to nickel compounds associated with respirable ambient air particles does not pose a significant risk of excess of lung cancer deaths to the general population of California; this conclusion is substantiated by the findings of the International Committee on Nickel Carcinogenesis in Man (ICNCM, 1990) which states that exposure of the general population to levels of nickel compounds below 1 mg/m^3 should pose no significant risk of excess respiratory cancer mortality.

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Appendix A

Summary of the Procedural Framework for Comprehensive Risk Assessments

According to the National Research Council[13], a comprehensive risk assessment contains four steps. They are summarized as follows:

- **HAZARD IDENTIFICATION** is a determination of whether there is a causal relationship between a chemical and a health effect. It involves gathering and evaluating toxicity data on the types of health injury or disease that may be produced by a chemical and on the conditions of exposure under which injury or disease is produced.[14] It may also involve characterization of the behavior of a chemical within the body and the interactions it undergoes with organs, cells, or even parts of cells. Data of the latter types may be of value in answering the ultimate question of whether the forms of toxicity known to be produced by a chemical agent in one population group or in laboratory animals are also likely to be produced in the human population group of interest. Note that risk is not assessed at this stage; hazard identification is conducted to determine whether and to what degree it is scientifically correct to infer that toxic effects observed in one setting will occur in other settings (e.g., are chemicals that are found to be carcinogenic in experimental animals also likely to be so in significantly exposed humans?; likewise, are chemicals that are found to be associated with excess cancer mortality in occupational settings likely to be so in humans exposed in ambient environments?).

- **DOSE-RESPONSE ASSESSMENT** involves describing the quantitative relationship between the amount of exposure to a chemical and the extent of toxic injury or disease. Data are derived from animal studies or, less

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[13]National Research Council. 1983. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: National Academy Press. 191 pp.

[14]Hazards other than toxicity (e.g., flammability, explosivity) are not considered in this type of review.

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frequently, from studies in exposed human populations. There may be many dose-response relationships for a chemical agent, depending on conditions of exposure (e.g., single versus repeated exposures) and the response (e.g., cancer, birth defects) being considered. This process is highly complex, taking into account diverse information about the body's ability to create metabolites more toxic than the parent compound, its ability to detoxify potentially toxic compounds or metabolites, variations in sensitivity to doses of toxic substances, and mechanisms of toxicity in test organisms (e.g., laboratory rodents) and in human target organs. In many cases the features of a dose (e.g., duration, frequency, route) have a great impact on the degree of toxic potency. Specialized procedures must be employed to assure that later characterization of toxic risk is as scientifically defensible as possible.

- **EXPOSURE ASSESSMENT** describes the nature of the various populations exposed to a chemical agent, their sizes, and the magnitude and duration of their exposures. The assessment might include past, current, and anticipated exposures in the future. This step also involves characterizing the activity patterns of the population likely to come into contact with the chemicals under evaluation [e.g., Californians spend 87 percent of their time indoors (Wiley *et al.*, 1990)]. This includes determinations of not only the numbers of individuals potentially exposed, but also consideration of the distribution of age, sex, and unique conditions such as pregnancy, preexisting illness, and lifestyle.

- **RISK CHARACTERIZATION** involves integration of the data and analyses from the other three steps of risk assessment to determine the likelihood that the human population of concern will experience any of the various forms of toxicity associated with a chemical under its known or anticipated conditions of exposure. The product generally includes estimations of risk for individuals

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and population groups, and a full exposition of the uncertainties associated with the conclusions. Scientific knowledge is usually incomplete, so that inferences about risk are inevitable. A well-constructed risk assessment relies on inferences that are most strongly supported by general scientific understanding and do not include conservative assumptions derived from risk management or public policy directives.

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RECOMMENDATIONS AND COMMENTS ON

THE PART A REPORT OF THE

TECHNICAL SUPPORT DOCUMENT

titled

PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT

Submitted to
California Air Resources Board,
Stationary Source Division

by

J. Stuart Warner, Vice-President
Occupational and Environmental Health
INCO LIMITED

on

August 22, 1990

C003107

RECOMMENDATIONS FOR IMPROVING THE PART A REPORT OF THE TECHNICAL SUPPORT DOCUMENT "PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT"

1. *Try to identify the nickel species in ambient air*

ARB proposes a linear extrapolate of the dose-response relationship determined for Copper Cliff sinter plant workers exposed to air containing tens to hundreds of **milligrams** of nickel per cubic metre and use it to estimate the lung cancer risk for the California public exposed to air containing less than 10 **nanograms** of nickel per cubic metre on average. This approach assumes that all the biological mechansims involved respond linearly over enormous ranges of exposure. I think this is a very questionable assumption.

There is an equally important issue with which ARB has not come to grips. ARB either has not focused on or has chosen to ignore the fact that the **forms** of nickel present in the sinter plant were **not** the same forms as those found in ambient air in California. The dust in the sinter plant consisted mainly of nearly pure nickel oxide and nickel subsulfide. It is certain that these are not the nickel species in ambient air in California. This important difference cannot be finessed simply by including the nickel species involved in both exposures under the rubric "insoluble nickel" as determined by a simple leaching procedure.

There are many forms of "insoluble nickel" and they have been shown, albeit by the questionable route of intramuscular injection in rats, to have very different carcinogenic potencies - including zero - at the same dose of contained nickel. See for example Sunderman (1984a) in Part B of the TSD. Thus a dose-response relationship determined for one form of "insoluble nickel" is unlikely to predict cancer incidence for another form of "insoluble nickel".

I believe that the nickel found in typical ambient air exists in relatively low concentrations in complex species. (This would not necessarily be true in "hot spots".) One should not think of low concentrations of, say, "oxidic" nickel in ambient California air as being a dilute version of the high concentrations of nearly pure nickel oxide that were present in the sinter plant. Not only would the nickel content of the ambient air be many orders of magnitude less than it was in the sinter plant, but the nickel-containing particles in ambient air would usually be complex oxides containing low concentrations of nickel.

Inco developed the speciation protocol described in Attachment A to Appendix II of Part A for use in occupational environments, where the nickel-bearing phases were relatively pure or well-characterized or both. Thus, knowledge of feeds, products and process could be used in conjunction with the information provided by the speciation protocol to deduce what nickel-bearing phases were present. We are concerned that applying this protocol to environmental sources of nickel may lead to

unwarranted conclusions about the species of nickel that are present. The protocol has yet to be applied to environmental samples which have been well-characterized with respect to the nickel-containing species as Inco did with occupational dusts.

If the principal sources of airborne nickel in the TACN network - e.g. oil-fired power plants, oil field steamers, dust from serpentinic soil, etc. - could be identified, it would be possible to obtain samples in which the nickel is more concentrated; i.e. before it is diluted with other sources of atmospheric dust. It might be possible to determine the nature of the nickel-bearing species with modern instrumental methods. If so, quantities could be synthesized that were large enough for testing in the speciation protocol and in *in vitro* and *in vivo* bioassays. In this way, it would be possible to learn whether the species of nickel in ambient dusts have carcinogenic potencies at all comparable to the forms associated with lung cancer in certain obsolete nickel refining operations.

Even a brief look at the air pollution literature makes it clear that ARB has been extremely active in defining source-receptor relationships. However, all of this activity seems to have been directed towards meeting PM-10 standards. Surely substances suspected of being toxic air contaminants should be given the same sort of analysis. ARB should see if it already has information for its PM-10 network that could identify the major sources of nickel being measured in the TACN.

I recommend strongly that total suspended particulate be routinely determined for samples collected in the TACN. This could be done at little extra cost since the volume of air sampled is presently being determined. The information should be useful for quality control and, possibly, for use in determining source-receptor relationships. The ratio of the ambient nickel concentration to TSP would be a measure of the nickel assay of the total particulate. Samples with nickel assays that departed significantly from the normal range are likely to represent faulty data or a sudden contribution by a new nickel-emitting source. The frequency distribution of nickel assays at a particular location might permit some reasonable deductions as to whether the ambient nickel at that location existed in relatively few species and whether any of them were significantly richer in nickel than the other species. It would also be useful to know whether the concentration of nickel in airborne particulate was similar at all TACN sampling locations.

2. *Analyze all the available data on ambient airborne nickel concentrations*

The Technical Support Document ("TSD") reports ambient nickel concentrations only for the period January 1985 through February 1987. Furthermore, only the November 1985 - October 1986 subset of these data were employed to make the population "exposure" estimate.

It is my understanding that ARB continues to sample ambient particulate throughout the 20-station toxic air contaminant network and, through January 1989, had analyzed some 3410 samples for their nickel content. ARB gave me access to these data through the courtesy of Mr. R. Rothacker, Manager, Air Quality Data Review Section, and the assistance of Mr. M.P. Redgrave. Table 1 qualitatively describes this larger, more current collection of ambient nickel concentrations.

Since the cost of analyzing the data is trivial compared with the cost of collecting and analyzing the airborne particulate, ARB should make use of all the available data on ambient nickel concentrations to estimate the current population exposure to airborne nickel in California. By analyzing more data, ARB will be able to narrow confidence intervals for mean nickel exposures and will be more likely to detect any seasonal variations or long-term trends that may exist.

Every effort should be made to expedite the analysis of samples of particulate that have been collected but not yet analyzed to obtain even more current information. If nickel should be identified as a toxic air contaminant, ARB would probably need such information to devise efficient regulations. It seems desirable to have access to these data through all of the deliberations concerning nickel.

As a simple example of the merit of including more data in the analysis, I summarized all of the concentration data supplied to me by ARB as well as the November 1985 - October 1986 subset of those data. Before doing so, I replaced all the determinations that were below the 1 ng Ni/m^3 limit of detection ("BLOD") with estimates obtained by Gleit's method. (Has ARB considered the estimation method favoured by Haas and Scheff (1990). It is claimed to be more robust and somewhat easier to implement than other methods.) To apply Gleit's method, I ignored any long-term trend in the nickel concentrations and assumed that they were lognormally distributed. Despite being based on more than twice as much data, the estimated BLOD concentrations were almost identical with those estimated by ARB. See Table 2.

By comparing Tables 3 and 4, it can be seen that the geometric mean nickel concentrations decreased at 16 of the 20 sampling locations when the more complete database was used even without explicitly testing for long-term trends. More important, the 95% confidence intervals for the mean were narrowed significantly by using all of the data. The widths of the confidence intervals shown in Table 4 ranged from only one-quarter to two-thirds and averaged less than one-half the widths of the corresponding confidence intervals given in Table 3.

3. Treat the nickel concentrations as being lognormally distributed

Although the TSD states on p. A9 that the "nickel data were generally lognormally distributed", the concentrations were generally summarized in the text, tables and figures in terms of the parameters relevant to a normal distribution; i.e. the arithmetic mean and standard deviation. If the nickel concentrations are indeed lognormally distributed, the geometric mean ("GM") and geometric standard deviation ("GSD") should be used to summarize the nickel concentration data throughout the TSD. Use of the incorrect model will result in significant overestimation of the ambient nickel concentrations in California.

Theoretical considerations and practical experience suggests that the frequency with which a particular ambient concentration of an analyte is observed at a given site is a lognormal function of the concentration (Crow and Shimizu, 1988). It seems worthwhile to investigate whether the California nickel data are an exception to this general rule. The Kolmogorov-Smirnov Goodness-of-Fit Test was employed to carry out this investigation. The K-S test examines the likelihood that the observed data could have been a random sample drawn from a population obeying an hypothesized, continuous distribution. It arranges the observed concentrations in increasing order and calculates the cumulative frequency as a function of concentration. It then compares the observed cumulative frequencies with the cumulative frequencies expected from the hypothesized distribution. D, the greatest difference between the observed and expected cumulative frequencies, is determined and compared with a critical value; i.e. the largest difference that could have been expected to occur by chance. Not surprisingly, the critical values depend on the size of the sample and the chosen level of significance, α.

Table 5 shows the results of applying the K-S test to each sampling location assuming in turn that the observed nickel concentrations were drawn from the lognormal and normal distributions. The results, like so many products of statistical analysis, are informative but inconclusive. The informative result may be seen by comparing the values of D given for each distribution. Except for Santa Barbara, Riverside and Upland, the lognormal distribution fit the observed nickel concentrations better (i.e. resulted in smaller maximum differences, D) than did the normal distribution.

The inconclusive result appears in the approximate levels of significance, α. The level of significance is the probability of making a Type I error; i.e. rejecting the hypothetical distribution when it is in fact the correct one. Thus a small value of α means one is unlikely to be wrong by saying that the observed concentrations were **not** a random sample drawn from the hypothesized distribution. Even for Bakersfield, which had the smallest value of D, one is only likely to be wrong half the time by rejecting the lognormal distribution as the correct one. While one would not like to be wrong half of the time, this is hardly a ringing endorsement of the lognormal distribution. However, the normal distribution generally produced even poorer fits to the data, the highest value of α being 0.03 (Upland).

I suspect that this lack of conviction stems at least partly from the fact that we want to know the likelihood that the nickel concentrations were drawn from **any** lognormal (or normal) distribution but the K-S test only tells us the likelihood that the sample was drawn from a **particular** lognormal (or normal) distribution; i.e. the one having the same mean and standard deviation as the sample. For example, if the lognormal distribution hypothesized to describe the Bakersfield data had a GM of 18.3 to 18.4 instead of the sample GM of 18.57 **or** a GSD of 20 to 20.2 instead of the sample GSD of 19.54, the level of significance from the K-S test would be increased from 0.502 to over 0.6. However, one can not make a silk purse from a sow's ear in this way. Varying the parameters of a normal distribution reduced the value of D for the Bakersfield data but the level of significance remained essentially zero.

Figures 1 and 1a through 6 and 6a show the nickel concentrations for six sampling locations expressed as frequency histograms superimposed on the theoretical lognormal and normal distributions whose parameters were derived from the data. Bakersfield, San Jose and El Monte were chosen because they gave the best fits to the lognormal distribution while Upland, Riverside and Santa Barbara were chosen because they were the only samples that were described better by the normal distribution than by the lognormal distribution. The reader may wish to compare his or her subjective impressions of these figures against the objective results of the K-S test presented in Table 5.

4. Identify any long-term trends in the nickel concentration data and take them into consideration

The TSD states on page A8 that there were "...no statistically significant changes between the mean nickel concentrations for 1986 and those of 1987 and 1988." Rather than comparing annual means, I performed simple linear regressions of the data summarized in Tables 1 and 4 against the time of measurement. Since I presume the nickel concentrations are lognormally distributed, I regressed the **logarithm** of the nickel concentrations against the time of measurement in calendar years. The observed nickel concentrations, the predicted GMs and the 95% confidence limits about the means are shown for each sampling location and air basin in Figures 7 through 31. The figures employ linear scales (except for Bakersfield and the San Joaquin Valley Air Basin) for the reader's convenience; that is why the regression line for the GM is non-linear. The regression statistics relevant to the slopes for each sampling location are given in Table 6. Note that the slope is the annual rate of change of the **natural logarithm** of the nickel concentration.

Three checks were made to ensure that the parameters found by regression were reasonably reliable. First, linear regression assumes that the variance of the dependent variable does not change with changes in the independent variable. Constancy of the variance can be qualitatively evaluated by plotting the residuals, the differences between the observed and predicted values, against the independent variable and against the predicted values to check for any unusual patterns. This was

done for each regression and plots such as those shown for the South Central Coast Air Basin in Figures 32 and 33 were obtained for all sampling locations and all air basins. The scatter of the residuals about the origin did not seem to vary with either time or with the predicted value. Second, regression theory also assumes that the residuals will be normally distributed. Figure 34 shows a typical plot of residuals against the normal distribution. The fit is far from perfect but the assumption does not appear unreasonable considering that r^2 for the South Central Coast Air Basin was only 0.05%; i.e. many important variables were not taken into account. Finally, since outliers, particularly at extreme values of the independent variable, can greatly influence the regression, each regression was recalculated after rejecting all concentrations that lay outside the 99% confidence limits for predicted concentrations. No points were rejected for 11 of the sampling locations; the maximum number of points rejected was five for El Monte, four low values and one high value. In no case did the rejection of outliers alter the previous conclusions about whether or not the slopes of the regression lines were statistically significant. The data in Table 6 are from the regressions using all of the data.

Seasonal variations in nickel concentrations could have affected the regression analyses. Examination of Figures 7 through 31 suggest that nickel concentrations at some locations may be significantly affected by the season in which the measurement was made. This could be due to increased emissions of nickel and/or decreased atmospheric ventilation in certain seasons. (As a crude test of this hypothesis, the logs of the nickel concentrations measured at Bakersfield were simultaneously regressed against time and against the month of measurement. The level of significance for the variable MONTH was 0.04; i.e. it was statistically significant even though seasonality can't be predicted from the calendar, at least over a period of just 3.5 years.) If a seasonal component exists for some locations and if, as it appears from the figures, that nickel concentrations are more likely to be elevated in the winter, the slopes of the regressions would have been more positive (or less negative) than the true long-term trends would warrant. This is because the data points available for the analysis ended in the winter of 1988-89. ARB should consider using more sophisticated analyses (e.g. Box-Jenkins ARIMA modeling) on smoothed nickel concentrations to detect and isolate any seasonal component of variability from the true long-term trend of nickel concentrations.

Taken at face value, the slopes reported in Table 6 indicate that the geometric mean nickel concentrations were increasing at half of the sampling sites and air basins while decreasing at the other half. However, the high level of significance associated with most of these slopes indicates that one is quite likely to be wrong if one rejects the hypothesis that these slopes are actually zero. Table 6 also presents r^2, the measure of how much of the variability in the data can be explained by the regression. The values of r^2 are generally small, the largest value being 17.65% for Bakersfield. The small values of r^2 indicate that many variables that significantly affect the concentration of airborne nickel at a given location at a given time (e.g. seasonality) have not been included in the regression. However, the small level

of significance associated with the slopes in seven locations indicates that the passage of time is one variable that should not be ignored when analyzing the data at these locations.

For those sampling locations with slopes that are significantly different from zero, four slopes are positive and three are negative. In order of decreasing **absolute** value of slope, the locations with positive slopes are Riverside, Fremont, El Monte and Upland. Similarly, the locations with significantly negative slopes are Stockton, Bakersfield and San Francisco. At this point it would be wise to have a "reality check". That is, the fundamentals of the situations throughout the toxic air contaminants network ("TACN") should be examined to see if there are reasonable physical explanations as to why geometric mean nickel concentrations seem to be increasing in four sampling locations while remaining constant or decreasing in the other 16 sampling locations and five air basins. Unfortunately my total lack of knowledge about the distribution, relative magnitude and possible seasonality of nickel-emitting sources in California combined with equal ignorance of weather patterns during the period covered by the ARB nickel database prevent me from doing this. Local knowledge is required.

While I can give no reasons to support the long-term trends revealed by the regression analyses, I have no reason to believe that they are artifacts of the data or of the regression analyses. I have therefore employed the results of the regressions to extrapolate the predicted geometric mean nickel concentrations 11 months beyond the data, to January 1, 1990 for the seven locations mentioned above. I resigned myself to this modest extrapolation so as not to do violence to the mathematical models and because it might encourage ARB to update its nickel database to at least January 1990 to see if the projections are reasonable. In any event, I believe that the extrapolated estimates are unlikely to be less accurate than the estimates obtained by averaging a smaller, older set of data.

The summary of the ARB nickel database presented in Table 7 is a combination of the data in Table 4 and the results of the regression analyses. It repeats the data from Table 4 for those sampling locations for which Table 6 did not reveal a statistically significant long-term trend. For the seven locations with significant long-term trends, Table 6 reports the GMs and GSDs predicted by the regression analyses for January 1, 1990. It is important to note that the GSDs reported in the table for the locations with long-term trends are different from the GSDs reported for the other locations. The former describe the dispersion of geometric means about the **predicted** GM for January 1, 1990 while the latter GSDs describe the dispersion of the **observed** concentrations about their GM.

Unless there are fundamental reasons to mistrust the extrapolations at the seven locations, the data in Table 7 should be used for estimating geometric mean nickel concentrations until more current data become available.

5. Use a more realistic formuation of exposure

Part A of the TSD estimated the state-wide average **"exposure"** to insoluble nickel to be the population-weighted average of the average ambient nickel **concentrations** (Nov./85-Oct./86) at various locations in the TACN. When these average "exposures" were combined with the unit risk factor in Part B, they were assumed to last for a lifetime. This approach requires **at least** the following assumptions:

a) the studied population of some 20,340,000 people will live their entire lives in California;

b) there will be no long-term trends in geometric mean nickel concentrations within the area covered by the TACN;

c) there will be no net shifts of population between areas with different geometric mean nickel concentrations;

d) the studied population spends 100% of its time outdoors

or

concentrations of airborne nickel are the same indoors (including workplaces) as outdoors.

None of these assumptions, let alone all of them, are likely to be correct. The TSD has, therefore, presented only estimates of **"potential"** exposure.

A more realistic estimate of the lifetime average inhaled insoluble nickel exposure ("LAINE") of a Californian can be obtained by evaluating equation (1).

$$(1) \quad LAINE = (1/Lifetime) * \sum_{t,e} (CNi * INS * ED * IR * UNIT)$$

where

CNI is the concentration of total nickel in ambient air
INS is the fraction of total nickel that is insoluble
ED is the exposure duration
IR is the inhalation rate
UNIT is a constant that ensures LAINE is expressed in ng Ni/m^3

The subscripts t and e indicate that the product in brackets is to be summed over the individual's lifetime and for all the different environments in which he or she spends time. The principal virtue of equation (1) is that it makes the risk assessor more conscious of the assumptions being made. The factors ED and IR should be taken just as seriously as CNi and INS even though the latter are the result of ARB measurements.

Theoretically, the equation (1) is evaluated for each person in real time and the resulting individual LAINEs would be combined to yield a frequency distribution of LAINE for the entire state. In practice, equation (1) is evaluated for larger blocks of time (no smaller than the seasons of the year) and for large groups of people. When the instantaneous values of the variables in equation (1) are averaged over time and larger groups of people, they must be replaced by distributions to ensure the risk manager knows the uncertainty involved in the state-wide estimate of LAINE. The desirability of explicitly dealing with uncertainties in risk assessment is dealt with at greater length in recommendation 6.

It would seem to be useful to consider some of the variables in equation (1) although ARB will be able to do this much more thoroughly than I can.

5a. *Lifetime*

EPA's Exposure Factor's Handbook ("EFH") (EPA, 1990) reports (p. 5-1) that current life expectancy for the entire U.S. population is now 74.7 years and suggests that 75 years be used for the estimated "lifetime" in exposure assessments instead of the conventional 70 years.

5b. *Concentration of nickel in the outdoor environment*

ARB has collected much information on ambient concentrations of total nickel. It should use all of these data and analyze them as discussed in recommendations 2 and 3. Geometric mean nickel concentrations can vary by a factor of four or more from location to location within the TACN. If any other term in equation (1) is sensitive to location - e.g. INS - the equation must be evaluated for the outdoor environment at each location before its contribution to LAINE can be aggregated.

Since equation (1) is to be evaluated for a lifetime, some assumption must be made about future values of CNI. Unless the availability of newer nickel concentration data suggests doing otherwise, I would use the GMs listed in Table 7 for the exposure assessment. This should be a conservative approach because control measures, whether directed towards nickel or not, are likely to lower ambient concentrations of nickel in the future.

Even though I recommend using constant values of CNi to evaluate equation (1), it may be necessary to re-analyze the ARB data on a seasonal basis, at least at some locations. If there is a seasonal component to ambient nickel concentrations, unless the residents of that area spend one-twelfth of their annual time outdoors each month, the **annual** GM will not be a good measure of their exposure. If my eyeballing of Figures 7 through 31 is correct, seasonal trends, if any exist, seem to result in increased nickel concentrations in winter months. As a Torontonian, I expect even Californians would spend less of their annual outdoor time in winter months and more in summer months. If this is true, the annual GMs in Table 7 would be likely to **overestimate** the exposures of people in locations where the nickel concentrations are elevated in winter months. For such locations, seasonal means should be calculated; for this purpose, the "seasons" would be defined by the observed patterns in the concentration data.

5c. *Fraction of insoluble ambient nickel*

The discussion that follows assumes that the "insoluble" fraction of nickel is the appropriate measure of exposure to combine with the unit risk factor developed in Part B. The significance of this assumption is addressed in recommendation 1. I do not think "insoluble" nickel is the appropriate fraction but I have commented nevertheless because whatever the relevant species is/are, it/they may well constitute different fractions of total ambient nickel at different locations.

ARB has taken the extreme values of INS from Table 2, Appendix II of the TSD and applied them to all locations. I believe it is at least premature, and possibly wrong to do so. First, if the data in Table 2 were trusted, they would argue against using the same value(s) of INS at different locations. The data for Bakersfield-Oildale in Table 2 shows only a modest dispersion of values (s=5.4%) about the mean (INS=61.4%). I assumed that Mammoth Lakes and Quincy represent a different kind of environment and might be expected to have a different value of INS. A small-sample test showed that the two means were significantly different at the 0.05 level. Based on these data, mean values of INS for Bakersfield-Oildale would have been 61.4% and that for Mammoth Lakes-Quincy would have been 80%.

However, I think Table 2 presents too optimistic a picture of consistency for the Bakersfield-Oildale data. In 1989, Inco Limited co-operated with ARB's Southern Laboratory Branch in some experiments to speciate ambient nickel. Thus I have access to more data on the insoluble fraction of ambient nickel than are presented in Appendix II of the TSD. I have assembled the information on INS on INS for Bakersfield-Oildale in Table 8.

I have gleaned the impression from talking with various members of the ARB staff that the ambient nickel in Bakersfield comes principally from the combustion of petroleum. If this impression is correct, it seems reasonable to expect that, even though concentrations of ambient nickel may fluctuate with time about a declining

mean, the **composition** of the nickel-containing particulate should be reasonably constant over time. Instead, Table 8 shows that the insoluble fraction varied from as little as 16.7% to as much as 77.7%. It would have been interesting to see the individual variations in the monthly composites analyzed by the Southern Laboratory Branch but the lo-vol system employed by ARB for the TACN collects so little nickel to begin with that it is very difficult to split it into sub-categories with confidence. Thus composite samples were analyzed. The information provided by the five filters reported in Appendix II provides a tight distribution. Attachment A to Appendix II indicates these filters were the same as those used in the normal lo-vol sampling process. If they were collected over a period of months, I wonder how these individual filters could give more reproducible results than did the monthly composites of four and five lo-vol filters.

The lack of reproducibility of the insoluble fraction, at least in the coarser sizes, is shown dramatically by the hi-vol samples collected simultaneously on May 30 to June 1, 1989; INS differed by a factor of two. It appears that the two PM-10 samples collected at the same time were much more alike despite the low value obtained on one of the four filter strips analyzed by Inco.

It seems like more experimental work is needed before the fraction of insoluble nickel at any sampling location can be specified with confidence. INS should be measured a sufficient number of times to establish the mean and the dispersion with some certainty at each location. ARB could include the determination of INS in a program to expedite the nickel analysis of those samples of airborne ambient particulate that have already been collected.

5d. Exposure duration

Unless the concentration of nickel is the same everywhere in California, ED must be estimated for each of the environments for which equation (1) must be evaluated. For example, one must be outdoors to be exposed to ambient concentrations of nickel. Since Part A (Appendix III, p.1) recognizes that Californians, on average, spend 13% of their time outdoors, ARB should have taken this into account when converting **ambient concentrations** to **ambient exposure**. While ARB may have underestimated total nickel exposure by not accounting for indoor and occupational exposures to nickel, it overestimated the exposure to ambient nickel by a factor of 7.7 on average!.

Fortunately, it seems that sufficient information on human activity patterns is available to make reasonable apportionments of time between various indoor and outdoor activities. Chapter 5 of the EFH contains extensive tables of national data categorized by sex and age. The report by Wiley et al. (1990) listed in the references to Appendix III of the TSD appears to contain current, comparable information specific to California. I expect the Wiley et al. reference to provide information that will permit breaking Californians' activities into component parts. For instance, it would seem

reasonable to expect that the time spent outdoors might vary with location in the state; e.g. because of differences in recreational opportunities and in the concentration of industries such as farming or logging. Furthermore, it would seem reasonable to expect that, at each location, the time outdoors would vary with the season. If time outdoors varies with season, in locations where the ambient nickel concentrations have a seasonal component, both time outdoors and nickel concentrations should be averaged over the same "season". In such locations, annual averages should not be used.

The estimates described in the two paragraphs above simply allow one to make a reasonable estimate of state-wide exposure to nickel in, say, January 1990. One must also consider whether this estimate is likely to remain good for a lifetime, the assumption being made when the exposure is multiplied by the unit risk factor to estimate cancer incidence. It would seem that population mobility could affect this assumption in one or two ways. First, since residence location can affect mean ambient nickel concentrations by a factor as large as four, net population flows between locations in the TACN with different mean concentrations of nickel, could result in under- or over-estimates of the state-wide lifetime exposure. If such intra-state redistributions are now recognized and can be quantified, it would be easy to correct the estimated lifetime exposure.

Population mobility across California's borders could also affect the assumption that average exposures won't change over a lifetime. Whether ARB uses 70 or 75 years for a conventional lifetime, it is clear that the entire population of California will **not** live out its lives within the state. It is incorrect to calculate a cancer incidence that assumes greater exposures than could have occurred. The EFH (p. 5-70) indicates that 8.5% of the Californians surveyed in 1980 had lived in a different state sometime between 1975 and 1980. I take this to mean that the annual rate of immigration to California was 1.7% for that period. The EFH did not give any information on the emigration rate for the same period. Although the population was probably growing at the time, it is easier to see the effect of immigration and emigration on the average number of years lived in the state if one assumes the rates were equal and that no emigrant returned to the state. Under this scenario, the entire population would have been replaced after 58.8 years (=100/1.7) and the average number of years lived in the state would have been half of the replacement time; i.e. about 30 years or only 40% of a 75-year lifetime. Since the population was probably increasing during that period, the average fraction of a lifetime lived in the state would have been somewhat longer than 0.4. However, ARB should determine what the situation is **now**. Even if the current rate of immigration were only 1%, the average fractional lifetime lived in the state would still be only about two-thirds if, as I believe to be the case, California's population is no longer growing. So a figure from one old survey, one off-the-wall estimate and some naive mathematics suggest that the average fraction of a lifetime lived in the state could be on the order of one-half.

The only rationale for ignoring this factor is to determine that the immigrants were and the emigrants will be exposed to the same concentrations of nickel (outdoors, indoors and occupational) in the places that they came from and went to as they would have been in California.

I would expect a number of state agencies - e.g. census, tax, motor vehicles, urban planning, etc. - to be able to supply ARB with good estimates of the fraction of a lifetime for which current residents might possibly be exposed to ambient nickel in California.

5e. *Inhalation rate*

It might seem that including the inhalation rate in equation (1) is gilding the lily. (I am not about to sugest that particle size distributions, regional deposition and clearance, etc. be taken into account. That is for the next generation of risk assessors to do.) However, the dose-response relationship developed in Part B of the TSD was based on an industrial population. It is likely that the workers inhaled larger volumes of air as well as much dustier air than will the average Californian. The EHF provides extensive tables of inhalation rates as a function of sex, age and activity level. Table 3-1 from the EHF has been reproduced on the following page. It shows a three-fold difference in the inhalation rate of the average male engaged in moderate activity compared with light activity. Such rates could be combined with the activity patterns given in Wiley et at. (1990) and used to estimate inhalation rates for a given population in each of the environments of interest.

5f. *Concentration of nickel in other environments*

I understand ARB is required by law to "identify the relative contribution of indoor exposure to the total air exposure". While Part A of the TSD gives estimates of "presented daily doses" of nickel from various indoor sources, it has not made any estimate of the expected overall indoor nickel exposure. Dr. Saloum has my sincere sympathy for being charged with such a difficult task. All I can suggest is that the information she has gathered on specific sources be combined with other information – e.g. the fraction of homes heated by wood in an area; cigarette-smoking habits; activity patterns from Wiley et al. (1990) – to estimate the distribution of indoor nickel concentrations. Some of the techniques mentioned in recommendation 6 could be useful for this task.

The indoor exposure estimates all seem to be directed to personal residences and vehicles. What can be done to estimate nickel exposures in the wide variety of non-residential indoor environments in which Californians spend much their time; e.g. schools, office buildings, retail establishments, churches, places of entertainment?

Table 3-1. Summary of Human Inhalation Rates for Men, Women, and Children by Activity Level (m^3/hour)[a]

	Resting[b]	Light[c]	Moderate[d]	Heavy[e]
Adult male	0.7	0.8	2.5	4.8
Adult female	0.3	0.5	1.6	2.9
Average adult[f]	0.5	0.6	2.1	3.9
Child, age 6	0.4	0.8	2.0	2.4
Child, age 10	0.4	1.0	3.2	4.2

[a] Values of inhalation rates for males, females, and children presented in this table represent the mean of values reported for each activity level in USEPA (1985).

[b] Includes watching television, reading, and sleeping.

[c] Includes most domestic work, attending to personal needs and care, hobbies, and conducting minor indoor repairs and home improvements.

[d] Includes heavy indoor cleanup, performance of major indoor repairs and alterations, and climbing stairs.

[e] Includes vigorous physical exercise and climbing stairs carrying a load.

[f] Derived by taking the mean of the adult male and adult female values for each activity level.

Copied from EPA's Exposure Factors Handbook

Since there seems to be so little data for indoor environments, it would seem that ARB should engage in a crash program of sampling indoor air and analyzing the collected particulate for nickel. Dr. Saloum's identification of significant indoor sources of nickel could help to plan an efficient sampling strategy. If the observed indoor exposures are as large as suggested in Appendix III, Table 1, the exposure to ambient concentrations of nickel would be trivial in comparison.

I don't know what ARB's responsibility is to investigate occupational exposures. They will generally be "indoor" exposures and will be the preponderant part of total inhalation exposure of nickel for many people. A person occupationally exposed to nickel at one-tenth the PEL, would be exposed to the same amount of nickel in nine hours as would a person who lived in El Monte for 75 years and spent 13% of his or her time out of doors, assuming their physical activity levels were the same!

5g. *INS in other environments*

This problem parallels the discussion in 4h. The resolution seems to require including speciation analyses in the crash program of indoor (and occupational?) monitoring.

6. Deal explicitly with the uncertainties in estimated quantities and calculated risk

For a balanced, readable discussion of the methods and merits of incorporating uncertainty into risk assessments, I recommend the publication titled "Confronting Uncertainty in Risk Management: A Guide for Decision-Makers" by Adam M. Finkel of the Center for Risk Management, Resources for the Future. This brief publication (68 pp.) will amply reward the time spent reading it. Finkel points out several important benefits that arise from explicitly acknowledging uncertainty and factoring it into the risk management process:

- "a better understanding of the spectrum of possible states of nature that could occur in the absence of any action on the decision-maker's part, and of the relative probabilities of each;
- an appreciation of the costs of being wrong - that is taking an action appropriate for one state of nature when the real situation is different than one believes;
- a blueprint for taking action to reduce uncertainty if one feels the outcomes are too precarious (and the stakes too high) to make a definitive choice;

- a means for justifying the choice made - to demonstrate to any interested observer (be it a peer, the news media, a judge, or a jury) that the decision made was neither arbitrary nor ill-informed."

The TSD could be improved substantially by introducing some of Finkel's suggestions. For example, one purpose of the Part A Report is to estimate a population lifetime exposure to certain forms of nickel. The Part B Report is supposed to develop a relation between cumulative exposure to the same forms of nickel in a particular occupational setting and the subsequent risk of developing lung cancer. The products of Parts A and B are simply multiplied to estimate the lung cancer risk to Californians as a result of exposure to ambient levels of insoluble nickel. Even if one were to accept this extremely simple model as adequately representing cancer causation, one should recognise and explicitly account for the uncertainty in the exposure estimate and in the unit risk factor. Instead of using point estimates, attempts should be made to develop probability density functions for each component variable in the model used to calculate risk. These should then be combined (say by Monte Carlo simulation) to arrive at the estimated risk and its probability density function.

Part A of the TSD provided some idea of the uncertainty in the mean ambient nickel concentrations by reporting upper and lower bounds for the mean. (As pointed out in the COMMENTS that accompany these RECOMMENDATIONS, I believe the mean concentration should have been the geometric mean and I cannot understand how the bounds were calculated.) However, with little extra effort, the TSD could provide risk managers with the probability for observing **any** particular value of the GM. This can be done easily with the same information needed to calculate the 95% confidence interval. Since it is the log of the nickel concentration that is thought to be normally distributed, one simply forms the ratio

$$X = (\log(\text{arbitrary GM}) - \log \text{GM}) / \log \text{GSD}$$

and looks up the normal probability corresponding to X. The GSD must refer to the sampling distribution of the mean. The values of GSD presented in Table 7 for the seven locations for which there was a long-term trend in ambient nickel concentrations can be substituted directly into the above equation. The GSDs for the other 13 locations describe the dispersion of the concentrations around the mean. The standard deviation of the sampling distribution of the means for these 13 locations is log(GSD)/SQRT(N) where the denominator is the square root of the number of nickel concentrations included in the analysis. For a given GM, GSD (and N where necessary), one can repeatedly solve the above equation and look up the normal probabilities associated with a series of arbitrary values of GMs until the range of probabilities of effectively 0 to effectively 1 has been covered. A plot of the probabilities versus the arbitrarily chosen values of GM is the cumulative frequency distribution for the GM. Figure 35 shows the results of these calculations for the five sampling locations that comprise the San Francisco Bay Area Air Basin.

The probability distributions for the other variables involved in equation (1) may not be so elegant as that for the geometric mean. In the absence of evidence as to how variables such as ED are distributed among the population residing at a given sampling location, it is safest to assume a uniform distribution; i.e. that all values in the observed or theoretically possible range are equally likely. While this simple approach may seem to be a waste of time, it **ensures** that the uncertainty in LAINE will be made explicit.

C00624

COMMENTS ON THE PART A REPORT OF THE TECHNICAL SUPPORT DOCUMENT "PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT"

I have attempted to minimize the overlap between the following COMMENTS and the preceding RECOMMENDATIONS. If I have made a recommendation that something be done differently, I generally won't say that I disagree with the results of the original approach when I come upon them in Part A. However, I sometimes comment on items that I do not understand even though I have previously recommended that a different approach be used.

Paragraph numbers used to identify text on a page include any fraction of a paragraph on the page.

p.A1, para.1: Does Section 39655 of the Health and Safety Code or ARB policy rely on the level of estimated risk to decide whether a substance is a toxic air contaminant? Or does the Code require only a finding that a substance has produced an adverse health effect in animals or humans regardless of the dose or the route of administration?

p.A1, para.2: It is important to repeat that the TSD presents only estimates of **potential** exposure.

p.A3, para.1: It states that 1454 samples were collected in the 1985-1987 period but Table II-1 indicates only 1392 samples.

p.A8, line 1: ARB should indicate whether it used Gleit's method on the logarithms of the nickel concentrations or on the concentrations themselves.

p.A8, para.4: Table II-2 shows that data for January and February 1987 were collected at respectively only six and three of the 20 sampling locations. Why was such a small sample of data included in the three figures that follow?

p.A9, para.4: It states that the upper and lower bounds shown in Figure II-5 (and presumably in Table II-4) were calculated "using logarithms and represent plus or minus two standard errors." The asymmetry of the bounds around the mean in the table and figure indicate that logarithms were indeed "used". However, something seems to have gone awry with the calculation. The means shown are the arithmetic means. If lognormality of the nickel concentrations was accepted, the geometric means should have been employed. Furthermore, I am unable to figure out how the

upper and lower bounds were calculated. Bounds calculated at two standard errors should be nearly identical with the 95% confidence limits so the bounds in Table II-4 of the TSD should agree with the 95% confidence limits shown in my Table 3. They do not. Neither do they agree with the 95% confidence limits about the arithmetic mean. I believe the means and bounds shown in Table II-4 and Figures II-5, II-6 and II-7 are in error. Conclusions in the text based on these sources are therefore also likely to be wrong.

p.A13: I feel strongly enough about this point that I will repeat recommendation 3; the nickel concentration data should be summarized in terms of geometric, not arithmetic, parameters.

p.A14, para.2: Is it simply coincidence that the population-weighted "exposure" estimates (lower bound, mean, upper bound) in Table II-4 for the South Coast and San Francisco Bay Area air basins are, with one exception, the arithmetic averages of the corresponding estimates for the individual sampling locations within the basins?

p.A14, para.3: The 95% confidence limits do not "represent the range of values that the mean exposure could assume." They represent the range in which the mean ambient nickel concentration would be expected to fall 95% of the time if similarly-sized samples were drawn from the same population.

p.A15: I cannot deduce how the Statewide Population-Weighted Exposure at the bottom of the table was calculated. The only number that fits the description is the upper bound. It appears to me that, **based on the data in Table II-4**, the lower bound and mean should be 5.3 and 6.7 respectively instead of 6.0 and 7.4 as shown.

p.A16 and Fig.II-6: I have pointed out in recommendation 5 that the data used here - even if properly calculated - would represent only **potential** exposure. The figure does not take into account the uncertainty in each of the means. Beyond these complaints about the philosophy underlying the figure, I simply cannot understand how it was created from the data. For one thing, it seems to account for all of the population yet shows no estimated mean nickel concentration greater than 10. Yet four of the sampling locations were shown in Table II-4 to have mean concentrations greater than 10; one air basin was shown with a mean concentration of 11. Where are these people represented in Fig. II-6?

p.A16 and Fig.II-7: The title is wrong in using "exposure" in place of "potential exposure" and may mislead readers by referring to "cumulative nickel exposure". Some may take this to mean the amount of nickel that accumulates in the body with the passage of time. This kind of graph should refer to "cumulative frequency" or "cumulative probability". Incidentally, cumulative distributions of frequency are traditionally presented as **increasing** from left to right. The presentation used in Figure II-7 may therefore confuse readers.

p.A19, para.1: On p.A2, it was stated that "Studies are now underway to investigate indoor concentrations of nickel;" Wouldn't this chapter be an appropriate place to give at least a brief description of these studies? Are they experimental studies or are they to be based on the kind of scattered information found in the literature and reported in Appendix III? If they are experimental, how many of each kind of building will be sampled and when can the results be expected? What will ARB do if it can't satisfy the requirement of the Code to provide the quantitative information needed to establish a "relative contribution"?

Does the Code include occupational exposures in "indoor environments"? How are such exposures factored into the ARB evaluation?

p.A23, para.3: Sunderman et al. (1989) have confirmed earlier work by Solomons et al. (1982) that showed the extent of nickel absorption from food is generally less than 1%. Sunderman et al. reported an average absorption of 27% from water after a 12-hour fast. Solomons et al. showed that the absorption from milk, coffee, tea and orange juice after fasting was less than it was from water. Thus the extent of absorption depends significantly on temporal patterns of eating and drinking as well as on the nickel content of the foods and beverages consumed.

p.A24, para.1: As more data are accumulated on nickel in diet, the upper range limit seems to be decreasing markedly. For example, the Sunderman et al. (1989) paper referred to above referenced six studies of nickel in diet and the upper limits were 300 ug or less.

p.A25, para.2: Can't the nickel content of California's surface waters be pinned down to better than "less than 70 ug/l"? This range includes zero and thus isn't very useful.

p.A27, para.3: ARB has already estimated the amount of nickel ingested in food and water which must include nickel deposited from the atmosphere. ARB concluded (p.A22, para.2) that "Cutaneous absorption appears negligible relative to total intake." It would therefore seem that trying to estimate Deposition Exposure is either double-counting or irrelevant.

p.A28, para.3: Will the public know what the ISCST model is? I certainly don't.

Table II-6: The title and footnotes should indicate that the concentrations presented represent **estimated potential** exposures unless the people in the area live outdoors. Are the ranges on the left some kind of confidence interval about the mean? If so, the footnotes should indicate that the ranges represent likely values of **mean** nickel concentrations? The second footnote is confusing. It says the people enumerated at the right are exposed to as many as five different concentrations at the same time! The cumulative frequency is expressed opposite from the way it is customarily done. Why not recast the data to include all the probabilities and present the information in one cumulative frequency distribution?

Whenever I see the results of dispersion models, I feel a burning need for a reality check. Dispersion models always seem to overestimate actual concentrations. Modelers used to take delight in projecting the concentrations of substances emitted from Inco's "Superstack" in Sudbury, Ontario. Needless to say, the projections were always frightening. Finally, the Ontario Ministry of the Environment operated eight hi-vol samplers in the Sudbury area for two years. The Ministry used wind direction, nickel and sulfate concentrations to select samples collected when the sampler at least had the potential to be impacted by the plumes from one or both of the two large nickel smelters in the area. Despite this deliberate attempt to sample the plumes, the arithmetic mean nickel concentration in 1235 samples was only 21 ng Ni/m^3; the geometric mean concentration was only 5 ng Ni/m^3!

Meanwhile, back in Bakersfield, the largest individual concentration of nickel **observed** in the second half of 1985 was 69 ng Ni/m^3. The 95% confidence limits for the geometric mean were 14 - 24 ng Ni/m^3. Most of the means estimated by dispersion **modeling** were very much higher than the means estimated from the observations. Can this discrepancy be explained by the location of the sampler?

Are there no programs for measuring actual concentrations at California "hot spots"?

p.A30, para.2: I believe this entire page is misleading. The use of the words "determination", "found", "demonstrate" and "concentration" without "estimated" in front of them make this sound like a physical experiment instead of a theoretical calculation. It goes on to say that unmodeled sources will raise the concentrations still further. In reality, the nickel emitted from **all** sources resulted in an **observed** mean that was in the lowest concentration range estimated by modeling. The modeling predictions should be compared with the observed data to provide some perspective.

p.A34, line 1: This sentence is true but very little nickel is used in the pure form. Most of it is used in ferrous and non-ferrous alloys.

p.A34, para.2: Figure III-1 shows more like 160,000 tons imported and 10,000 tons exported, differing from the figures given in this paragraph.

p.A34, para.3: Hanna's facilities in Oregon were reopened by Glenbrook Nickel in 1989. The smelter is currently processing ore that Hanna stockpiled before it closed the operation.

p.A36, para.1: AMAX closed its Louisiana nickel operations in the last quarter of 1985. We understand that a small section of the refinery has been reopened in a joint venture with Shell Oil to recover metals from spent petroleum catalysts.

p.A36, para.2: We don't believe that the amount of nickel recovered from secondary aluminum smelting is significant.

p.A39, para.3: We believe the forecast rate of nickel demand in the US is much too high. However, I am not permitted to suggest an alternative.

p.A40, para.1: This paragraph implies that stainless steel scrap will be a more important source of nickel for the US than will imported nickel. This is clearly not the case. While there are no primary nickel producers in California, Ni-Cal has been considering for years the possibility of treating laterite deposits at Gasquet Mountain in Del Norte county.

p.A40, para.2: Has ARB considered using the data on routine releases reported under the SARA III regulations as part of its estimate of nickel emissions? I guess it wouldn't cover "inadvertant" emissions such as from combustion of fuels nor emissions from mobile sources but it might be a useful estimate for a broad spectrum of other industries. The preliminary data released by Congressman Waxman on March 22, 1989 showed that only 11,502 pounds of metallic nickel and 6,807 pounds of unspecified nickel compounds were reported in California for the first reporting period. I expect these numbers will have increased in later periods as more companies become aware of their responsibility to report. The automatic reporting requirement should make it easy for ARB to update and refine its estimate.

p.A41: I believe several of the indicated nickel species in emissions have been improperly indicated. Combustion of fossil fuels also releases oxidic nickel, as would iron and steel foundaries. Metallic nickel is very unlikely to be released from sewage sludge incineration. I have not checked the estimated annual emissions.

p.A43: Since the combustion of petroleum products seems to be the major anthropogenic source of ambient nickel in California, ARB should expend some effort to reduce the enormous uncertainty in the estimated amount of nickel emitted by oil combustion. A range of "10.5 to 345 tons" is so broad as to be useless. Appendix V shows that some current nickel assays of oil products is required to reduce the uncertainty in this estimate. In fact, analyzing residual oil alone would probably be sufficient. Obtaining this information should not be difficult or costly.

p.A45: I would not expect metallic nickel to be emitted from a sewage sludge incinerator as indicated in Table III-1. An EPA contractor has just speciated the emissions from two sewage sludge incinerators and found no metallic nickel. The nickel was found to exist in widely varying proportions in soluble and oxidic phases. E.P. Crumpler of the EPA (204-475-7310) could provide details of the tests.

p.A46: Practically no oxygen is emitted at nickel anodes in commercial plating baths and only about 3% of the current releases hydrogen at the cathode. Furthermore, wetting agents are added to the bath to control the formation and collapse of the hydrogen bubbles in order to get a smooth plate. Thus it is not surprising that NIOSH (1984) found very low concentrations of airborne nickel around even unventilated nickel plating baths. The highest measured personal sample was 6 μg Ni/m^3 and the highest measured area sample was 7 μg Ni/m^3. Eight of ten personal samples and 39 of 42 area samples were below the limit of detection. NIOSH concluded that the nickel plating baths tested did not need control ventilation.

ARB may have been aware of the low emissions from nickel plating baths and assumed that metallic nickel released during grinding, polishing and cutting operations are the major source of nickel emitted from plating operations. However, about 90% of the nickel plating done in the US involves the deposition of bright coatings so the plated objects are not ground, polished or cut. Thus metallic emissions should also be small.

Appendix V does not back up the estimated 1.4 tons of nickel emitted from platers in the SCAQMD. Some support should be presented for this figure.

p.A48, para.3: The insoluble nickel in fly ash is oxidic nickel, not nickel oxide. There is a substantial difference in the two terms.

p.A49, para.3: The potential to have high concentrations of nickel in airborne particles of soil derived from serpentine rock indicate the importance of recommendation 1.

p.A58, para.2: It states here that fine airborne particles of nickel "...undergo chemical reactions...". I would like to know what these chemical reactions are because the TSD states, on p.A2, para.4, that "Little information is available, at present, about the chemical transformations of nickel and its compounds in the atmosphere."

I have included as Appendix A, some thermodynamic calculations I submitted to the EPA in 1983 in an attempt to answer which, if any, reactions involving inorganic nickel compounds are thermodynamically feasible in different environments. They supported the observations in the literature on the nickel species emitted from various high temperature sources. They indicate the following relationships at ambient conditions:

- sulfides cannot be formed from metal, oxide or sulfate;
- sulfate cannot react to form other common nickel compounds;
- metal and oxide could be concerted to sulfate if the kinetics were favourable;

- complex oxides are more stable than NiO.

p.A58, para.3: Does the first sentence imply ARB thinks nickel carbonyl exists in California air despite its short half-life? EPA (1986) said it had reviewed the available data and did not expect nickel carbonyl to occur in ambient air in significant quantities.

I would like to see a reference that demonstrates the formation of nickel carbonyl during the combustion of fossil fuels. Inco produces refined nickel by the carbonyl process in which the carbonyl is decomposed at temperatures of about 230 C.

p.A59, para.1: Nickel carbonyl has been used industrially since 1902 although we are not aware of any uses of carbonyl in California. What is the "process of pigmentation" and is it used in California?

p.A59, para.2: Appendix A provides some information on the possible transformations of nickel that might take place in ambient air. I disagree with the assumption that Schroeder et al. (and too many other authors) make for two reasons; (1) source sampling has shown that combustion sources can emit soluble nickel as well as oxidized nickel; and (2) because the insoluble nickel emitted from a combustion process is present as complex oxides, not as nickel oxide.

Appendix I, para. 7.5: A statement is made about the degree of agreement between laboratories on the different methods of analyzing for lead. What methods were tested for nickel and how well did the different laboratories agree?

Appendix II, p.6: It would be unfortunate if readers thought Inco advocated supporting a filter with 0.2 μm pore size on a coarser filter. This is bad practice. We have also expressed our concern to the analysts in the Southern Laboratory Branch about their practice of minimizing the volumes of liquids, particularly wash solutions. The geometry of the commercial filter holder makes it difficult to thoroughly wash the area around the perimeter of the supporting membrane. It is preferable to use larger volumes of solution and evaporate it later if necessary.

Inco's Dr. Zatka has continued to refine the speciation protocol to compensate for some of the surprises encountered in real-world samples. The latest version is attached as Appendix B.

The next series of comments all refer to Appendix III.

p.1, para.3: Nickel in insoluble fly ash is not present as nickel oxide. It is present in complex oxides with other metals.

p.2, para.4: Alexander et al. (1983) showed that, if nickel carbonyl existed in mainstream cigarette smoke, it must have been below the 0.1 ppm detection limit of their Fourier-transform infrared spectroscope.

p.3, para.2: Is ARB undertaking the research outlined here with respect to the contamination of the indoor environment by cigarette smoking.

p.8, para.2: I urge Dr. Shaloum to try to estimate the probability distribution of the total indoor concentration of nickel from the data she has identified. Until these separate sources are combined and weighted according to typical number of smokers or frequency of wood burning, etc., it will not be possible to put the indoor environment into perspective relative to the outdoor environment. On the basis of the preliminary data in Part A, it looks like ARB should concentrate on the indoor environment if it wants to make significant reductions in total nickel exposure.

REFERENCES

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Haas CN and Scheff PA; **Estimation of averages in truncated samples**; Environ. Sci. Technol. 24:912-919

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Solomons NW, Viteri F, Shuler TR and Nielsen FH (1982); **Bioavailability of nickel in man: Effects of foods and chemically-defined dietary constituents on the absorption of inorganic nickel**; J Nutr 112:39-50

Sunderman FW, Hopfer SM, Sweeney KR, Marcus AH, Most BM and Creason J (1989); **Nickel absorption and kinetics in human volunters**; Proc. Soc. Exp. Biol. Med. 191: 5-11

Table 1: ARB's database on airborne nickel concentrations

Air basin Location sampled	Date of first sample (mm-dd-yy)	Date of last sample (mm-dd-yy)	Total no. of samples	No. of samples below limit of detection
San Francisco Bay Area				
Concord	07-06-85	01-31-89	186	2
Fremont	07-06-85	01-28-89	186	4
Richmond	07-06-85	01-28-89	193	0
San Francisco*	07-06-85	01-28-89	176	0
San Jose	07-06-85	01-28-89	197	0
South Central Coast				
Santa Barbara*	04-04-85	01-28-89	115	1
Simi Valley*	01-09-85	01-28-89	139	8
South Coast				
El Monte	08-12-84	01-28-89	327	0
Los Angeles	03-26-85	12-29-88	143	0
North Long Beach	02-13-85	01-22-89	144	0
Riverside**	02-21-85	01-22-89	148	5
Upland	02-10-85	01-22-89	139	2
San Diego				
Chula Vista	01-07-85	01-28-89	142	2
El Cajon	03-31-85	01-16-89	140	3
Sacramento Valley				
Citrus Heights	06-30-85	01-28-89	197	4
San Joaquin Valley				
Fresno	10-22-85	01-28-89	169	0
Bakersfield	07-07-85	01-28-89	186	0
Merced	09-16-85	01-28-89	146	2
Stockton	04-26-86	01-28-89	143	0
Modesto	06-12-85	01-22-89	190	1
			3410	34

* Sampling site moved once but remained in same general vicinity.

** Referred to as "Rubidoux" in CARB database.

Table 2: Concentrations of nickel below the limit of detection as estimated by ARB and Inco Ltd.

Air Basin / Location sampled	ARB data and estimates[#] Total No. of samples	% of samples BLOD*	Est. conc. of samples BLOD* ng Ni/m^3	Inco Ltd. data and estimates[+] Total No. of samples	No. of samples BLOD*	Est. conc. of samples BLOD* ng Ni/m^3
San Francisco Bay Area						
Concord	80	0	0.9	186	2	0.8
Fremont	70	1	0.8	186	4	0.76
South Central Coast						
Santa Barbara	50	0	0.9	115	1	0.85
Simi Valley	64	5	0.7	139	8	0.74
South Coast						
Riverside	60	7	0.7	148	5	0.75
Upland	62	2	0.8	139	2	0.80
San Diego						
Chula Vista	58	2	0.8	142	2	0.77
El Cajon	49	0	0.8	140	3	0.78
Sacramento Valley						
Citrus Heights	84	0	0.8	197	4	0.77
San Joaquin Valley						
Merced	46	0	0.8	146	2	0.72
Modesto	81	1	0.8	190	1	0.76

Taken from Tables II-1 and II-2 of the Part A Report, Technical Support Document

\+ Calculated from the ARB database on airborne nickel described in Table 1.

* BLOD = below limit of detection.

Table 3: Statistical summary of nickel data for the period November 1985 through October 1986

Air basin Location sampled	No. of samples	Max. conc.,* ng Ni/m^3	Geom. mean conc., ng Ni/m^3	Geom. std. dev.	95% Conf. int. of geom. mean, ng Ni/m^3
San Francisco Bay Area					
Concord	56	9	2.80	1.62	2.47 - 3.18
Fremont	53	11	2.57	1.79	2.20 - 3.01
Richmond	54	12	3.82	1.68	3.33 - 4.39
San Francisco	49	19	4.21	1.85	3.54 - 5.00
San Jose	57	25	9.24	1.67	8.09 - 10.56
South Central Coast					
Santa Barbara	28	9	4.32	1.47	3.75 - 4.98
Simi Valley	33	16	3.76	2.15	2.90 - 4.88
South Coast					
El Monte	34	19	9.09	1.78	7.49 - 11.03
Los Angeles	28	18	6.41	2.14	4.84 - 8.50
North Long Beach	29	18	7.86	1.84	6.30 - 9.81
Riverside	30	16	4.01	2.37	2.94 - 5.46
Upland	30	9	3.81	2.13	2.91 - 4.[redacted]
San Diego					
Chula Vista	30	16	3.93	1.95	3.09 - 4.99
El Cajon	30	8	3.24	1.77	2.64 - 3.97
Sacramento Valley					
Citrus Heights	59	6	2.50	1.72	2.18 - 2.87
San Joaquin Valley					
Fresno	57	14	4.92	1.62	4.34 - 5.58
Bakersfield	57	77	17.82	2.06	14.77 - 21.50
Merced	42	19	4.46	2.32	3.46 - 5.75
Stockton	29	45	12.67	1.89	10.05 - 15.97
Modesto	58	19	3.54	2.06	2.94 - 4.26

* The minimum concentrations were 3 for San Jose, 2 for Santa Barbara, 2 for Fresno, 2 for Bakersfield and 1 for all other locations.

Table 4: Statistical summary of the ARB nickel database through January 1989

Air basin Location sampled	No. of samples	Max. conc.,* ng Ni/m^3	Geom. mean conc., ng Ni/m^3	Geom. std. dev.	95% Conf. int. of the mean, ng Ni/m^3
San Francisco Bay Area					
Concord	186	11	2.67	1.75	2.46 - 2.89
Fremont	186	12	2.87	1.92	2.61 - 3.15
Richmond	193	13	3.67	1.65	3.42 - 3.94
San Francisco	176	22	3.92	1.94	3.55 - 4.32
San Jose	197	35	8.96	1.67	8.34 - 9.63
South Central Coast					
Santa Barbara	115	10	3.82	1.67	3.48 - 4.20
Simi Valley	139	16	2.88	2.02	2.56 - 3.24
South Coast					
El Monte	327	45	7.08	1.74	6.67 - 7.52
Los Angeles	143	24	5.91	2.00	5.28 - 6.62
North Long Beach	144	33	7.93	1.81	7.20 - 8.74
Riverside	148	16	4.18	2.10	3.71 - 4.71
Upland	139	15	4.15	1.91	3.73 - 4.62
San Diego					
Chula Vista	142	16	3.37	1.94	3.02 - 3.76
El Cajon	140	11	2.75	1.84	2.49 - 3.04
Sacramento Valley					
Citrus Heights	197	9	2.39	1.81	2.20 - 2.60
San Joaquin Valley					
Fresno	169	23	4.88	1.76	4.48 - 5.31
Bakersfield	186	94	12.79	2.37	11.30 - 14.48
Merced	146	26	3.62	2.19	3.19 - 4.11
Stockton	143	45	7.20	2.21	6.32 - 8.20
Modesto	190	19	3.19	1.98	2.89 - 3.52

* The minimum concentrations were 2 for Bakersfield, 3 for San Jose and 1 for all the other locations. Locations with BLOD determinations are shown in Table 1.

Table 5: Results of Kolmogorov-Smirnov Goodness-of-Fit tests for ambient nickel concentrations

Air Basin / Location sampled	Hypothesized Distribution: Lognormal D*	Lognormal +	Normal D*	Normal +
San Francisco Bay Area				
Concord	0.173	< 0.001	0.196	< 0.001
Fremont	0.135	0.002	0.184	< 0.001
Richmond	0.143	< 0.001	0.191	< 0.001
San Francisco	0.134	0.004	0.234	< 0.001
San Jose	0.081	0.148	0.131	0.002
South Central Coast				
Santa Barbara	0.189	< 0.001	0.150	0.012
Simi Valley	0.170	< 0.001	0.179	< 0.001
South Coast				
El Monte	0.082	0.025	0.142	< 0.001
Los Angeles	0.116	0.042	0.136	0.010
North Long Beach	0.104	0.087	0.134	0.011
Riverside	0.185	< 0.001	0.121	0.027
Upland	0.161	0.001	0.123	0.030
San Diego				
Chula Vista	0.120	0.033	0.186	< 0.001
El Cajon	0.164	0.001	0.169	< 0.001
Sacramento Valley				
Citrus Heights	0.181	< 0.001	0.192	< 0.001
San Joaquin Valley				
Fresno	0.100	0.067	0.124	0.011
Bakersfield	0.061	0.502	0.204	< 0.001
Merced	0.118	0.034	0.208	< 0.001
Stockton	0.096	0.146	0.188	< 0.001
Modesto	0.143	< 0.001	0.228	< 0.001

* D is the maximum difference between the observed cumulative frequency distribution and the hypothesized cumulative frequency distribution.

\+ is the probability of incorrectly rejecting the hypothesized distribution as the true distribution from which the sample was drawn.

Table 6: Long-term trends in ambient nickel concentrations

Air basin Location sampled	Slope,* $(cal.yrs)^{-1}$	Std. error, $(cal.yrs)^{-1}$	Level of + significance	r^2, %
San Francisco Bay Area				
Concord	-0.0068	0.0378	0.86	0.02
Fremont	0.1337	0.0451	0.003	4.56
Richmond	-0.0161	0.0333	0.63	0.12
San Francisco	-0.0848	0.0454	0.06	1.96
San Jose	-0.0316	0.0337	0.35	0.45
South Central Coast				
Santa Barbara	-0.0365	0.0408	0.37	0.70
Simi Valley	-0.0081	0.0497	0.87	0.02
South Coast				
El Monte	0.1050	0.0222	0	6.45
Los Angeles	-0.0185	0.0507	0.72	0.09
North Long Beach	0.0281	0.0417	0.50	0.32
Riverside	0.1612	0.0504	0.002	6.54
Upland	0.1022	0.0460	0.03	3.48
San Diego				
Chula Vista	0.0476	0.0459	0.30	0.76
El Cajon	0.0110	0.0452	0.81	0.04
Sacramento Valley				
Citrus Heights	0.0414	0.0397	0.30	0.55
San Joaquin Valley				
Fresno	0.0112	0.0452	0.80	0.04
Bakersfield	-0.3332	0.0531	0	17.65
Merced	-0.0815	0.0756	0.28	0.80
Stockton	-0.3870	0.0732	0	16.53
Modesto	0.0059	0.0465	0.90	0.01

* Slope is the term b obtained by regression analysis of an exponential model (Nickel concentration = exp (a + b * calendar years)) over the periods of data availability shown in Table 1.

\+ Level of significance is the probability of incorrectly rejecting the hypothesis that the geometric mean ambient nickel concentrations do not vary from year to year.

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Table 7: Statistical summary of the ARB nickel database projected to January 1, 1990

Air basin Location sampled	No. of samples	Max. conc.,* ng Ni/m^3	Geom. mean conc., ng Ni/m^3	Geom. std. dev.	95% Conf. int. of the mean, ng Ni/m^3
San Francisco Bay Area					
Concord	186	11	2.67	1.75	2.46 - 2.89
Fremont+	186	12	4.08	1.14	3.17 - 5.24
Richmond	193	13	3.67	1.65	3.42 - 3.94
San Francisco+	176	22	3.13	1.14	2.42 - 4.05
San Jose	197	35	8.96	1.67	8.34 - 9.63
South Central Coast					
Santa Barbara	115	10	3.82	1.67	3.48 - 4.20
Simi Valley	139	16	2.88	2.02	2.56 - 3.24
South Coast					
El Monte+	327	45	10.50	1.09	8.82 - 12.50
Los Angeles	143	24	5.91	2.00	5.28 - 6.62
North Long Beach	144	33	7.93	1.81	7.20 - 8.74
Riverside+	148	16	6.39	1.16	4.80 - 8.52
Upland+	139	15	5.50	1.15	4.19 - 7.21
San Diego					
Chula Vista	142	16	3.37	1.94	3.02 - 3.76
El Cajon	140	11	2.75	1.84	2.49 - 3.04
Sacramento Valley					
Citrus Heights	197	9	2.39	1.81	2.20 - 2.60
San Joaquin Valley					
Fresno	169	23	4.88	1.76	4.48 - 5.31
Bakersfield+	186	94	5.13	1.17	3.77 - 6.99
Merced	146	26	3.62	2.19	3.19 - 4.11
Stockton+	143	45	2.98	1.20	2.09 - 4.23
Modesto	190	19	3.19	1.98	2.89 - 3.52

* The minimum concentrations were 2 for Bakersfield, 3 for San Jose and 1 for all the other locations. Locations with BLOD determinations are shown in Table 1.

\+ Summary statistics for these locations apply only to Jan. 1, 1990. The geometric standard deviations are for the distribution of means around the predicted mean.

Table 8: Determination of the insoluble fraction of ambient airborne nickel in Bakersfield[a]

Sampling method	Sampling date	Analyst	Insoluble nickel, %	Reference
CARB Low-vol	Jan. (2,8,14,20,26) 1986	CARB SLB	59.9	Rabano et al.; Speciation of Nickel in Ambient Particulate Matter; presented at Air & Waste Management Association meeting, June 25-30, 1989
ditto	Mar. (3,15,22,27) 1986	ditto	16.7	
ditto	May (2,8,14,20,26) 1986	ditto	77.7	ditto
ditto	July (1,7,13,19,25,31) 1986	ditto	29.0	ditto
ditto	Sept.(5,11,16,23,29) 1986	ditto	73.1	ditto
ditto	Nov. (4,10,16,22,28) 1986	ditto	73.8	ditto
ditto	Filter # 17642 [b]	ditto	55.4	Table II, Appendix II of Tech. Support Document
ditto	Filter # 17641 [b]	ditto	56.2	ditto
ditto	Filter # 89000782 [b]	ditto	63.3	ditto
ditto	Filter # 18166 [b,c]	ditto	64.3	ditto
ditto	Filter # 17890 [b]	ditto	68.0	ditto
Hi-vol[d]	May 30 - June 1, 1989	ditto	32.4(27.9, 36.9)[e]	Memo, R. Torre to J. Shikiya, June 22, 1989
ditto	ditto	Inco Ltd.	69.5 (71.4,64.8,72.2,69.7)[e]	Memo, V.J. Zatka to J.S. Warner, June 6, 1989
PM - 10[d]	ditto	CARB SLB	50.5	Memo, R. Torre to J. Shikiya, June 22, 1989
ditto	ditto	Inco Ltd.	55.0 (34.8,63.6,61.4,60.0)[e]	Memo, V.J. Zatka to J.S. Warner, July 8, 1989

(a) CARB SLB analyzed lo-vol filters collected in San Jose in March, May, July, August, October and December and found the % insoluble Ni to be 83, 79, 76, 68.1, 76.8 and 77%.
(b) Dates unknown to me.
(c) Sample taken in Oildale.
(d) 8" x 10" quartz fibre filters compared with 37 mm Teflon filters used in CARB 10-vol sampling.
(e) Figures in ( ) are the determinations made on equal-sized sections of filter

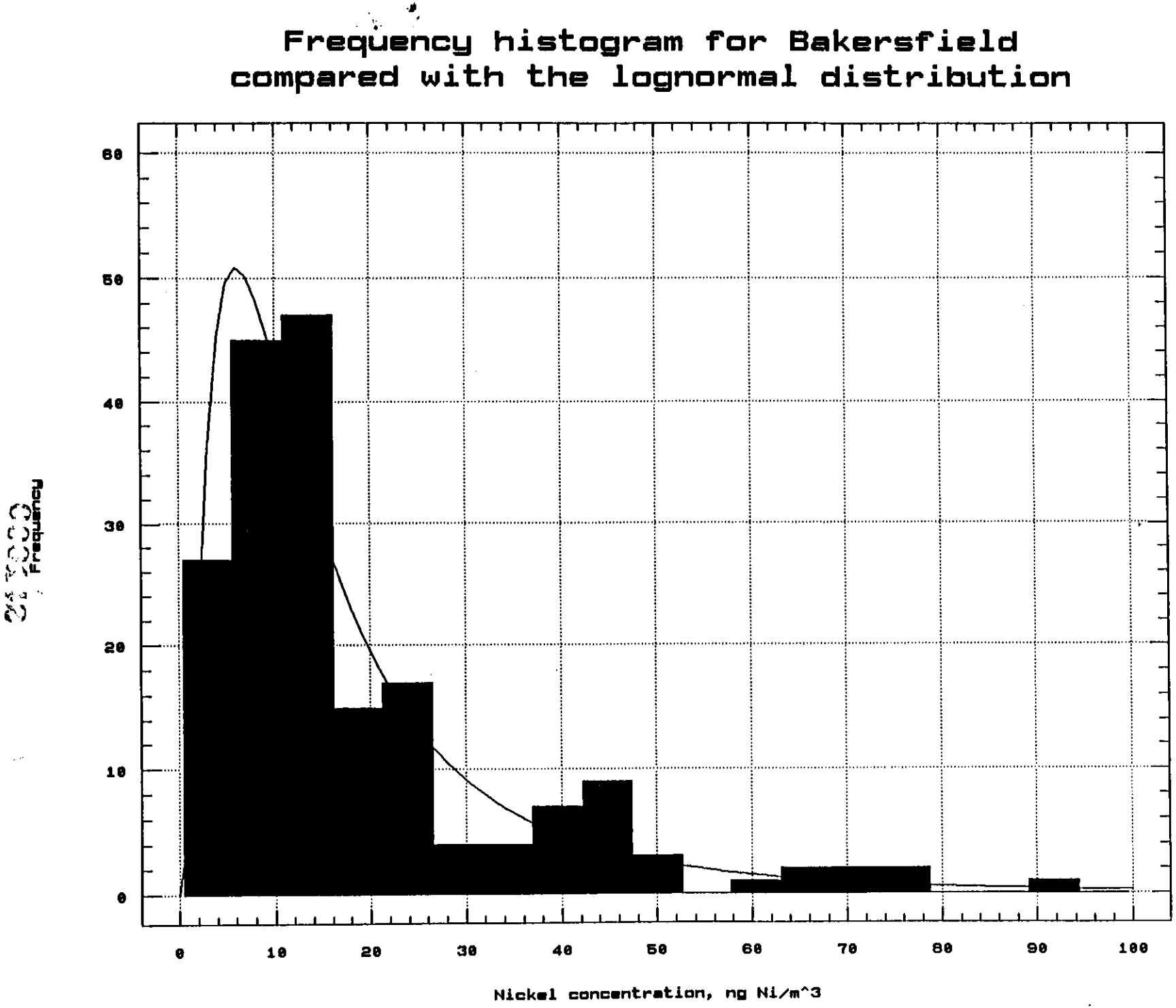
Frequency histogram for Bakersfield
compared with the lognormal distribution
Frequency
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
Nickel concentration, ng Ni/m^3

FIGURE 1

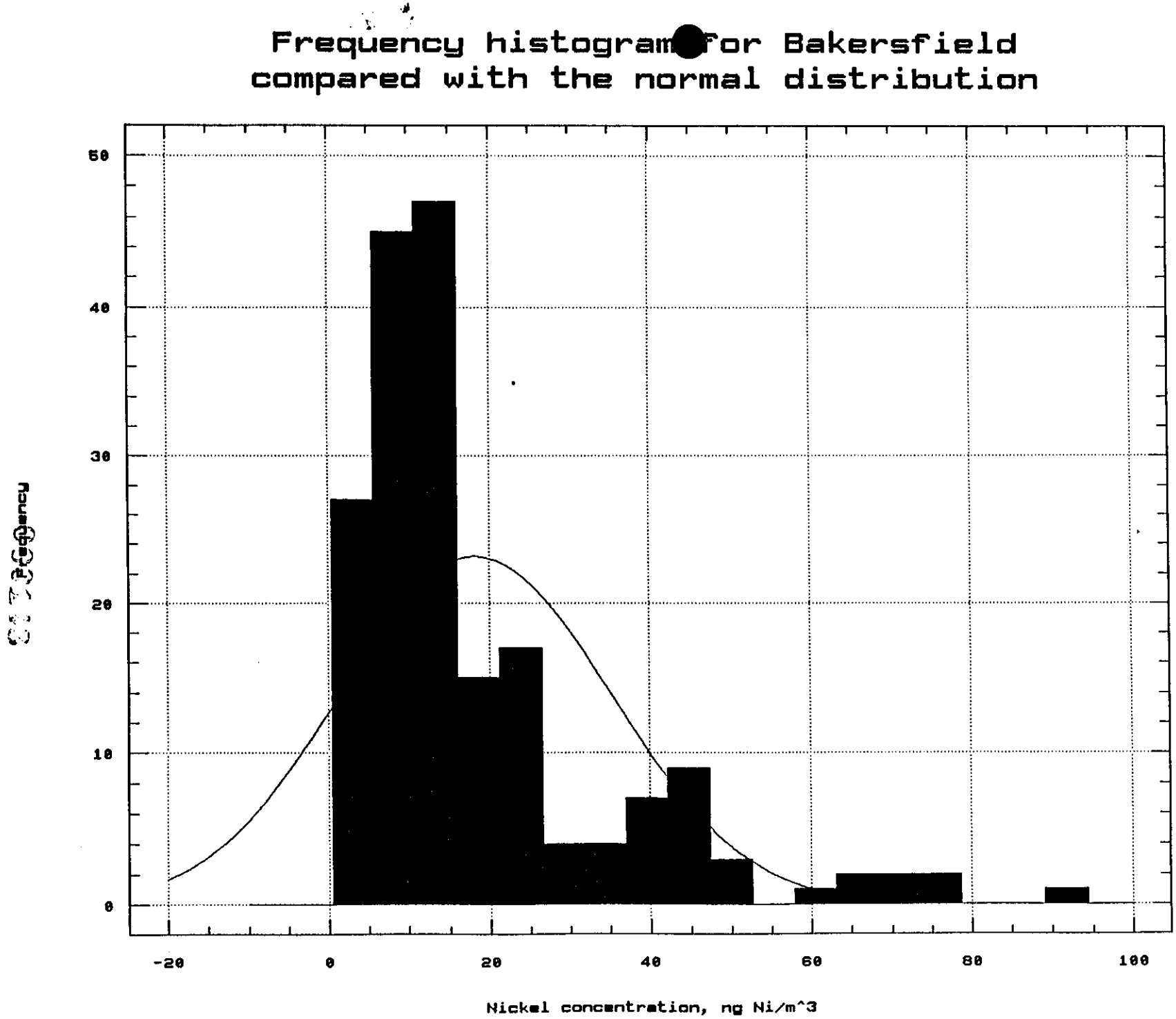
Frequency histogram for Bakersfield
compared with the normal distribution
50
40
30
20
10
0
-20
0
20
40
60
80
100
Nickel concentration, ng Ni/m^3

FIGURE 1a

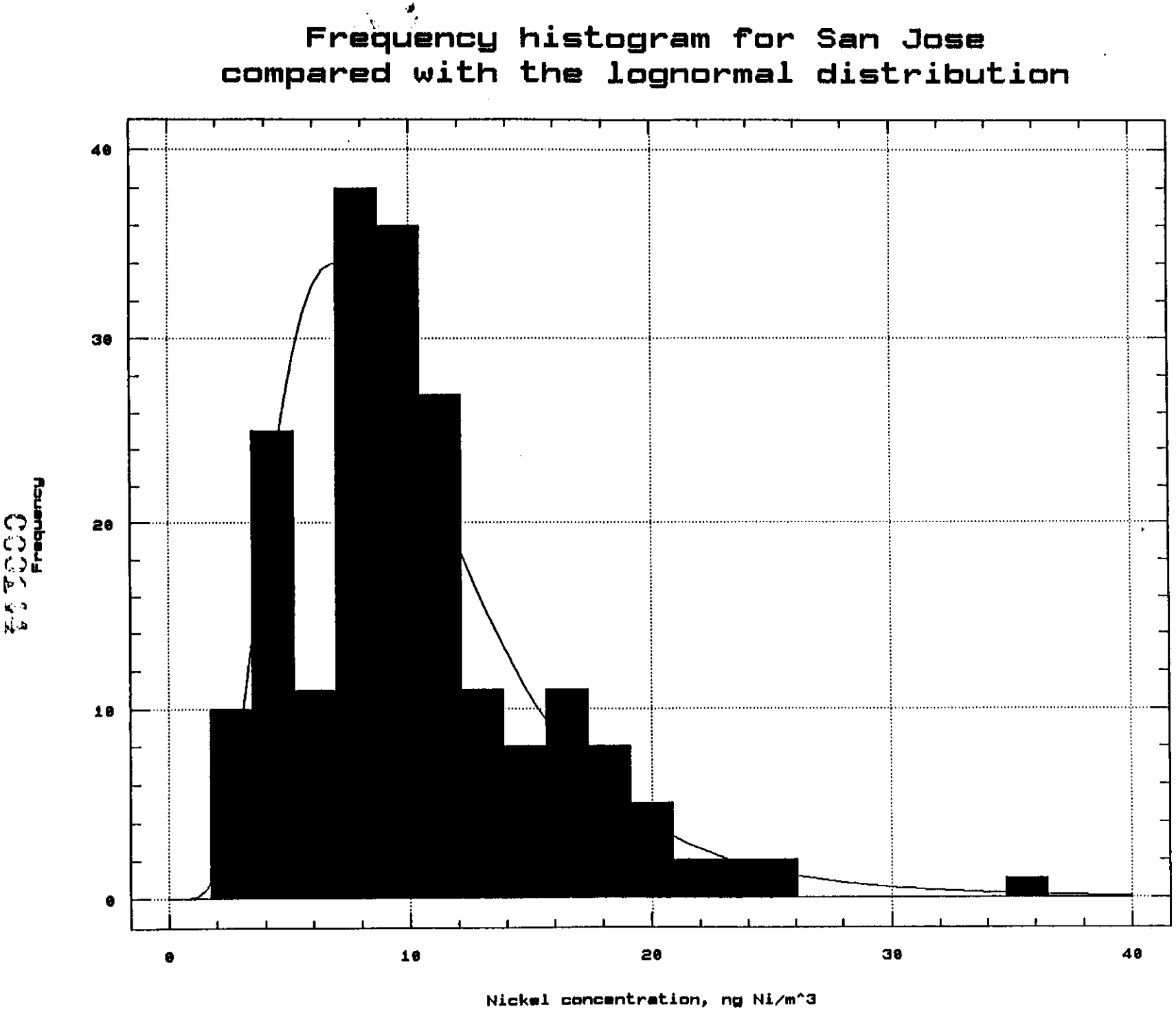
Frequency histogram for San Jose
compared with the lognormal distribution
40
30
20
10
0
Frequency
0
10
20
30
40
Nickel concentration, ng Ni/m^3

FIGURE 2

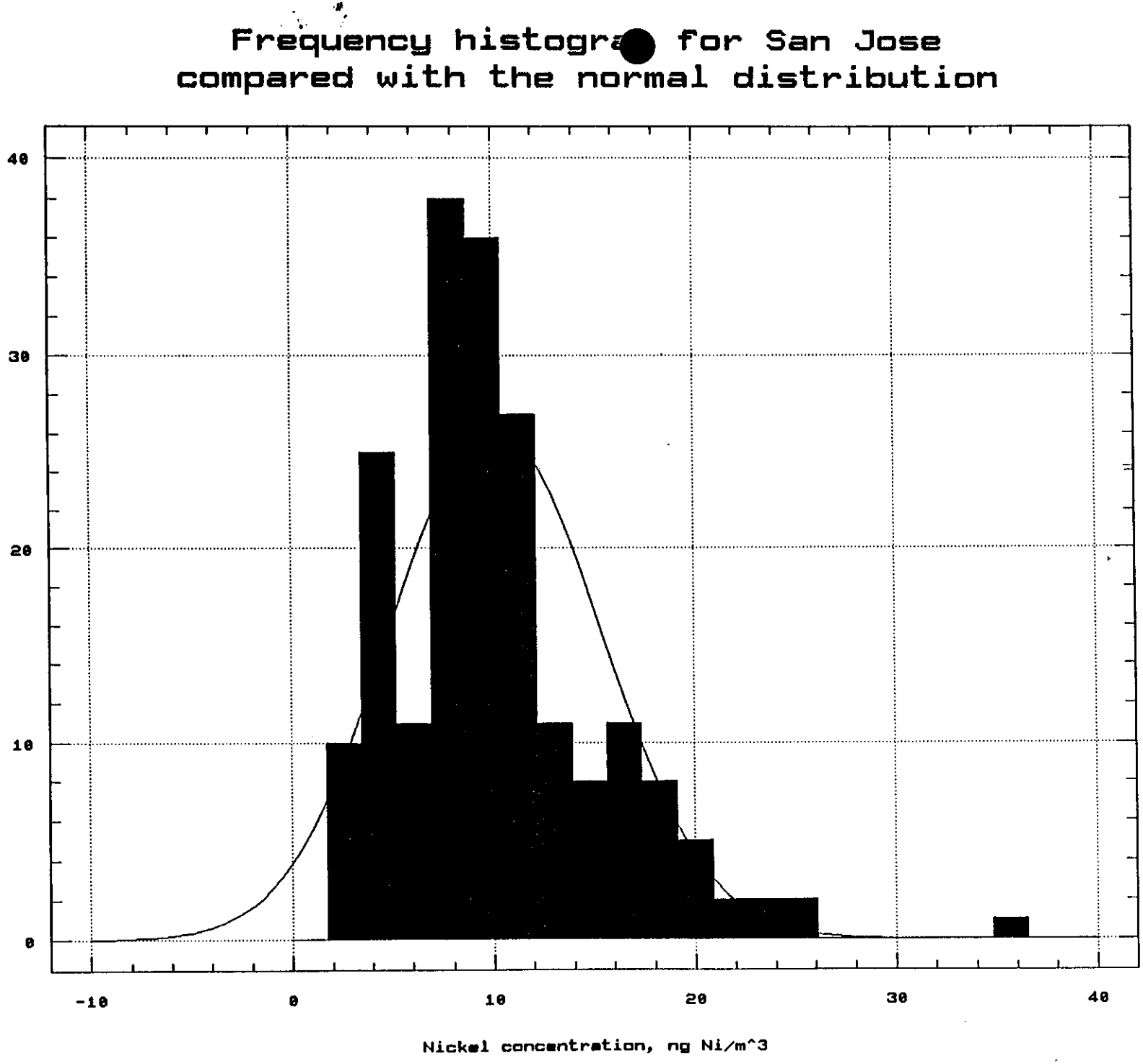
Frequency histogram for San Jose
compared with the normal distribution
40
30
20
10
0
-10
0
10
20
30
40
Nickel concentration, ng Ni/m^3

FIGURE 2a

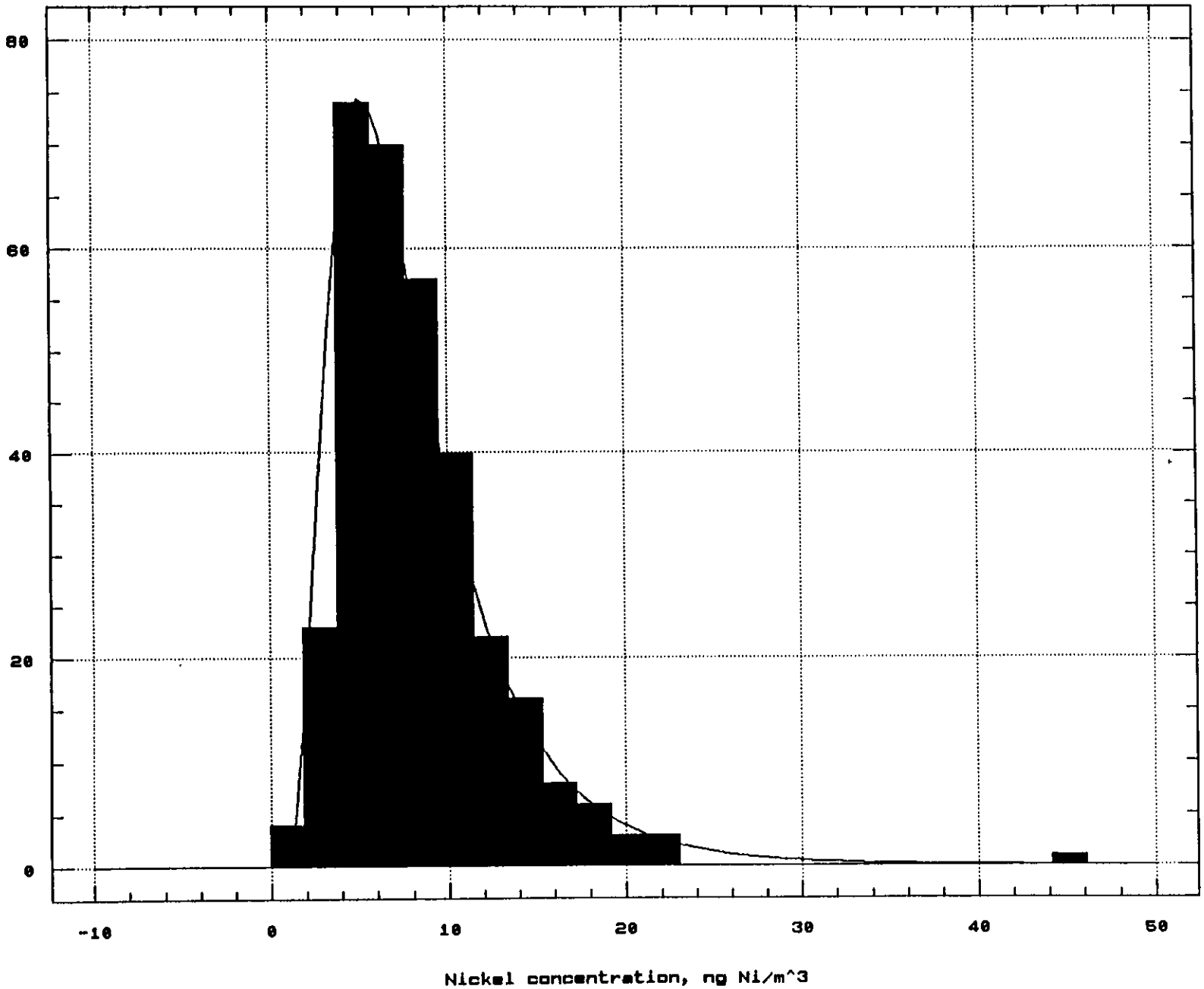
Frequency histogram for El Monte
compared with the lognormal distribution
80
60
40
20
0
-10
0
10
20
30
40
50
Nickel concentration, ng Ni/m^3

FIGURE 3

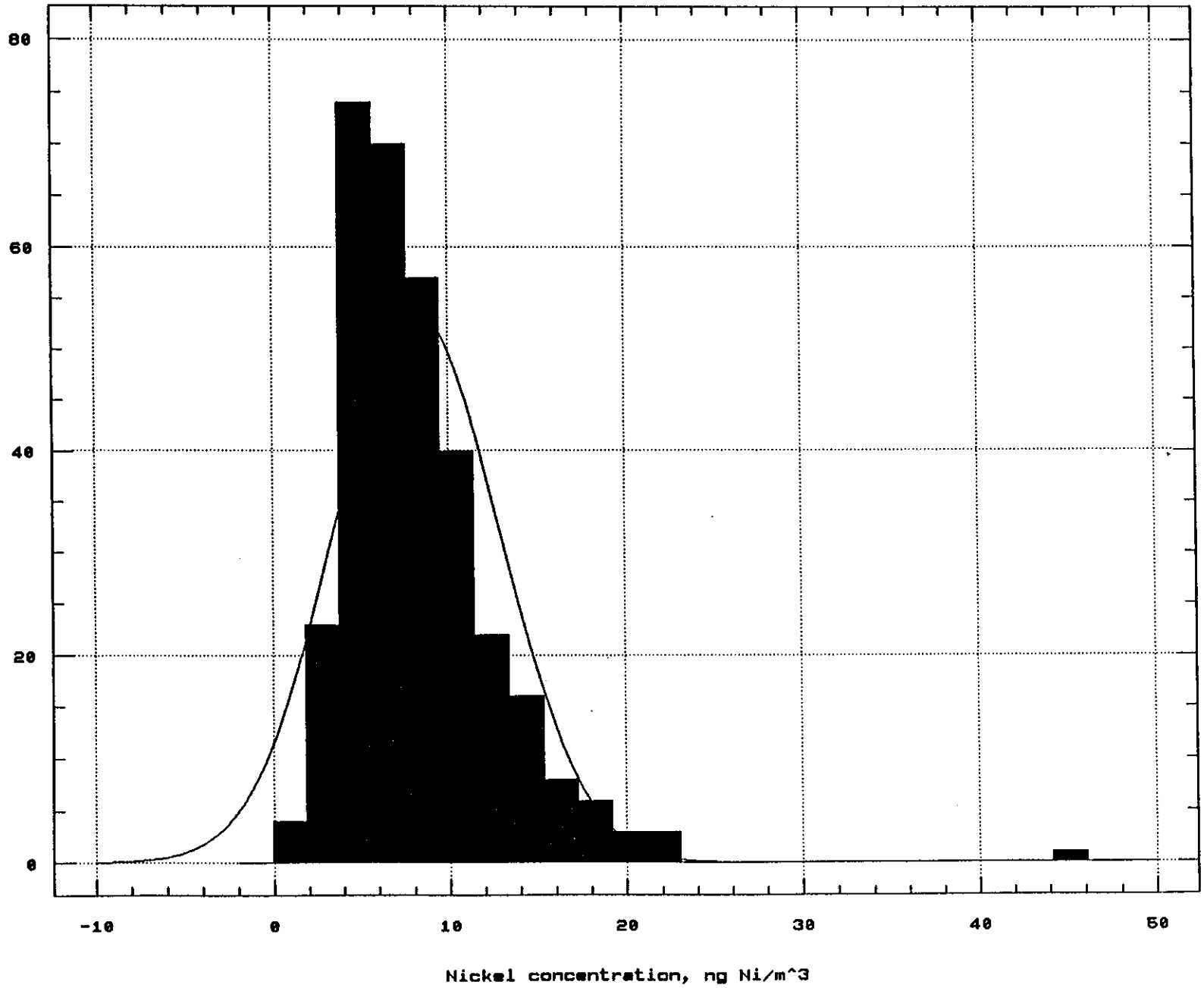
Frequency histogram for El Monte
compared with the normal distribution
80
60
40
20
0
-10
0
10
20
30
40
50
Nickel concentration, ng Ni/m^3

FIGURE 3a

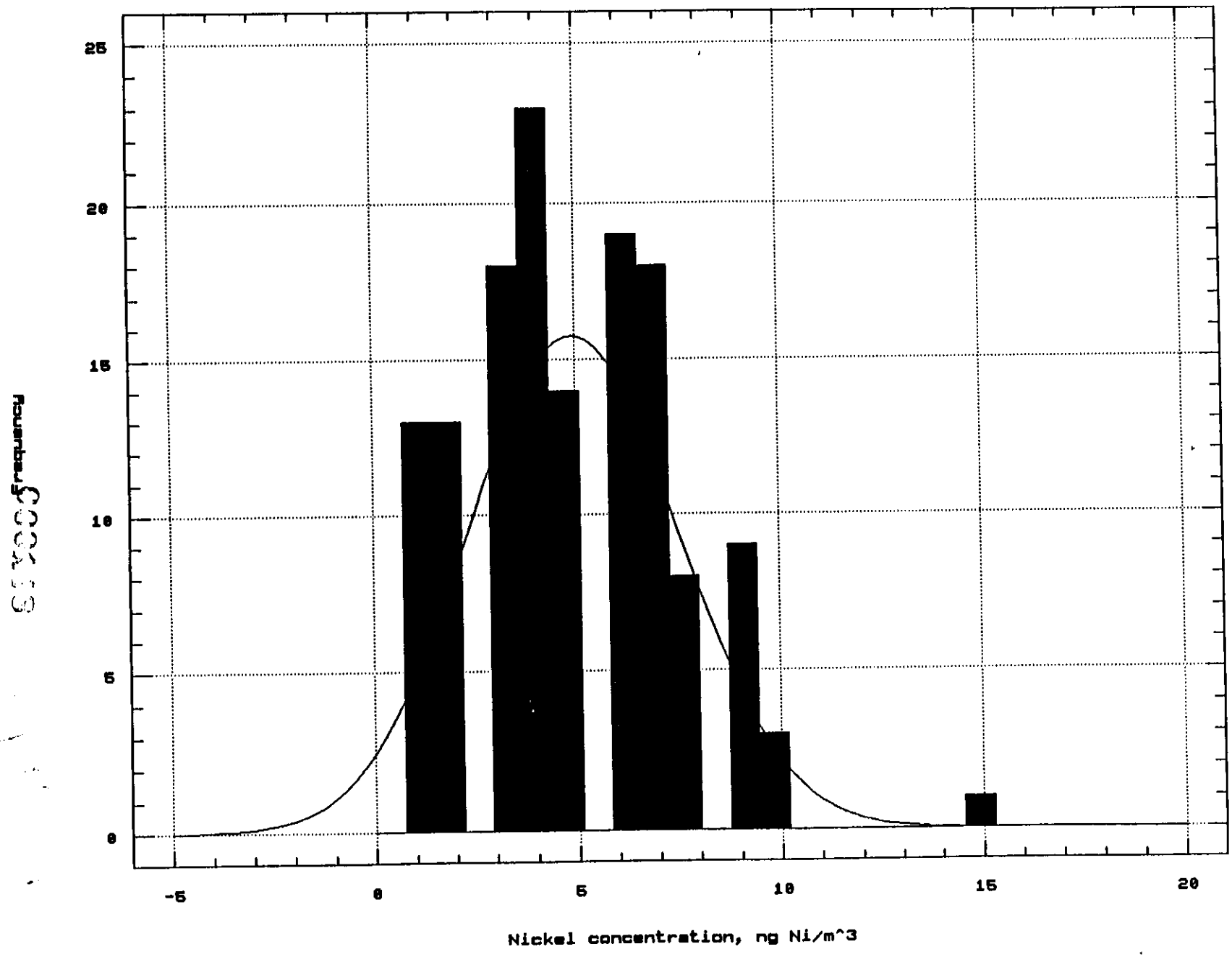
Frequency histogram for Upland
compared with the normal distribution
25
20
15
10
5
0
-5
0
5
10
15
20
Nickel concentration, ng Ni/m^3

FIGURE 4

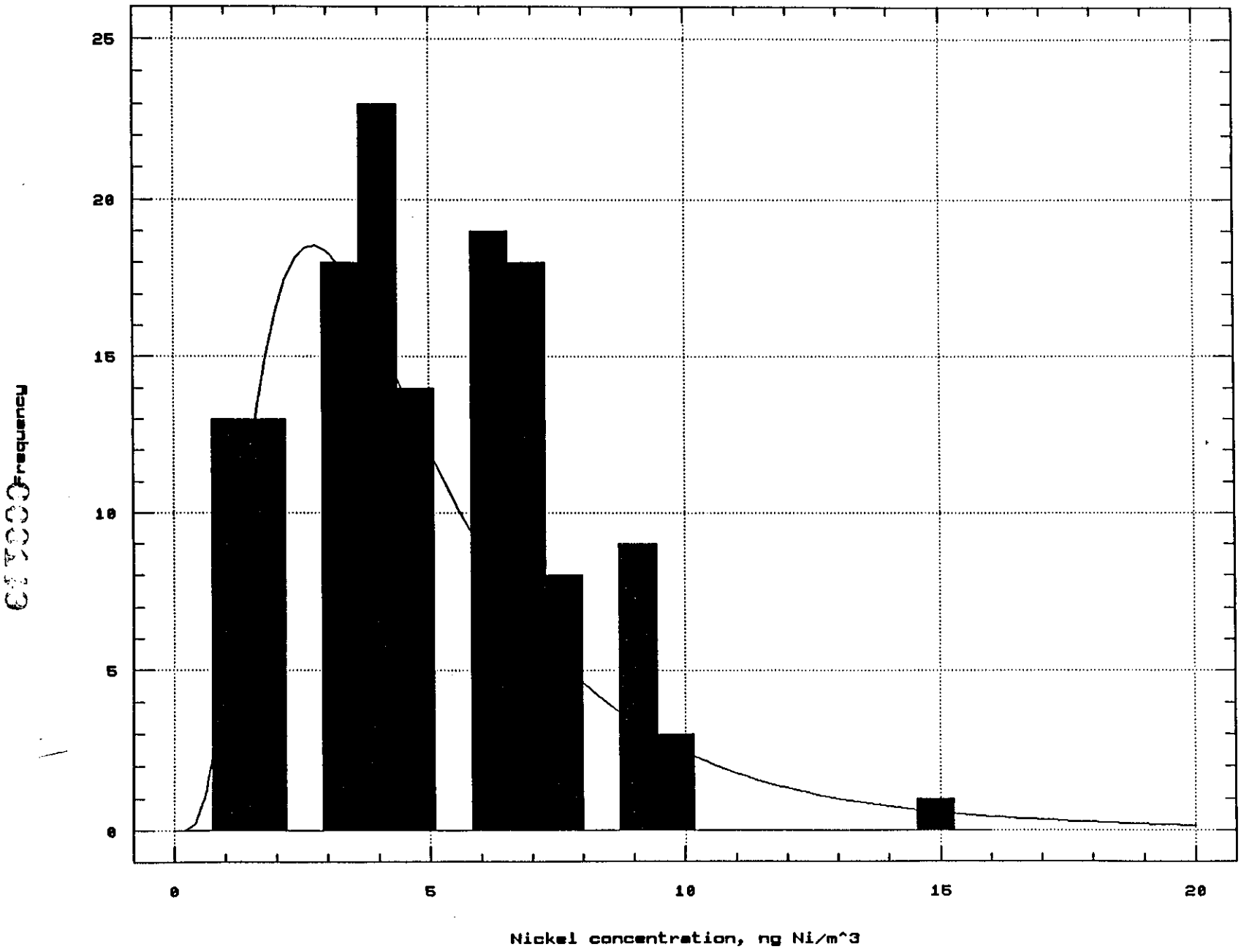
Frequency histogram for Upland
compared with the lognormal distribution
25
20
15
10
5
0
0
5
10
15
20
Nickel concentration, ng Ni/m^3

FIGURE 4a

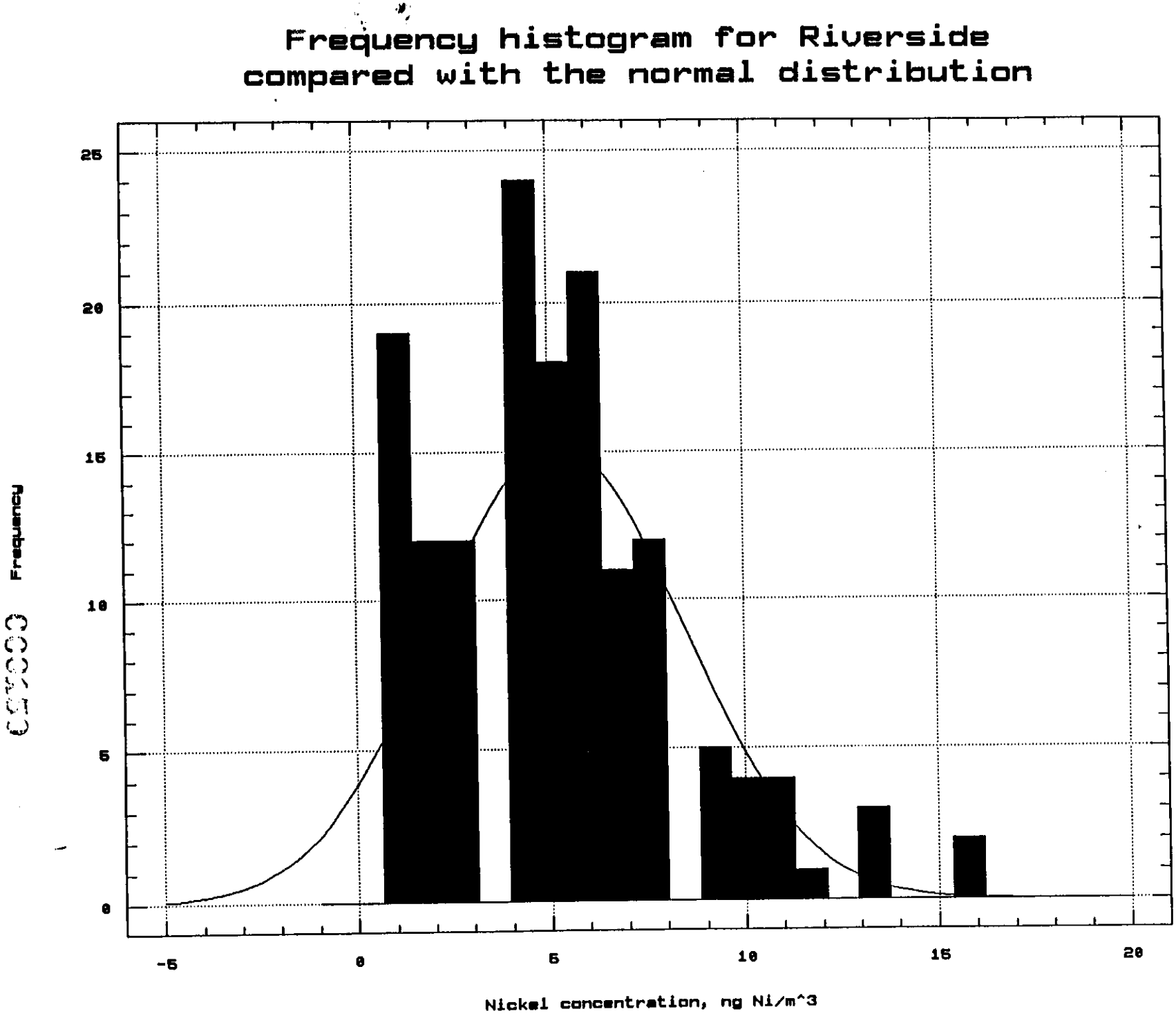
Frequency histogram for Riverside
compared with the normal distribution
Frequency
25
20
15
10
5
0
-5
0
5
10
15
20
Nickel concentration, ng Ni/m^3

FIGURE 5

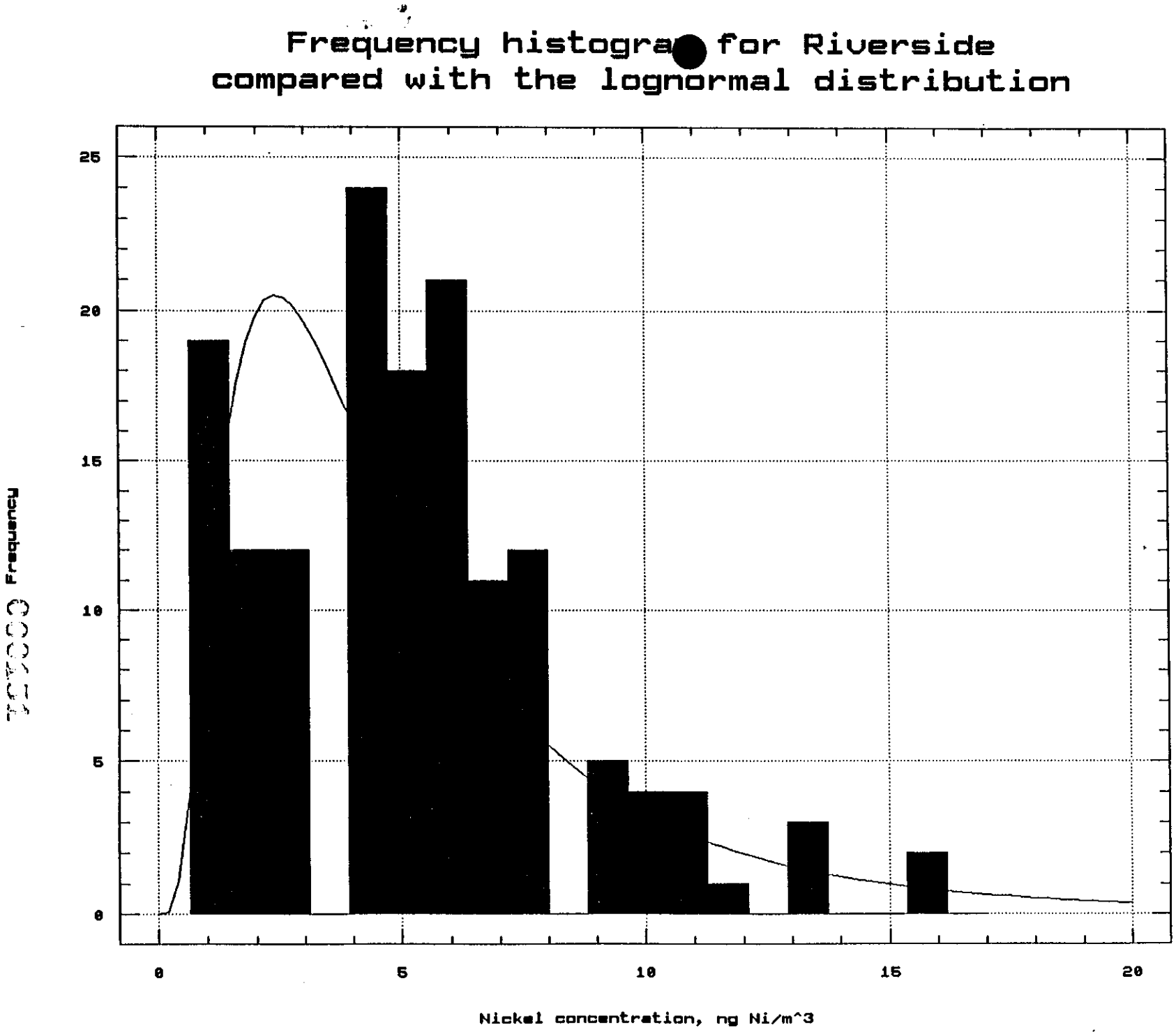
Frequency histogram for Riverside
compared with the lognormal distribution
25
20
15
10
5
0
0
5
10
15
20
Nickel concentration, ng Ni/m^3

FIGURE 5a

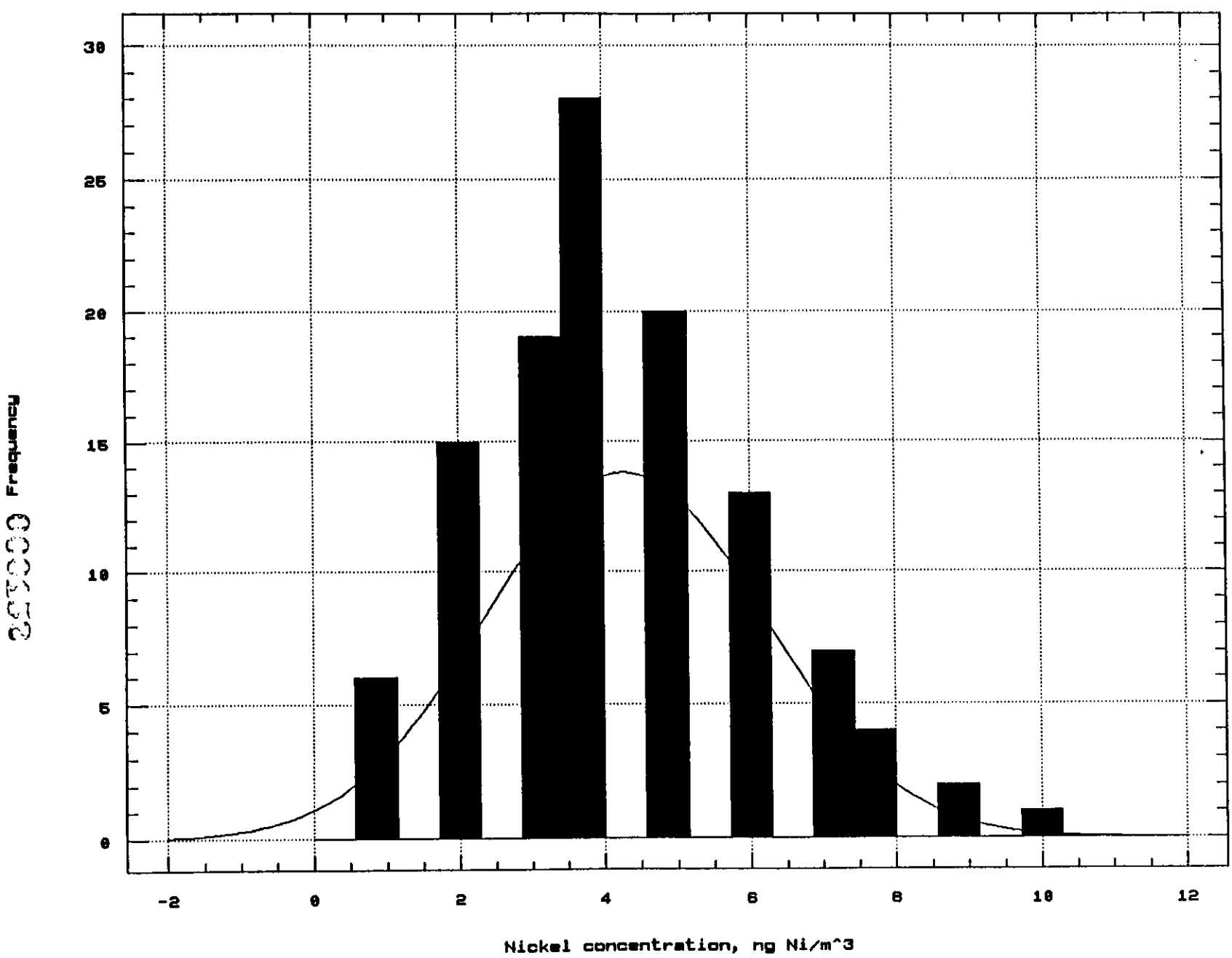
Frequency histogram for Santa Barbara compared with the normal distribution
Frequency
30
25
20
15
10
5
0
-2
0
2
4
6
8
10
12
Nickel concentration, ng Ni/m^3

FIGURE 6

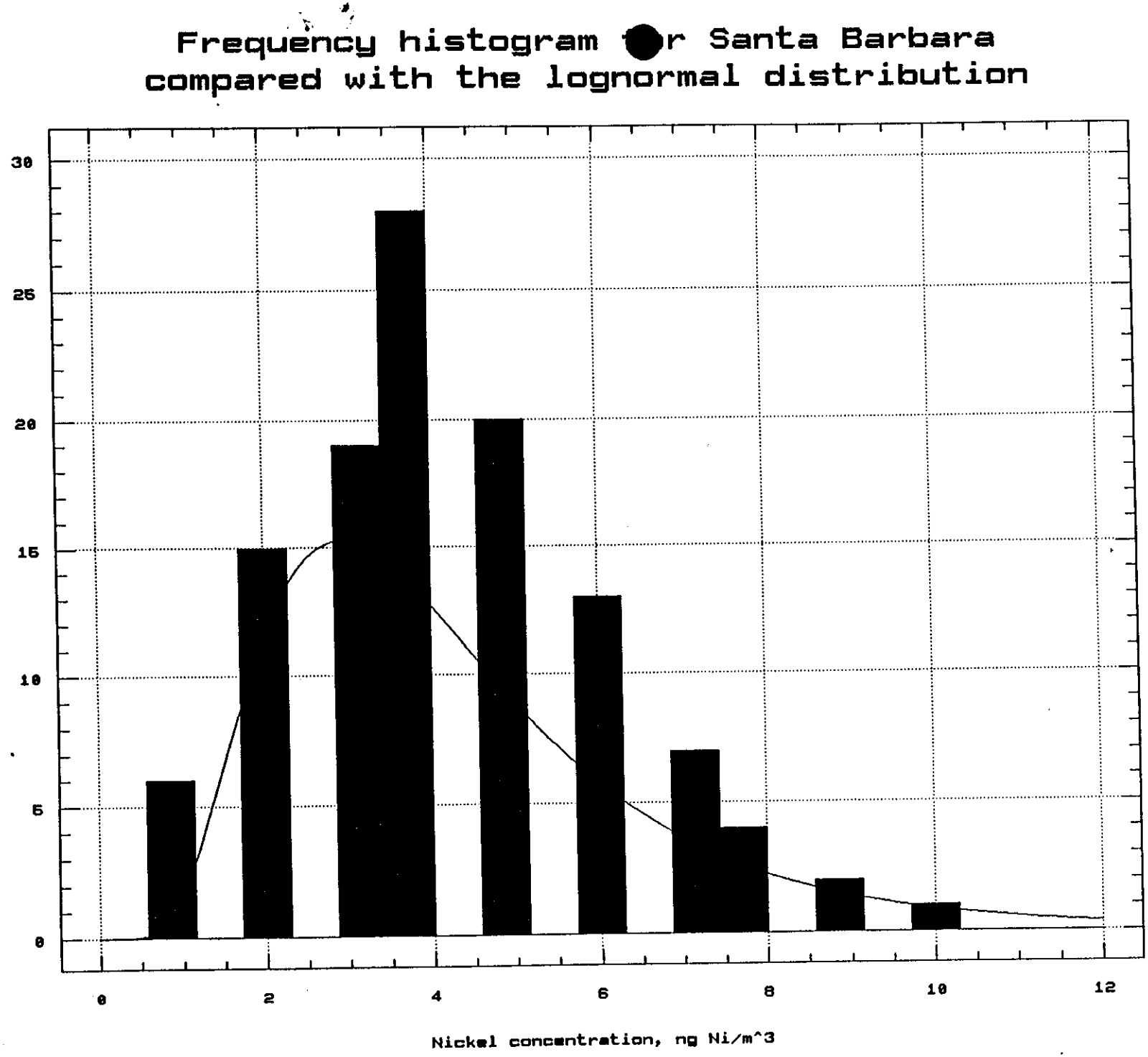
Frequency histogram for Santa Barbara
compared with the lognormal distribution
Frequency
30
25
20
15
10
5
0
0
2
4
6
8
10
12
Nickel concentration, ng Ni/m^3

FIGURE 6a

Regression of log nickel concentration against time in SFBA Air Basin

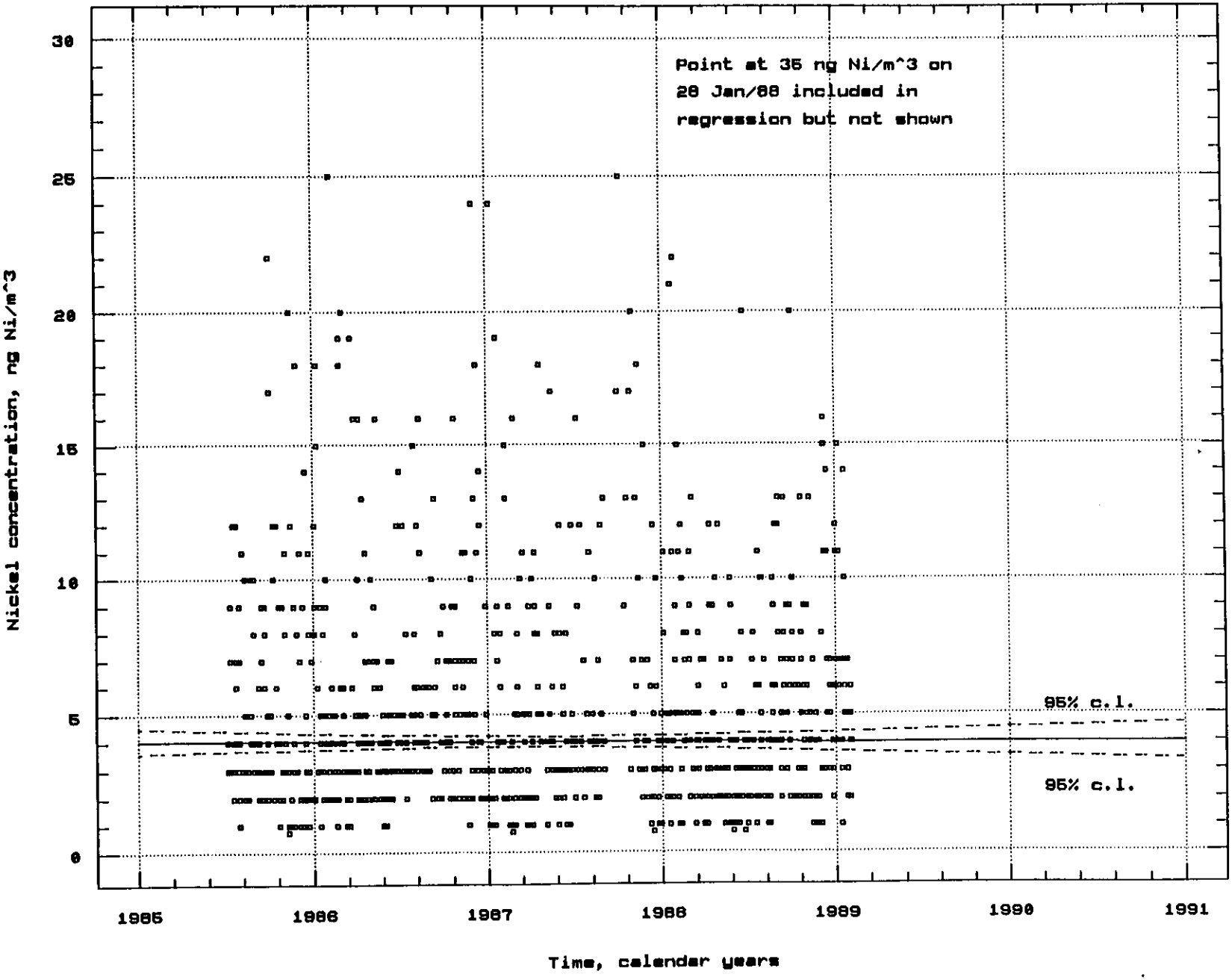

FIGURE 7

Regression of log nickel concentration against time in Concord

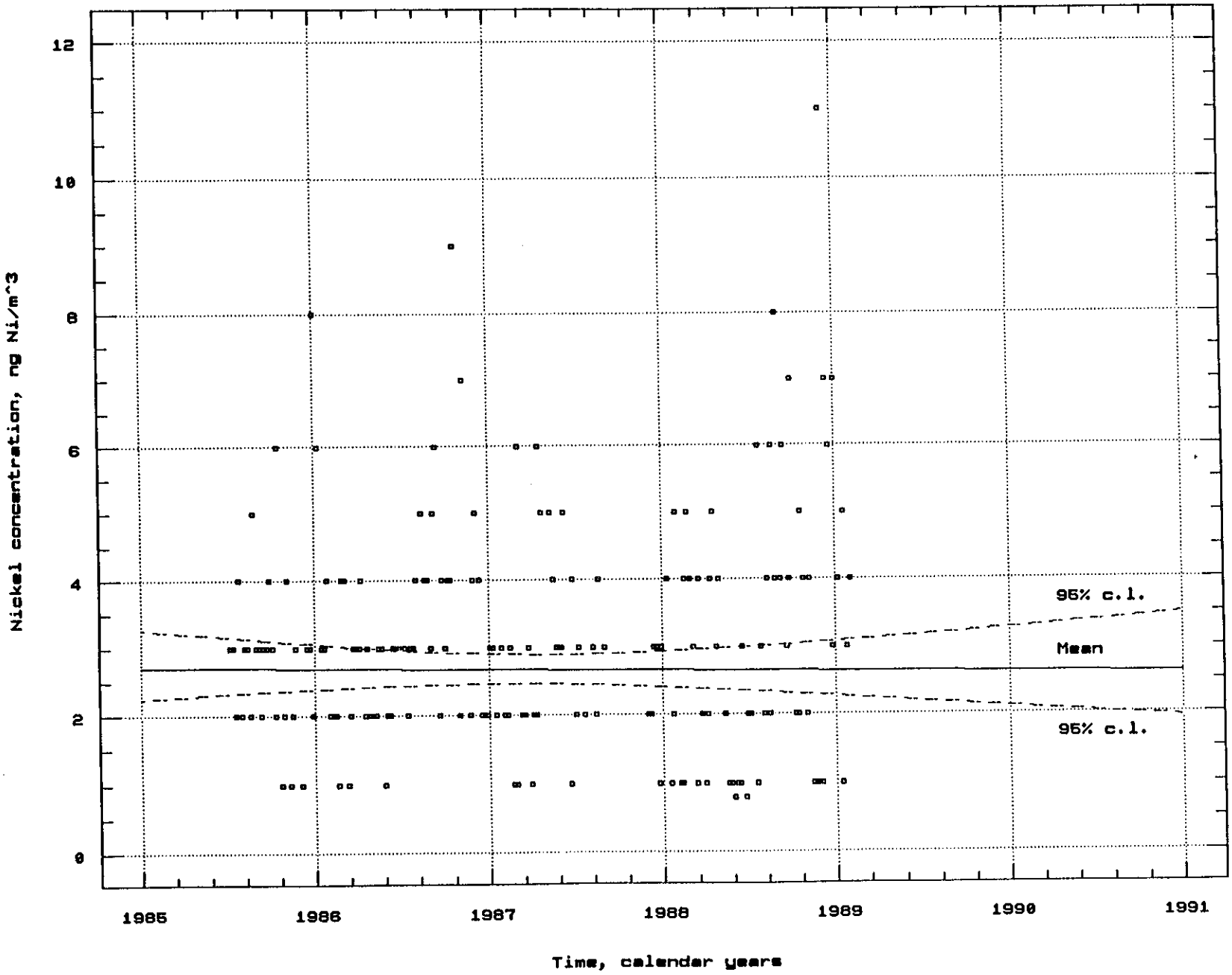

FIGURE 8

Regression of log nickel concentration against time in Fremont

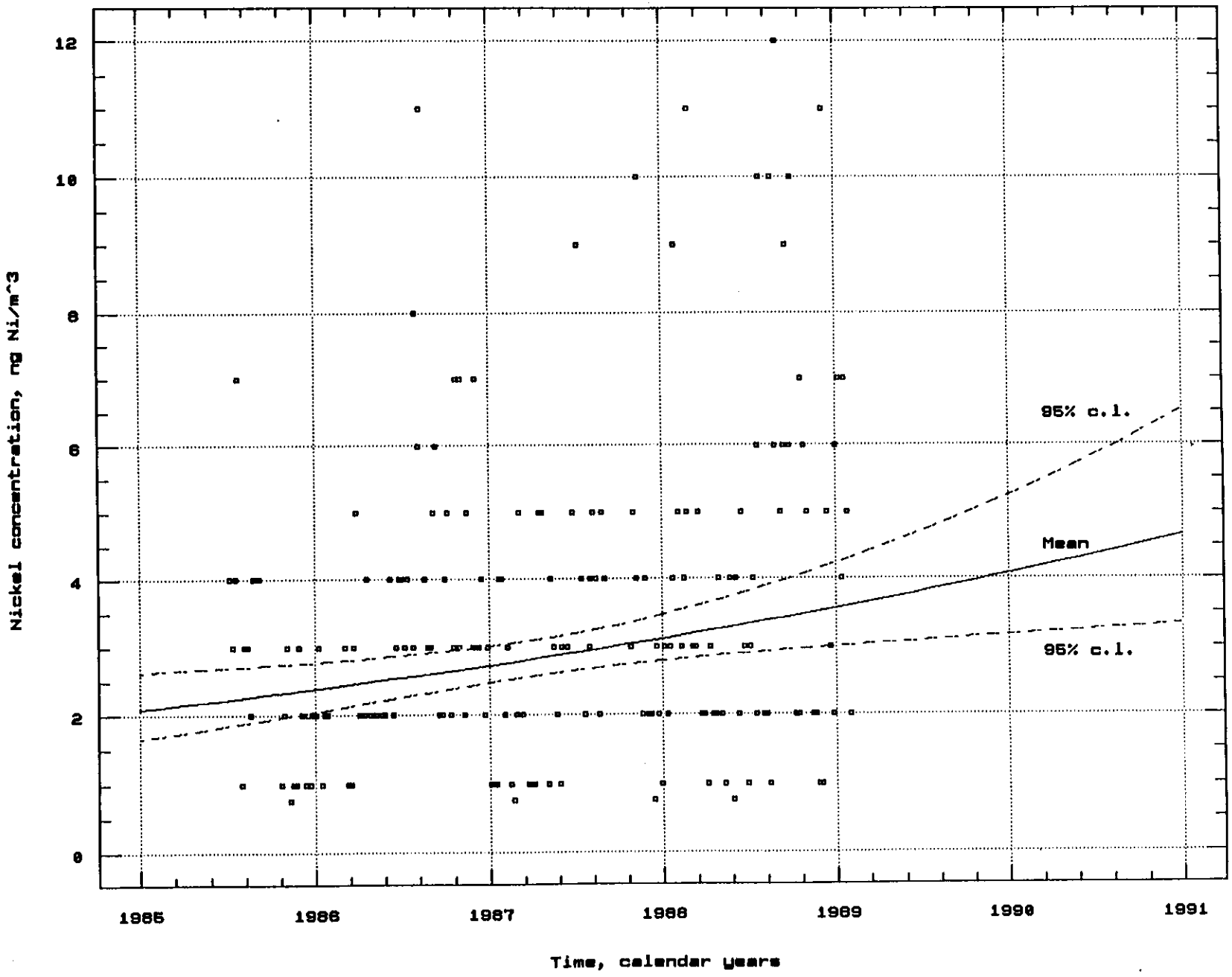

FIGURE 9

Regression of log nickel concentration against time in Richmond

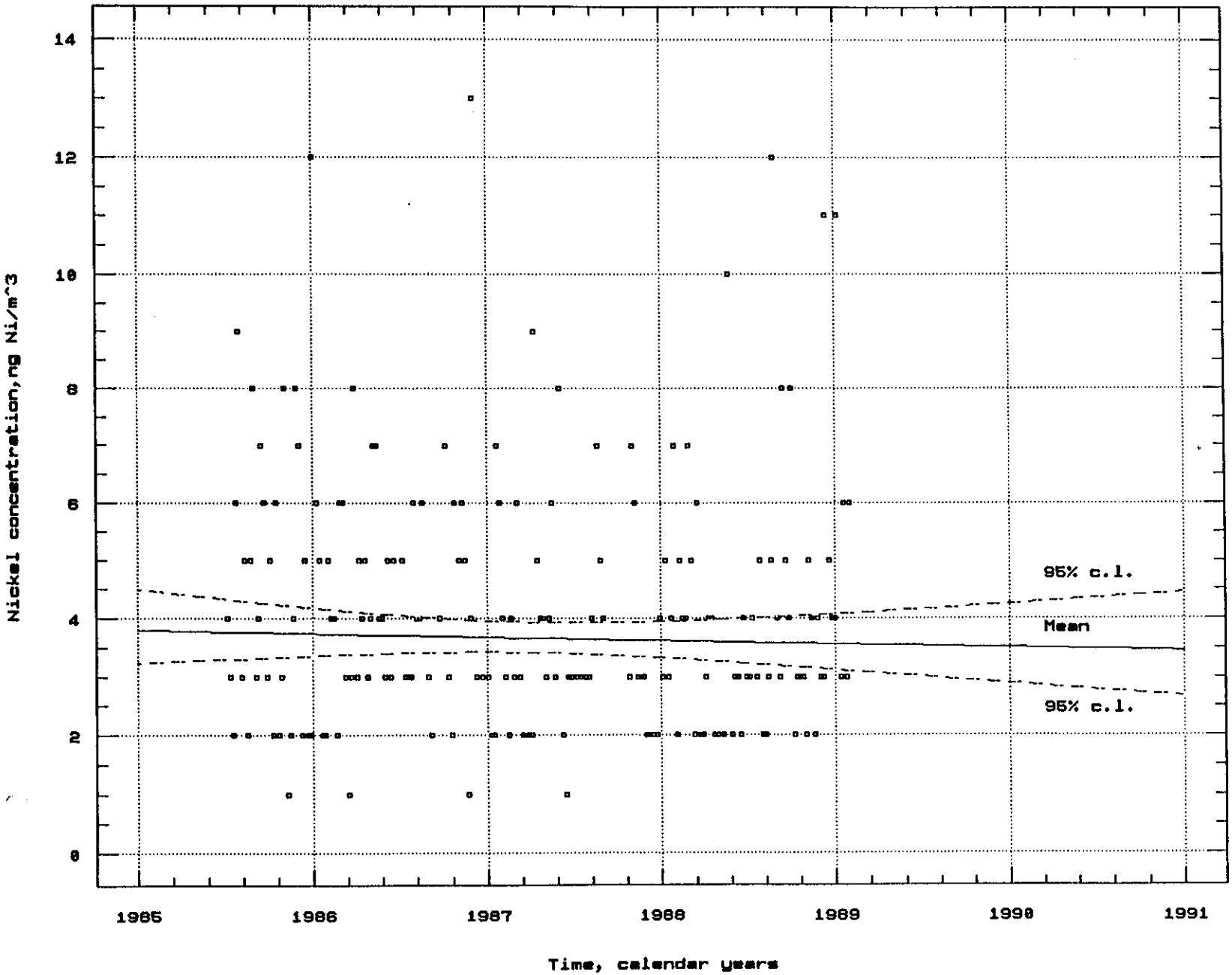

FIGURE 10

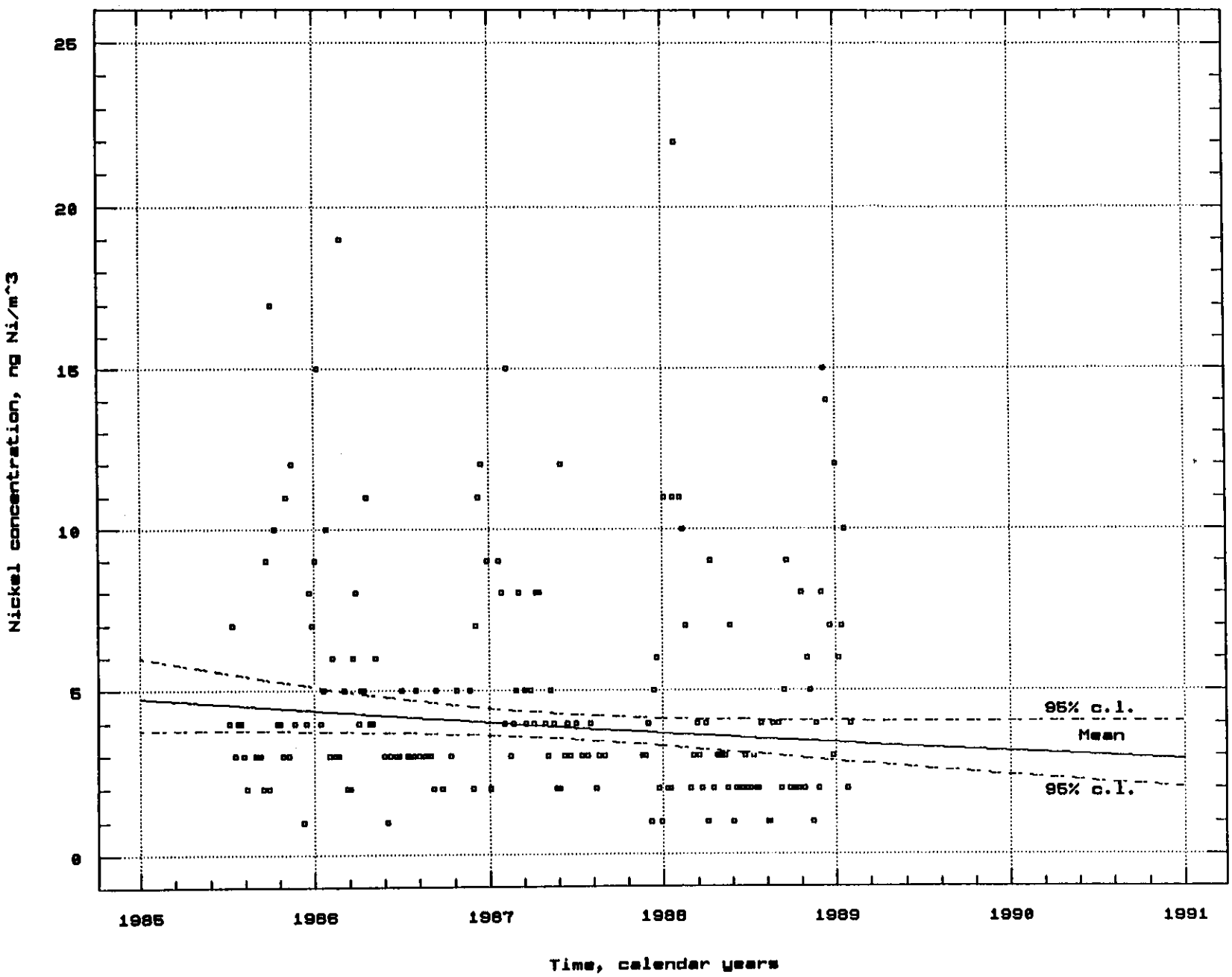
Regression of log nickel concentration against time in San Francisco
Nickel concentration, ng Ni/m^3
25
20
15
10
5
0
95% c.l.
Mean
95% c.l.
1985
1986
1987
1988
1989
1990
1991
Time, calendar years

FIGURE 11

Regression of log nickel concentration against time in San Jose

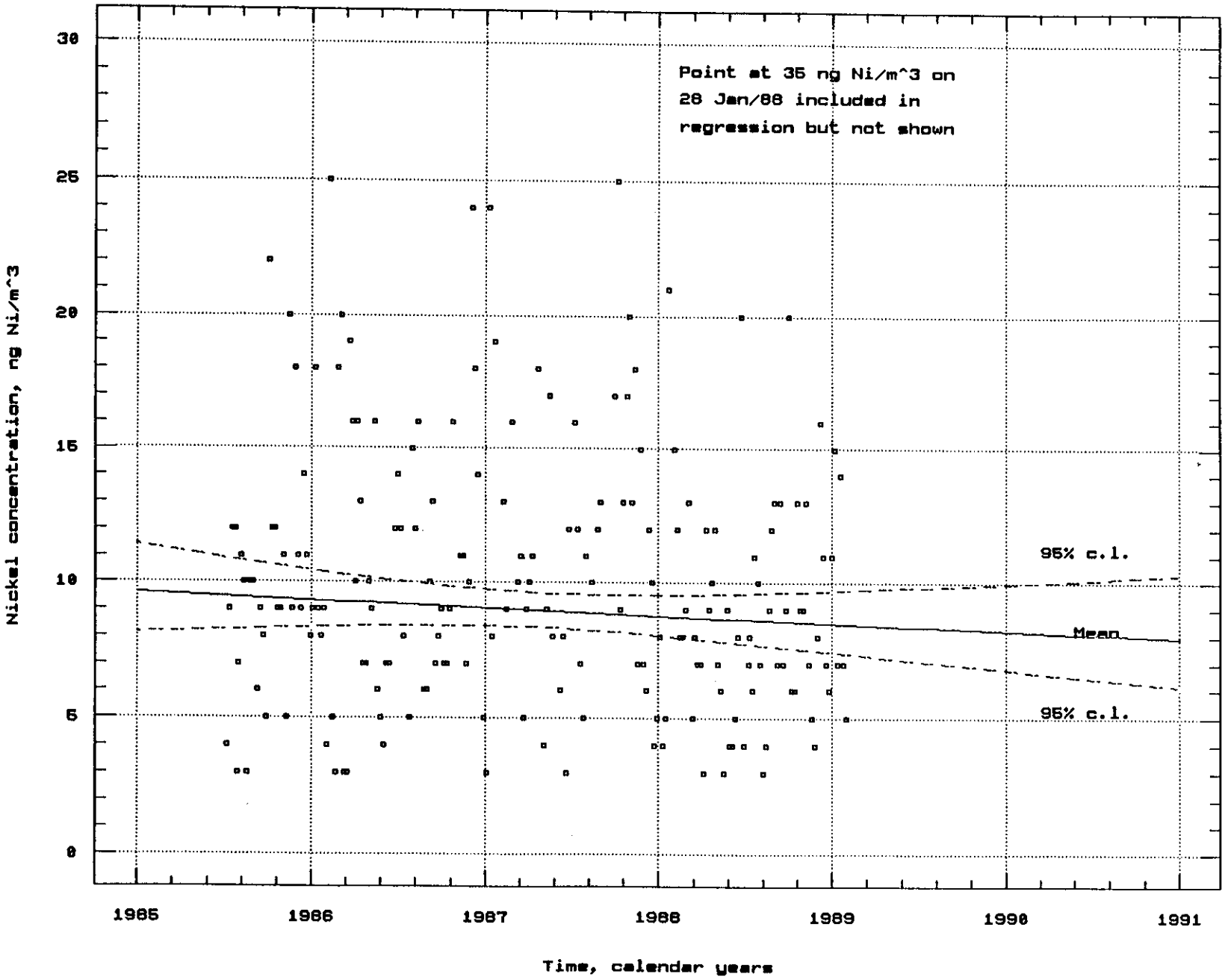

FIGURE 12

Regression of log nickel concentration against time in SCC Air Basin

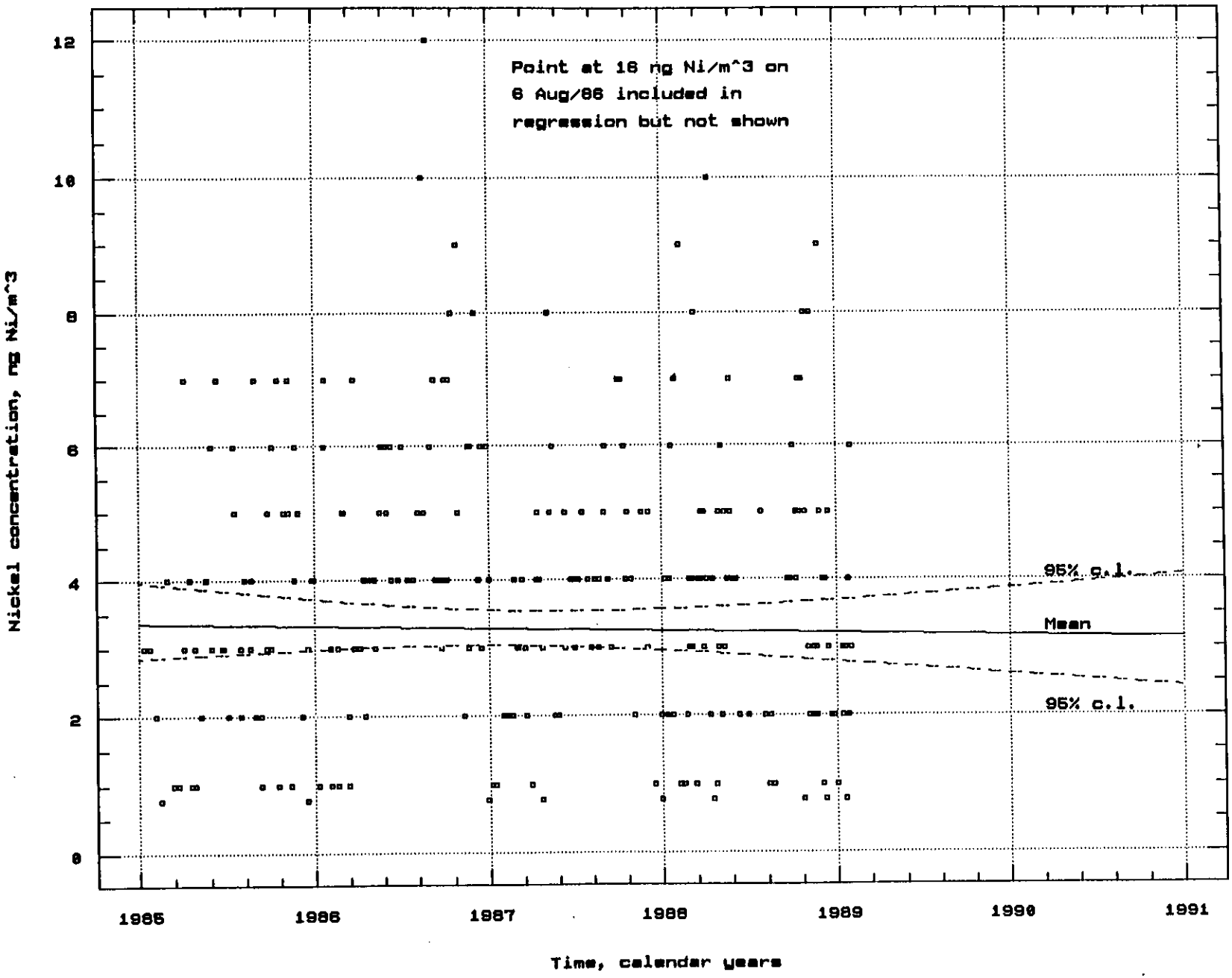

FIGURE 13

Regression of log nickel concentration against time in Santa Barbara

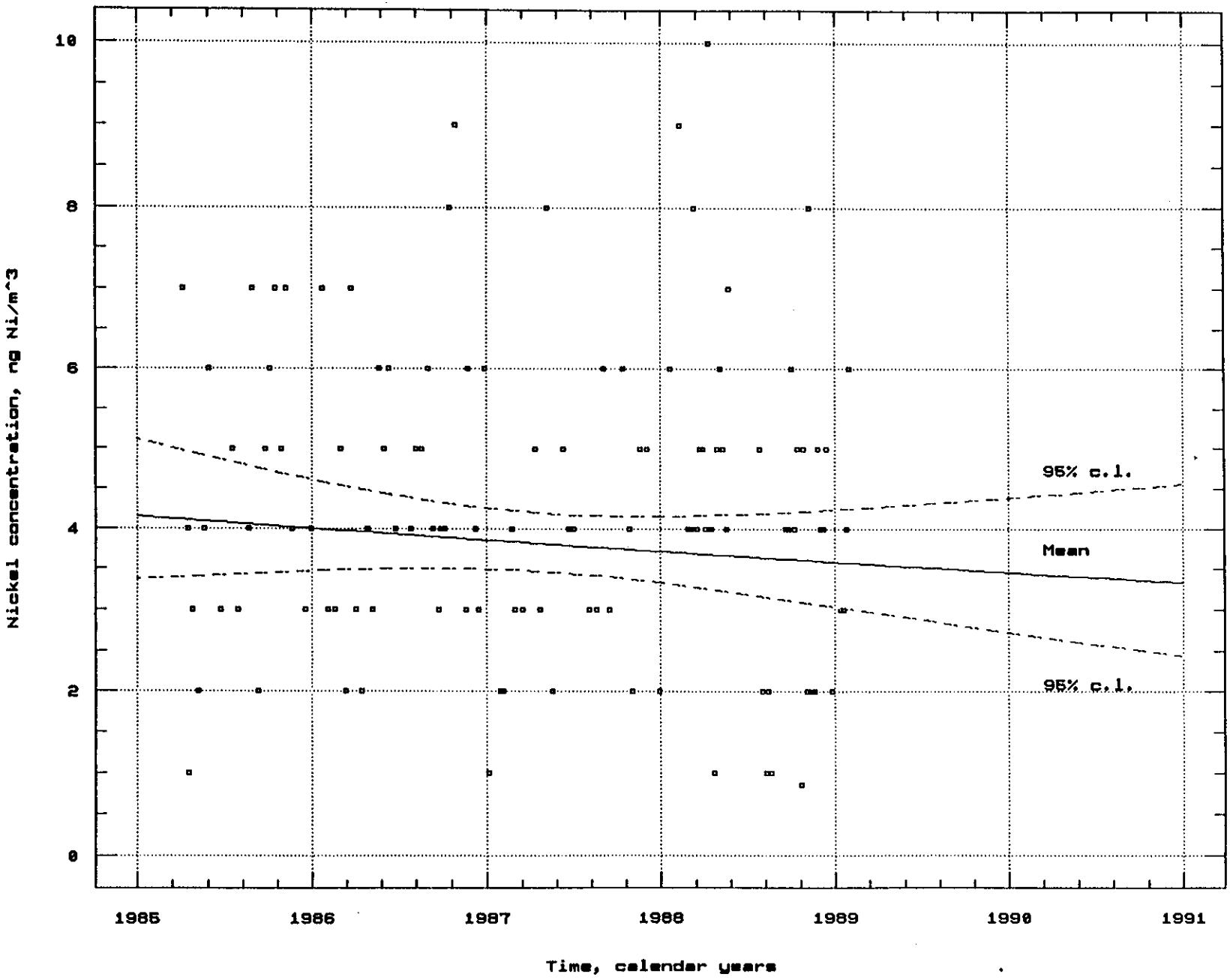

FIGURE 14

Regression of log nickel concentration against time in Simi Valley

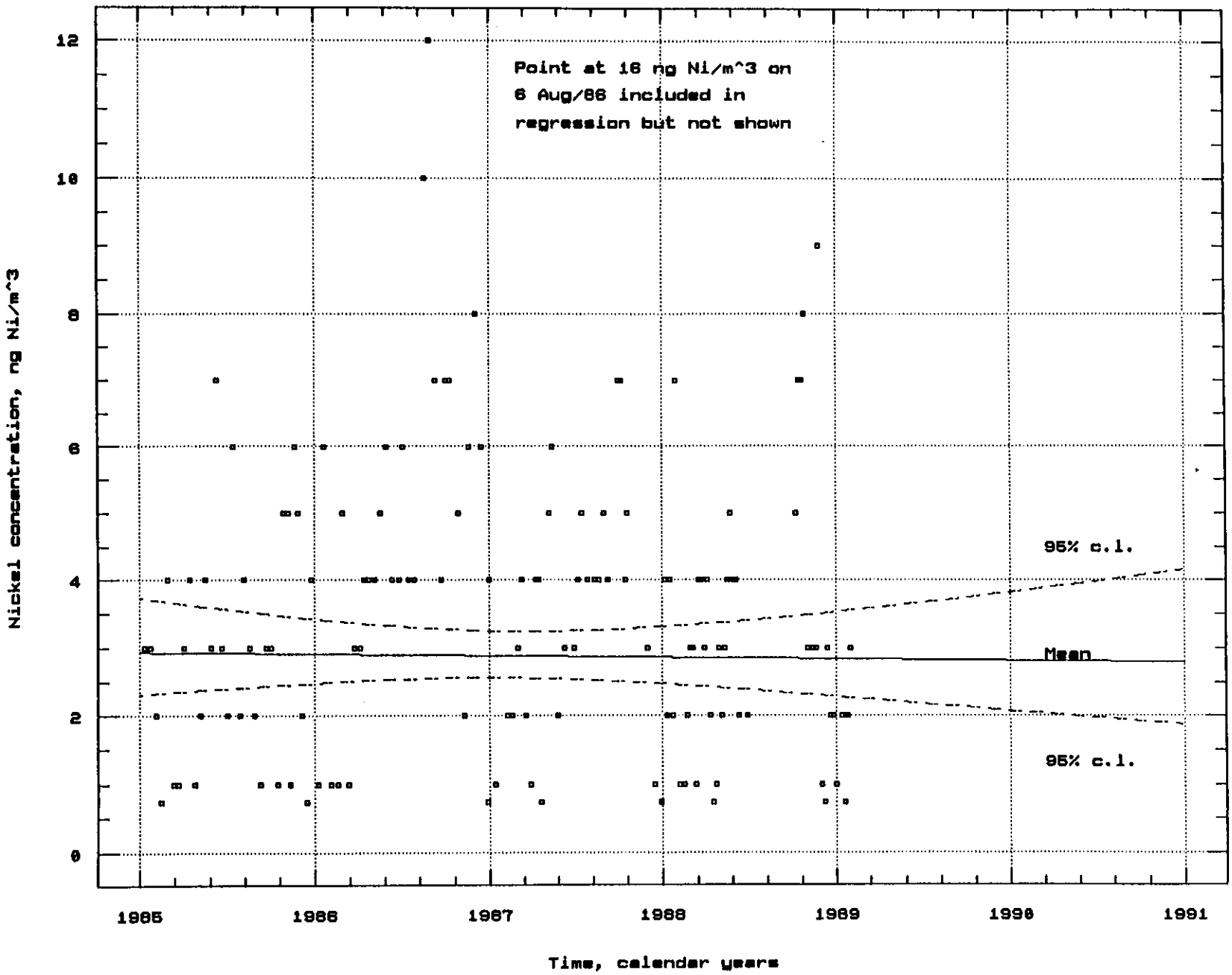

FIGURE 15

Regression of log nickel concentration against time in South Coast Air Basin

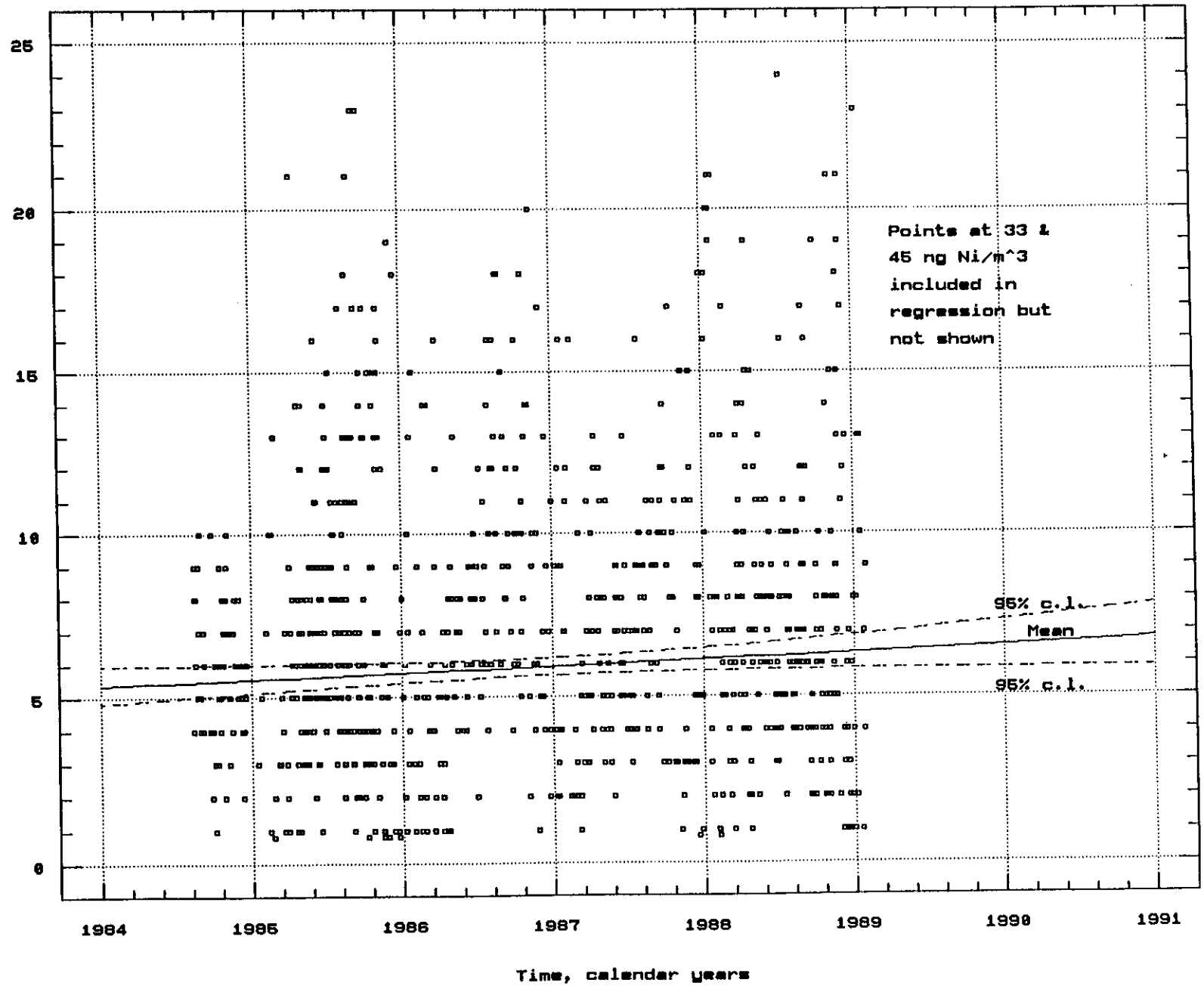

FIGURE 16

Regression of log nickel concentration against time in El Monte

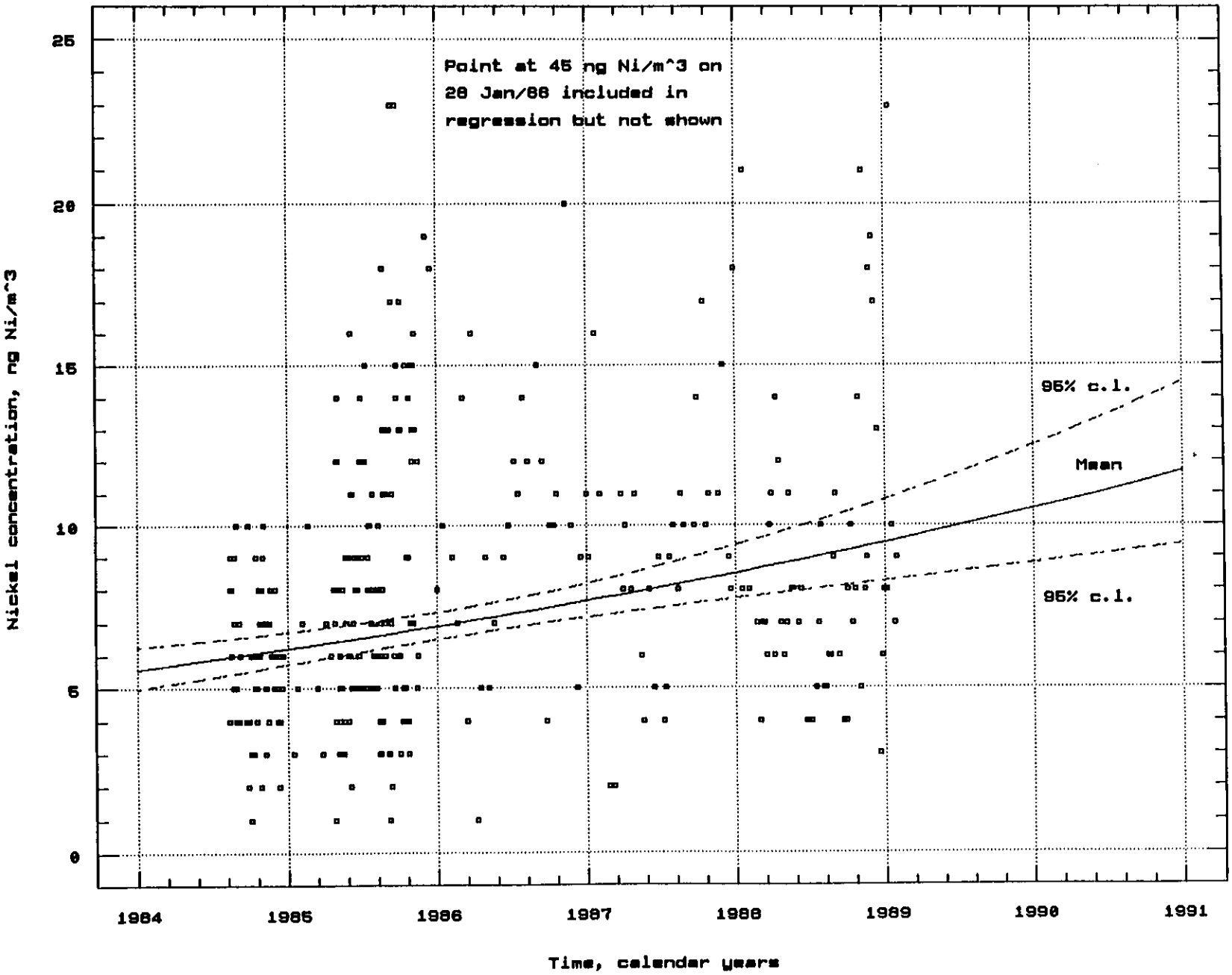

FIGURE 17

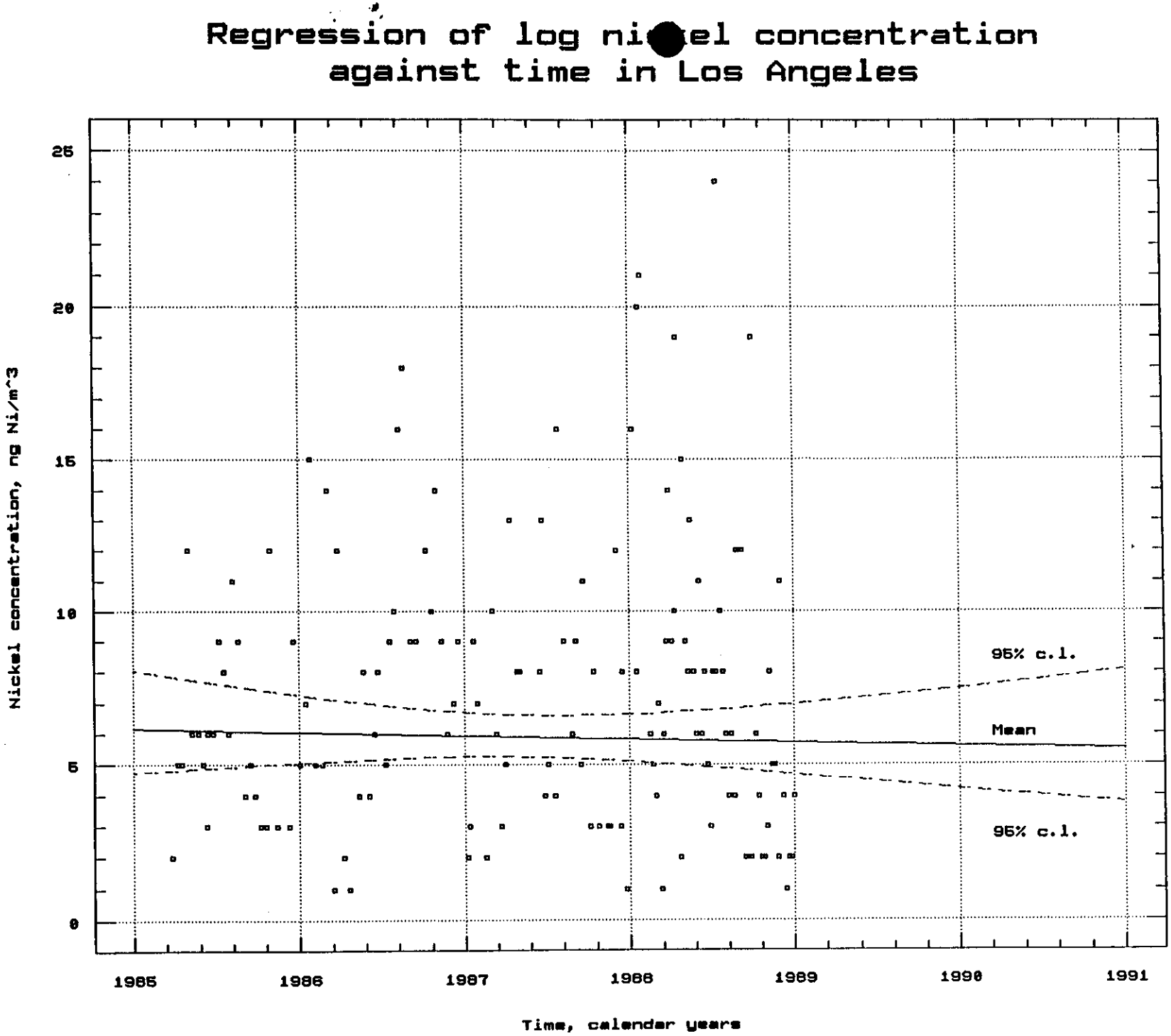
Regression of log nickel concentration against time in Los Angeles
Nickel concentration, ng Ni/m^3
25
20
15
10
5
0
1985
1986
1987
1988
1989
1990
1991
Time, calendar years
95% c.l.
Mean
95% c.l.

FIGURE 18

Regression of log nickel concentration against time in North Long Beach

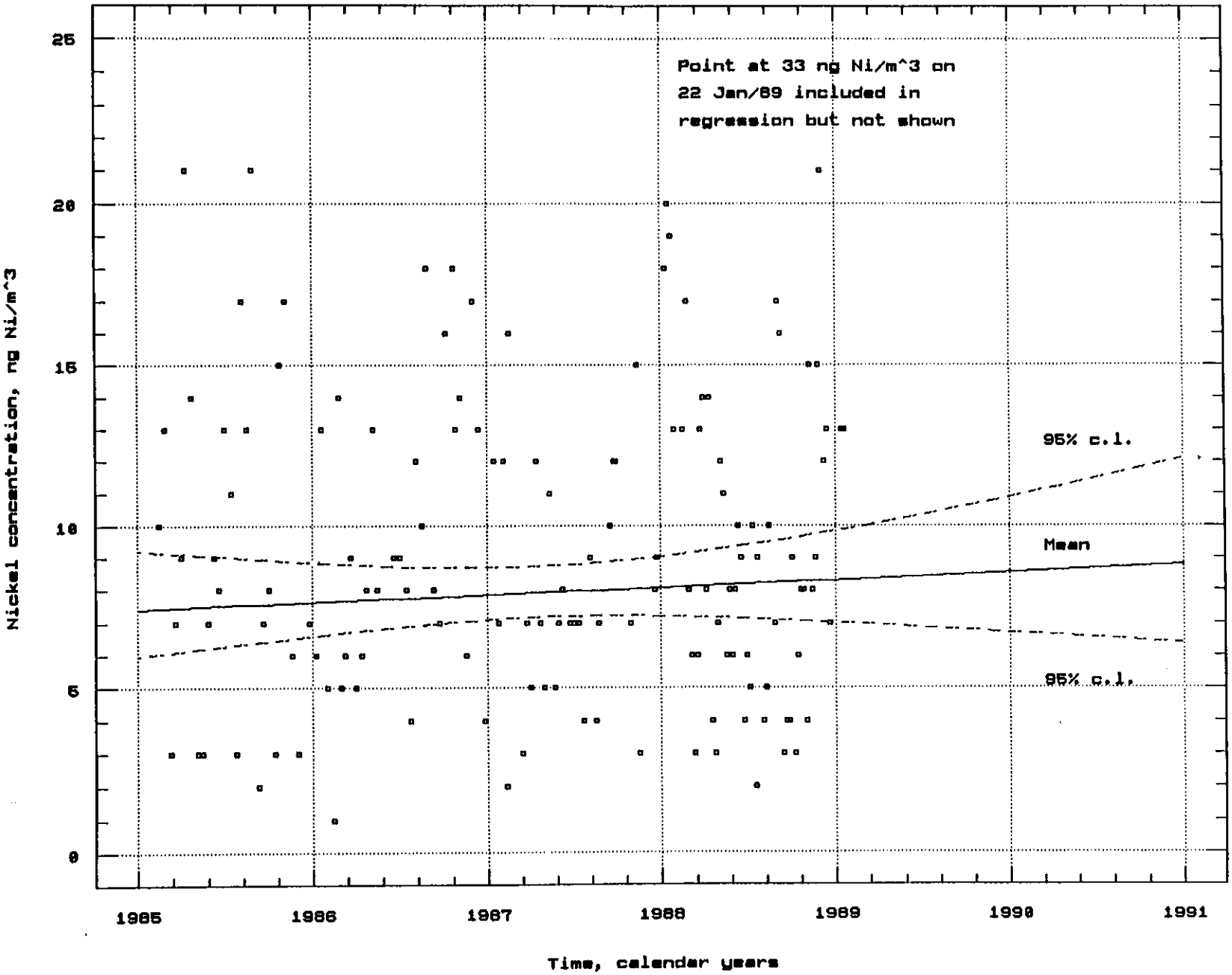

FIGURE 19

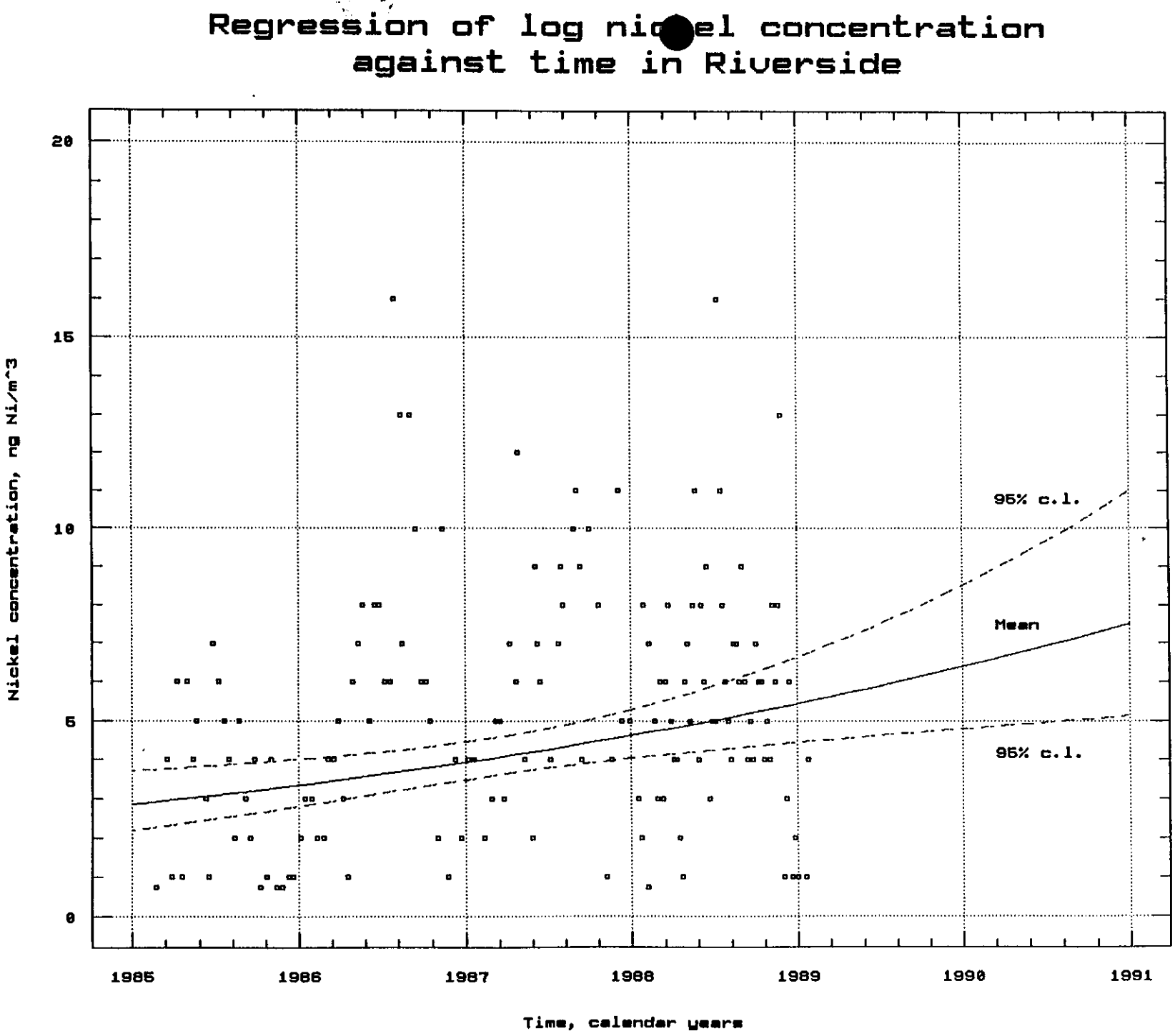
Regression of log nickel concentration against time in Riverside
Nickel concentration, ng Ni/m^3
20
15
10
5
0
95% c.l.
Mean
95% c.l.
1985
1986
1987
1988
1989
1990
1991
Time, calendar years

FIGURE 20

Regression of log nickel concentration against time in Upland

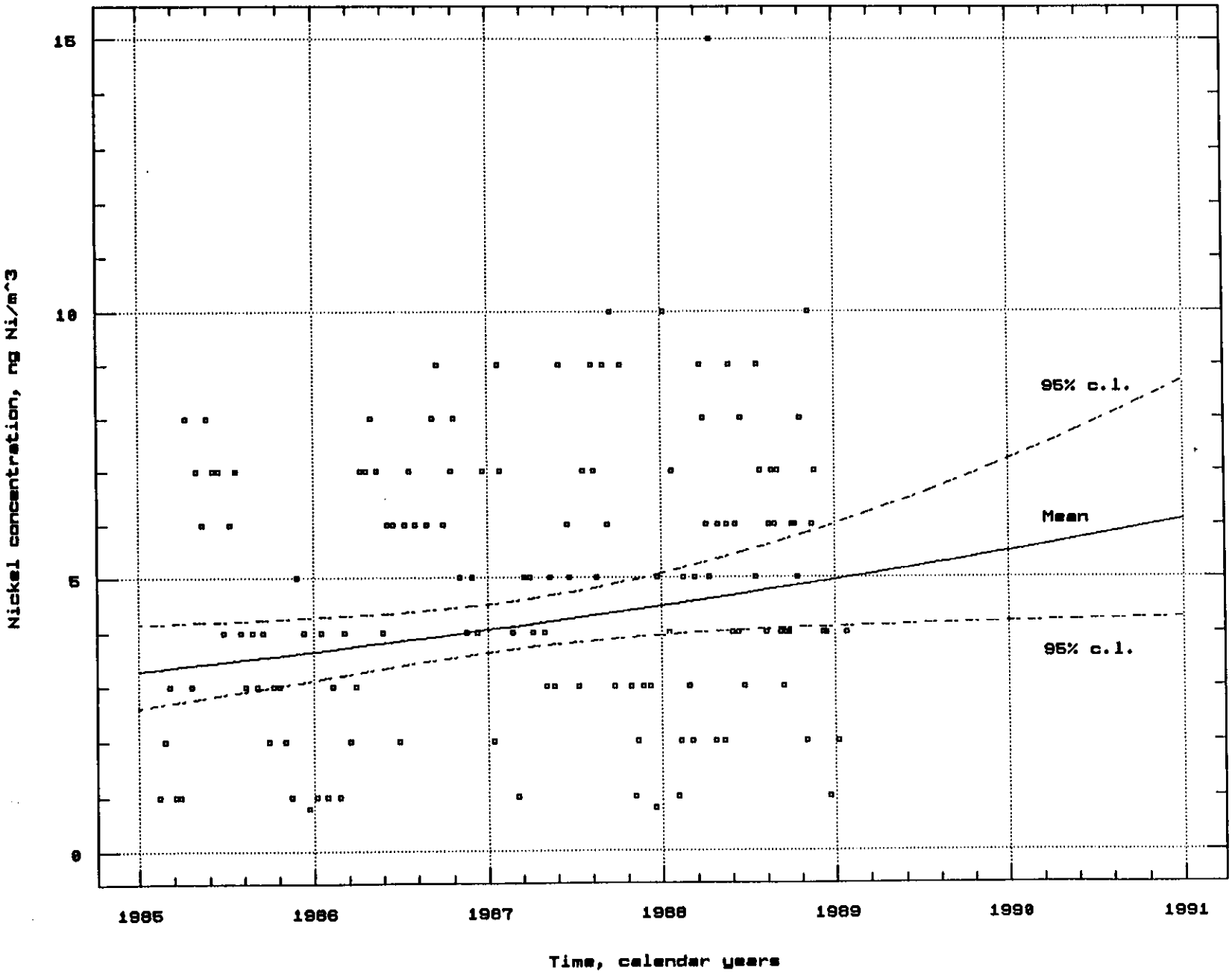

FIGURE 21

Regression of log nickel concentration against time in San Diego Air Basin

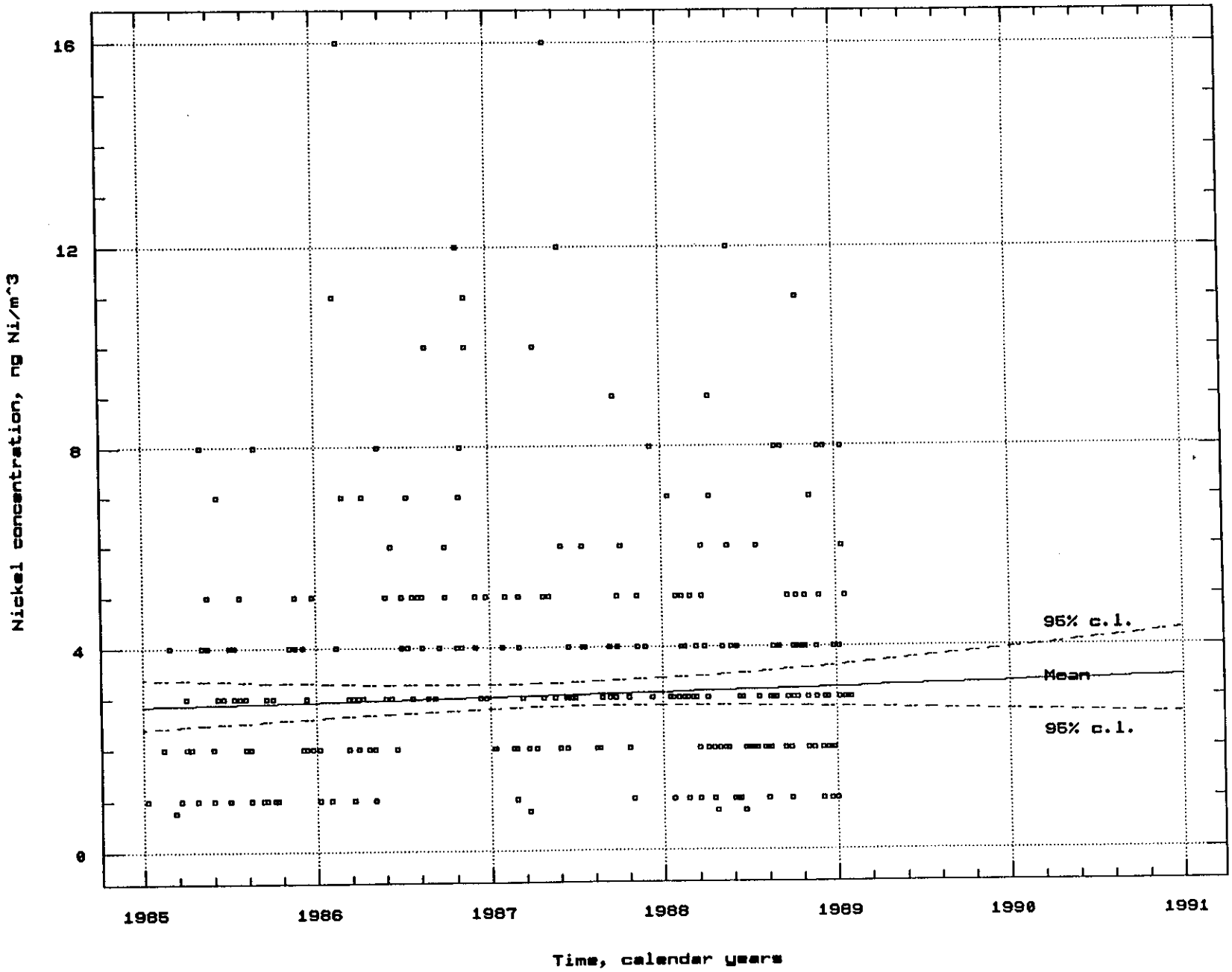

FIGURE 22

Regression of log nickel concentration against time in Chula Vista

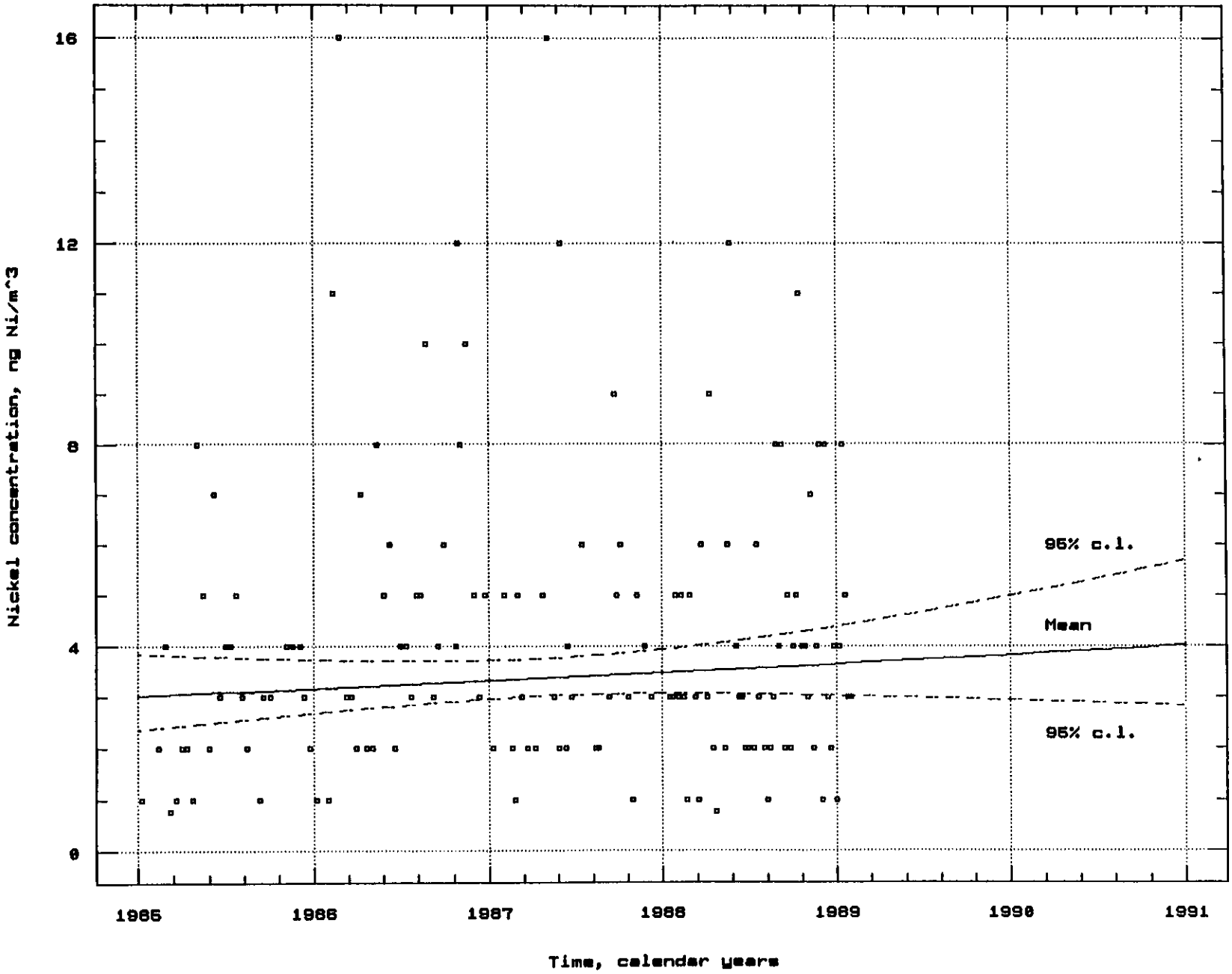

FIGURE 23

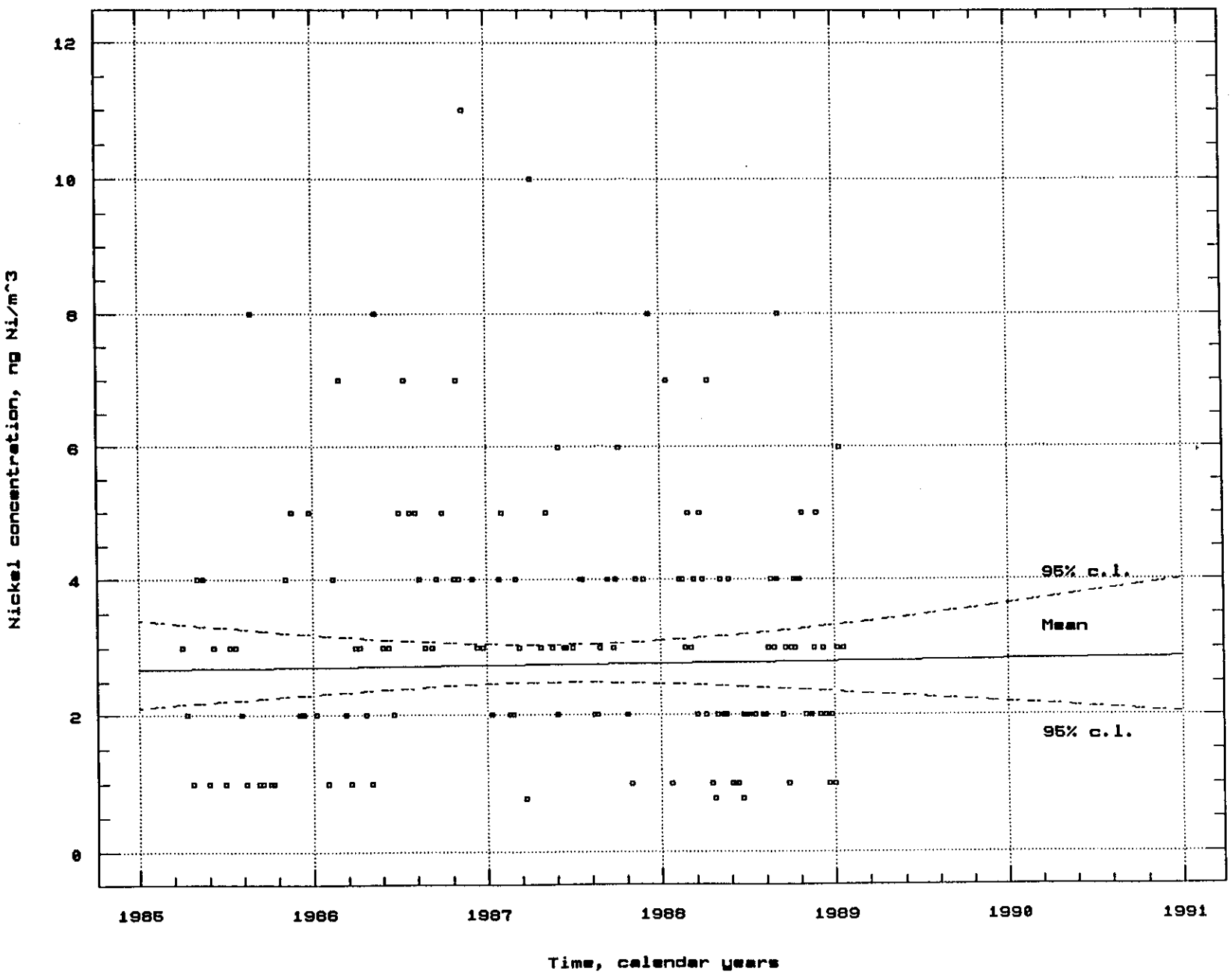
Regression of log nickel concentration against time in El Cajon
Nickel concentration, ng Ni/m^3
12
10
8
6
4
2
0
95% c.l.
Mean
95% c.l.
1985
1986
1987
1988
1989
1990
1991
Time, calendar years

FIGURE 24

Regression of log nickel concentration against time in Citrus Heights

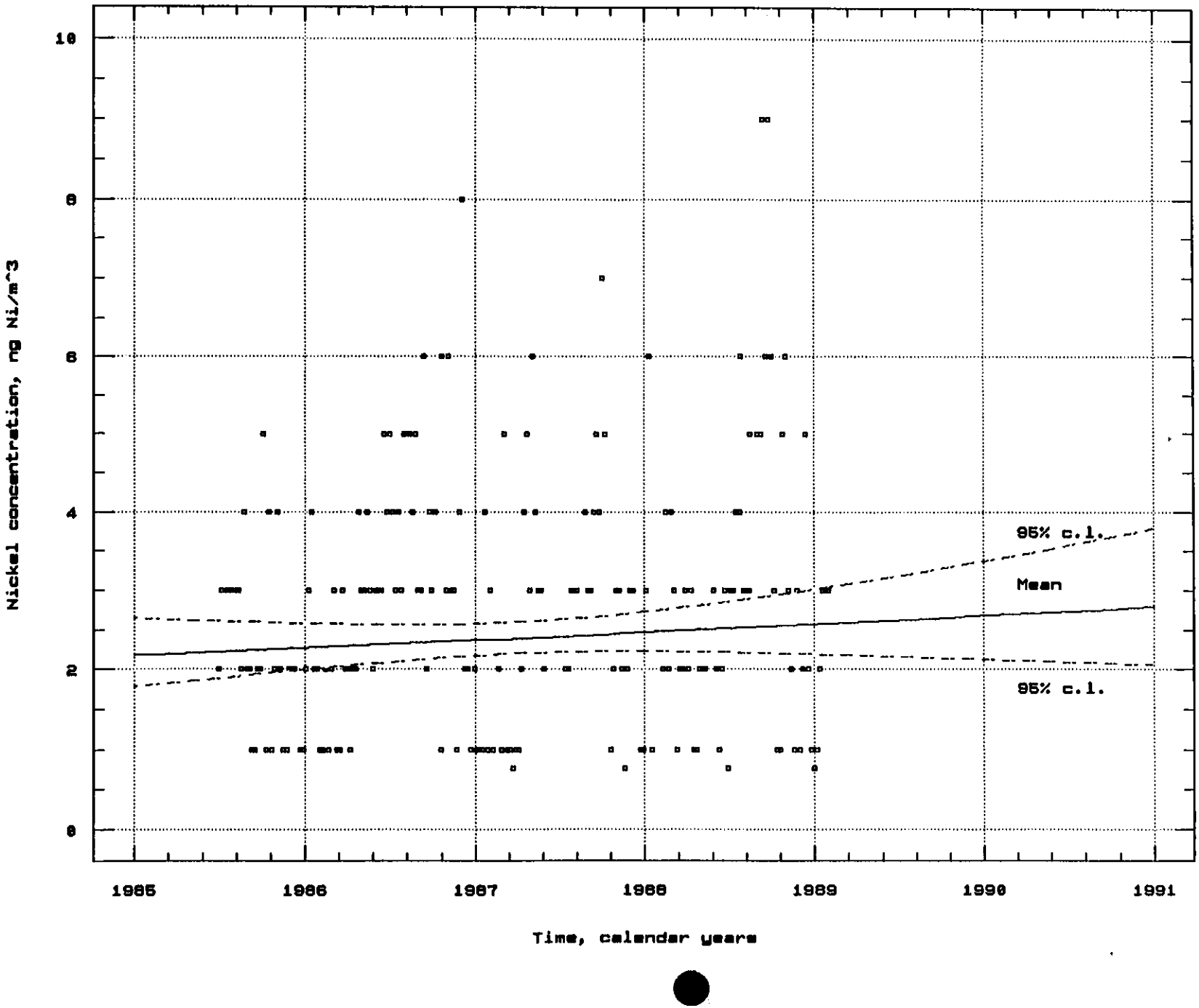

FIGURE 25

Regression of log nickel concentration against time in SJV Air Basin

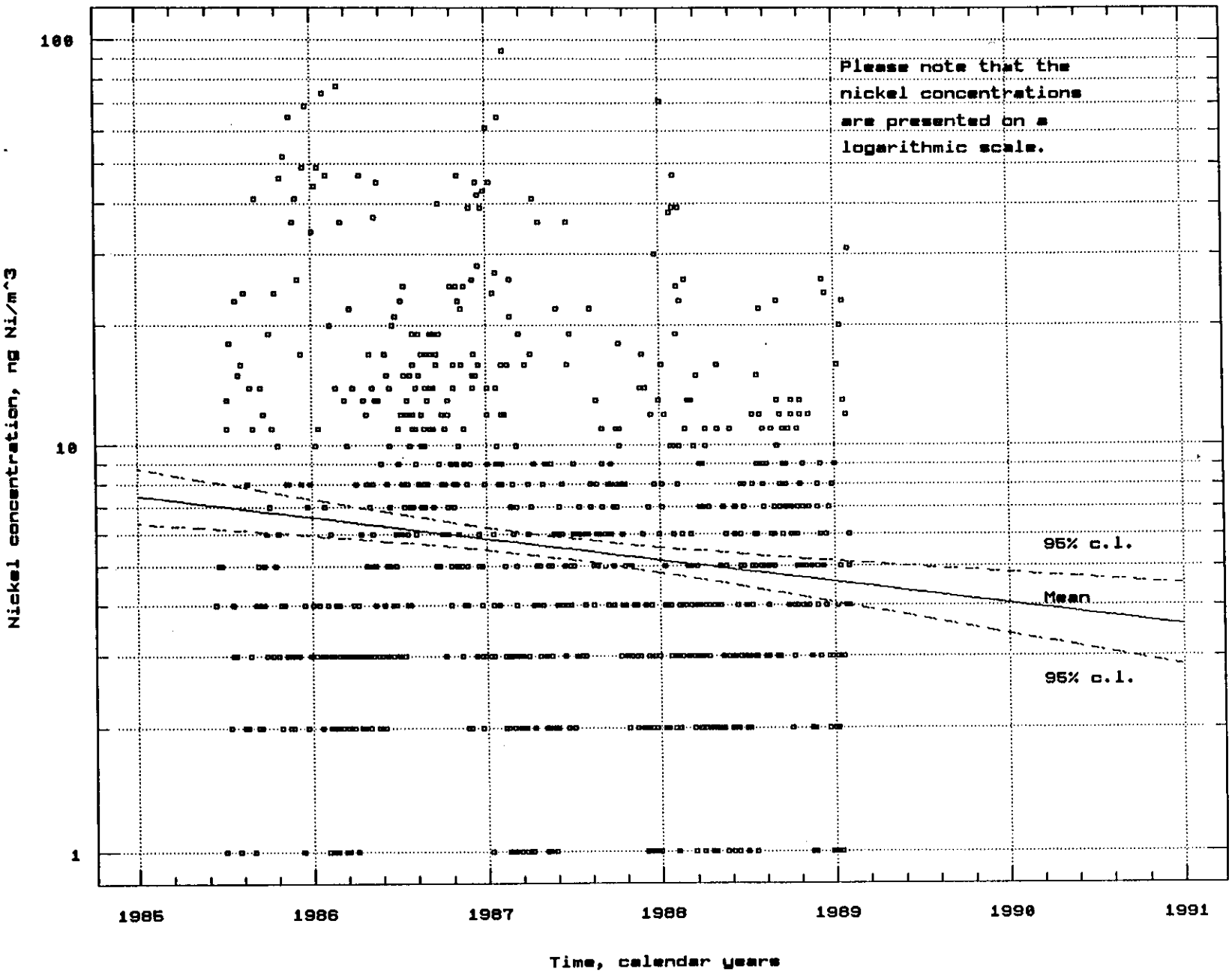

FIGURE 26

Regression of log nickel concentration against time in Fresno

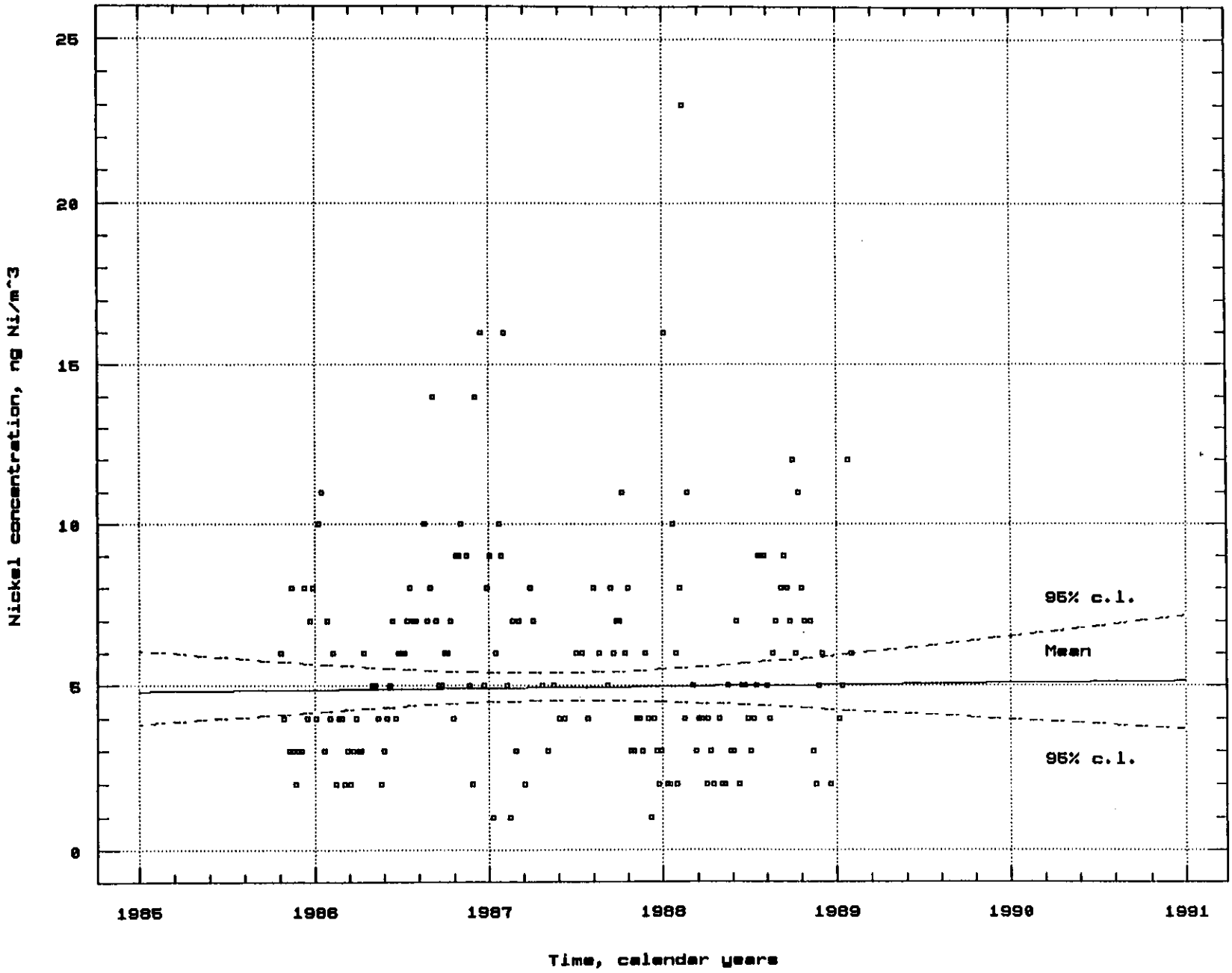

FIGURE 27

Regression of log nickel concentration against time in Bakersfield

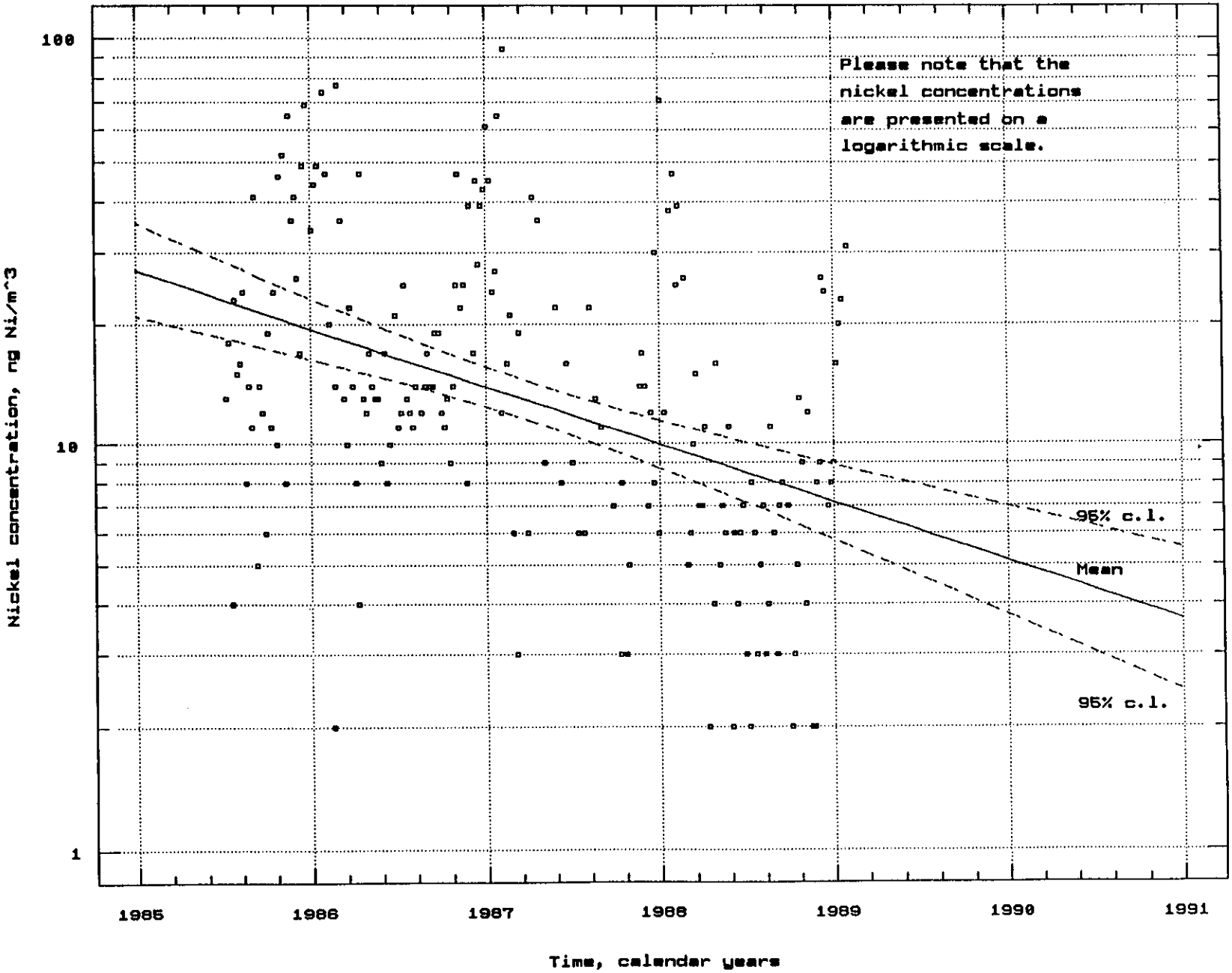

FIGURE 28

Regression of log nickel concentration against time in Merced

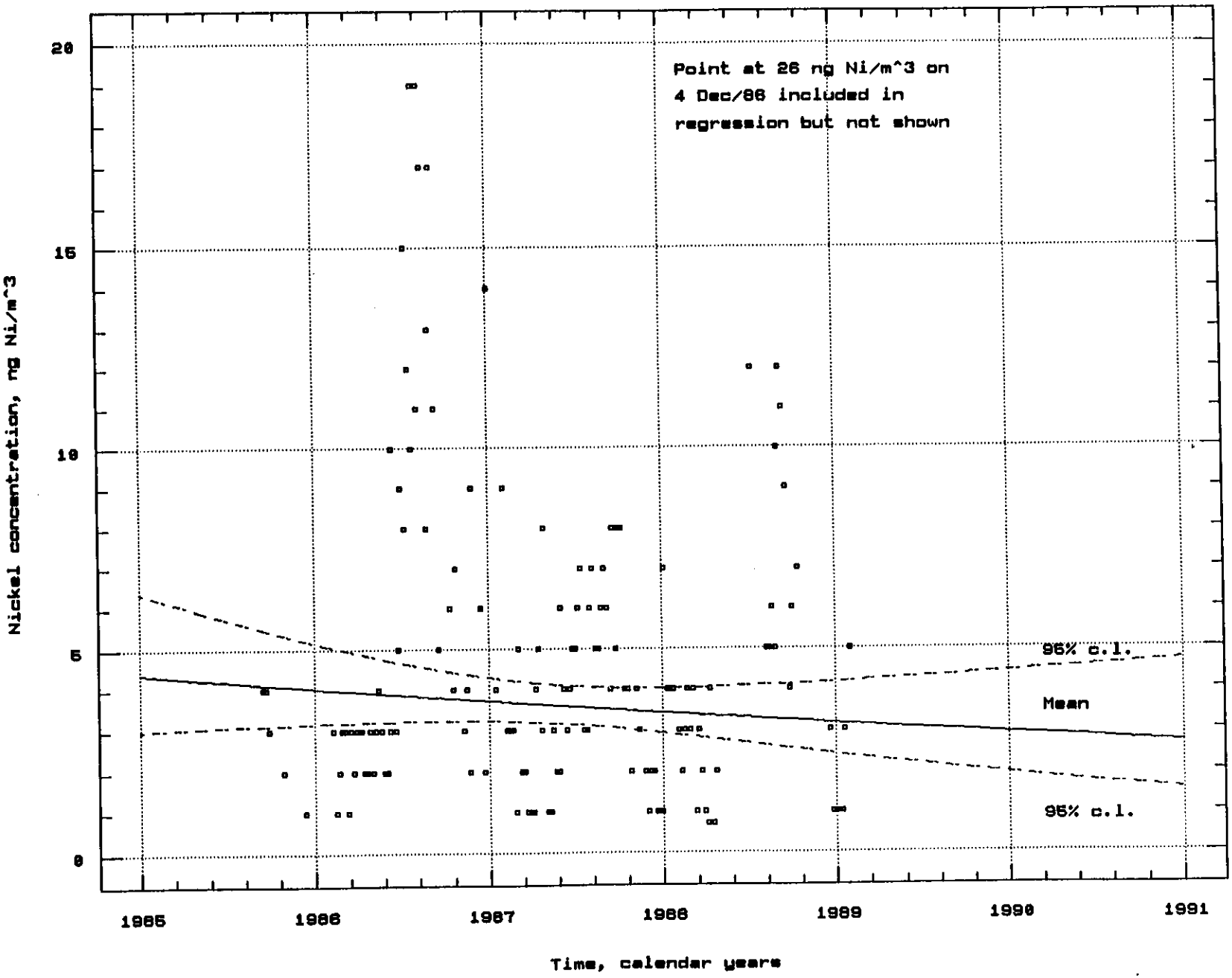

FIGURE 29

Regression of log nickel concentration against time in Stockton

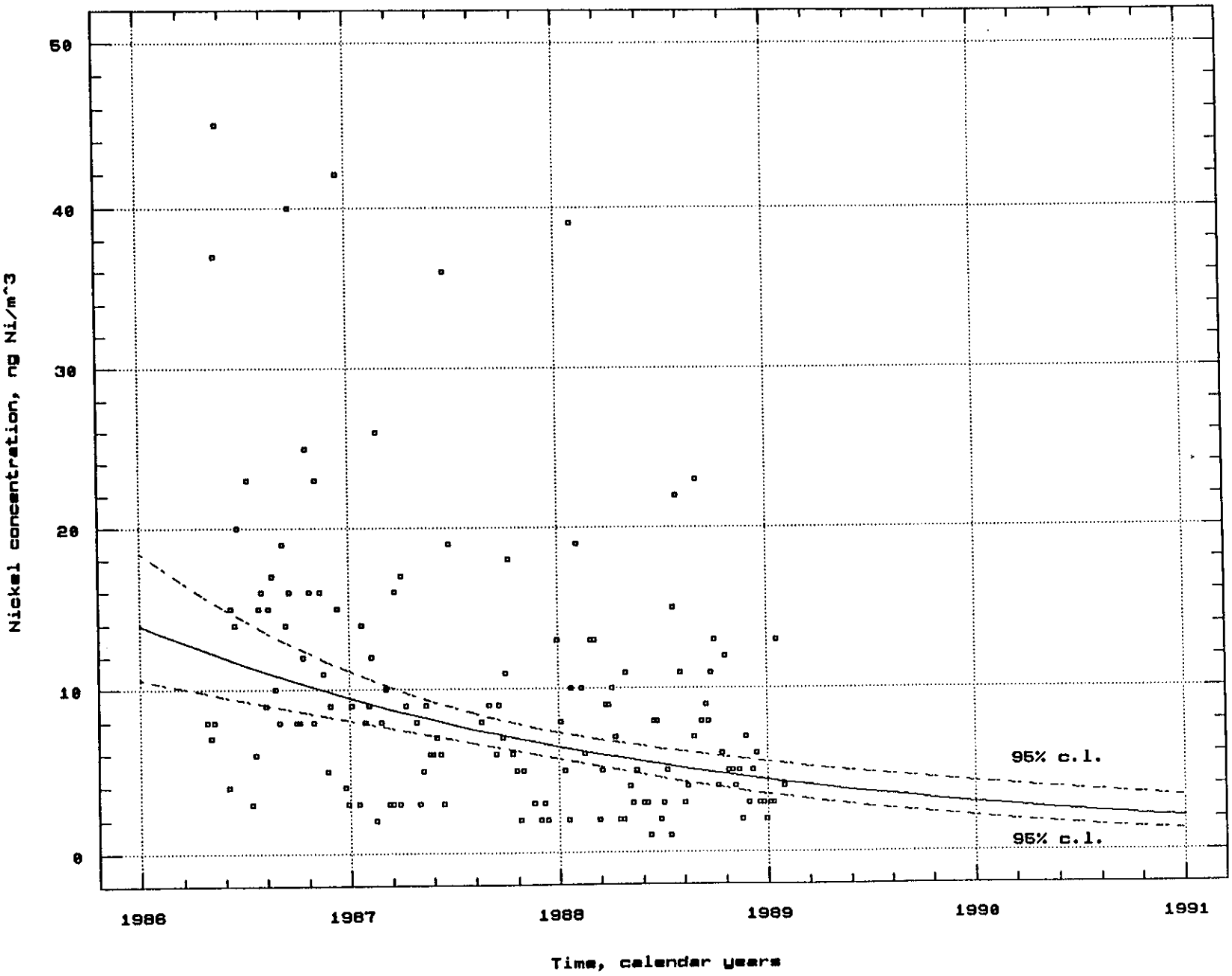

FIGURE 30

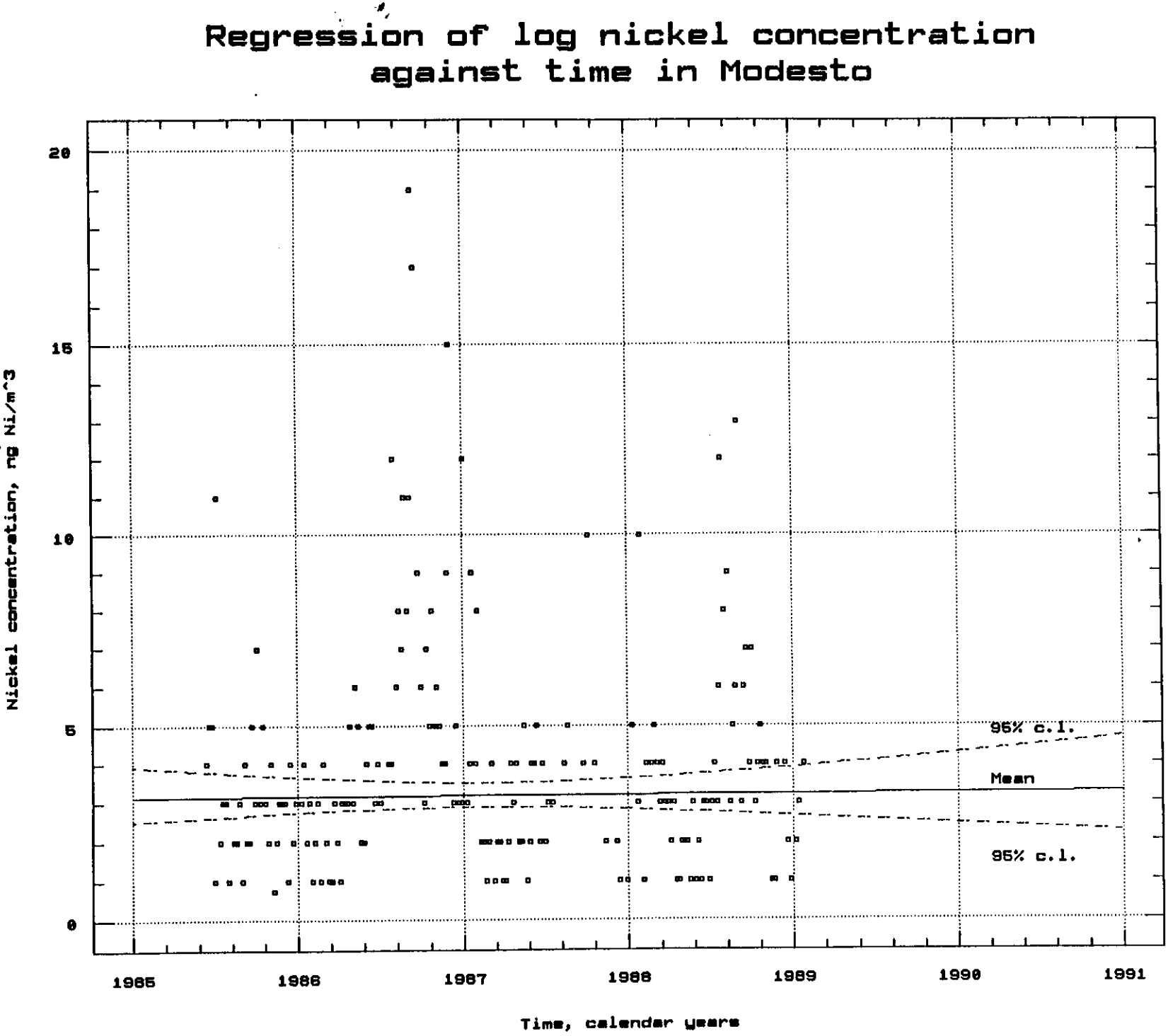
Regression of log nickel concentration against time in Modesto
Nickel concentration, ng Ni/m^3
20
15
10
5
0
95% c.l.
Mean
95% c.l.
1985
1986
1987
1988
1989
1990
1991
Time, calendar years

FIGURE 31

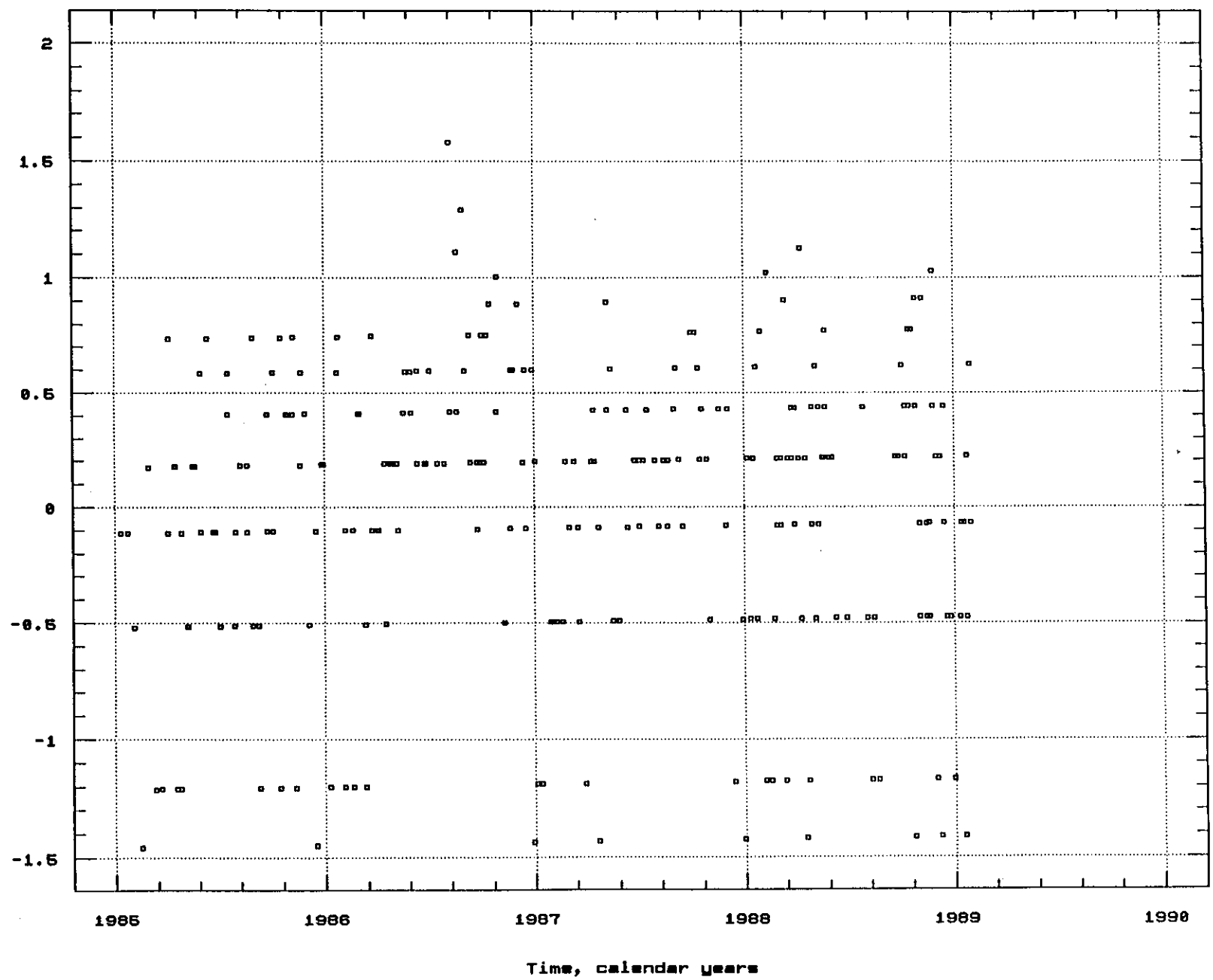
Residuals versus time for the
South Central Coast Air Basin
2
1.5
1
0.5
0
-0.5
-1
-1.5
Residuals
1985
1986
1987
1988
1989
1990
Time, calendar years

FIGURE 32

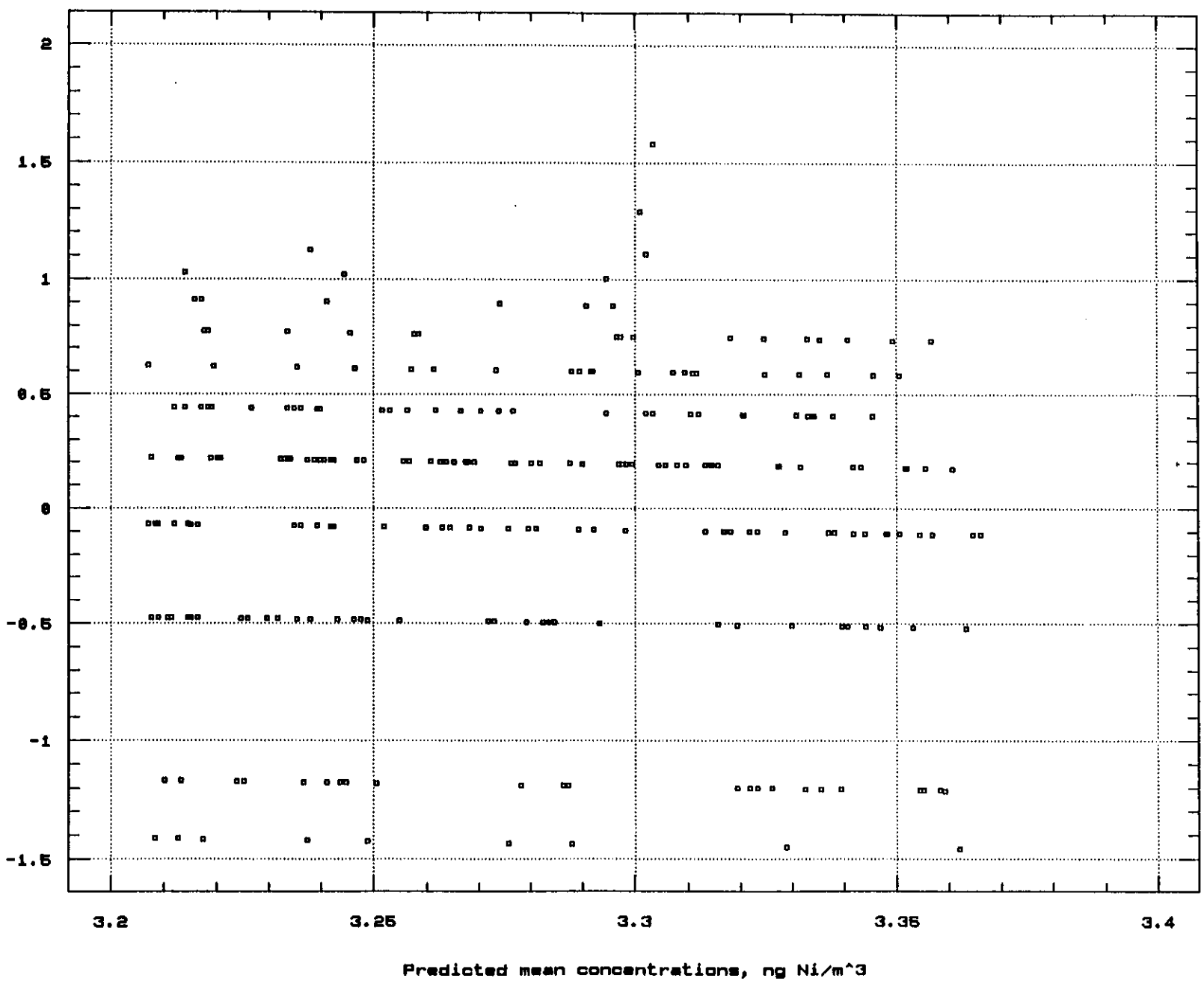
Residuals vs. predicted mean nickel concentrations for the SCC Air Basin
Residuals
2
1.5
1
0.5
0
-0.5
-1
-1.5
3.2
3.25
3.3
3.35
3.4
Predicted mean concentrations, ng Ni/m^3

FIGURE 33

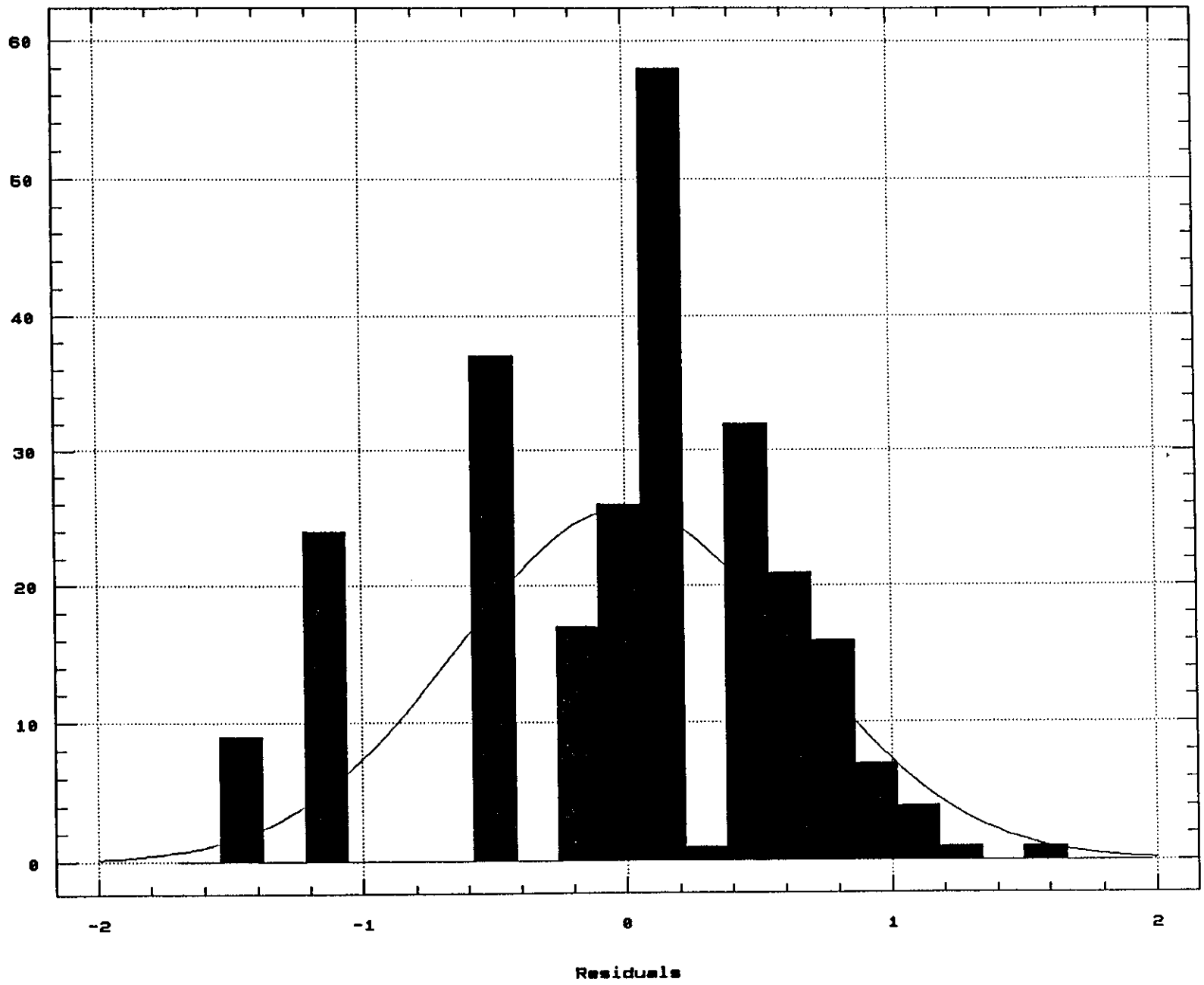
Frequency histogram of residuals for the
South Central Coast Air Basin
60
50
40
30
20
10
0
Frequency
-2
-1
0
1
2
Residuals

FIGURE 34

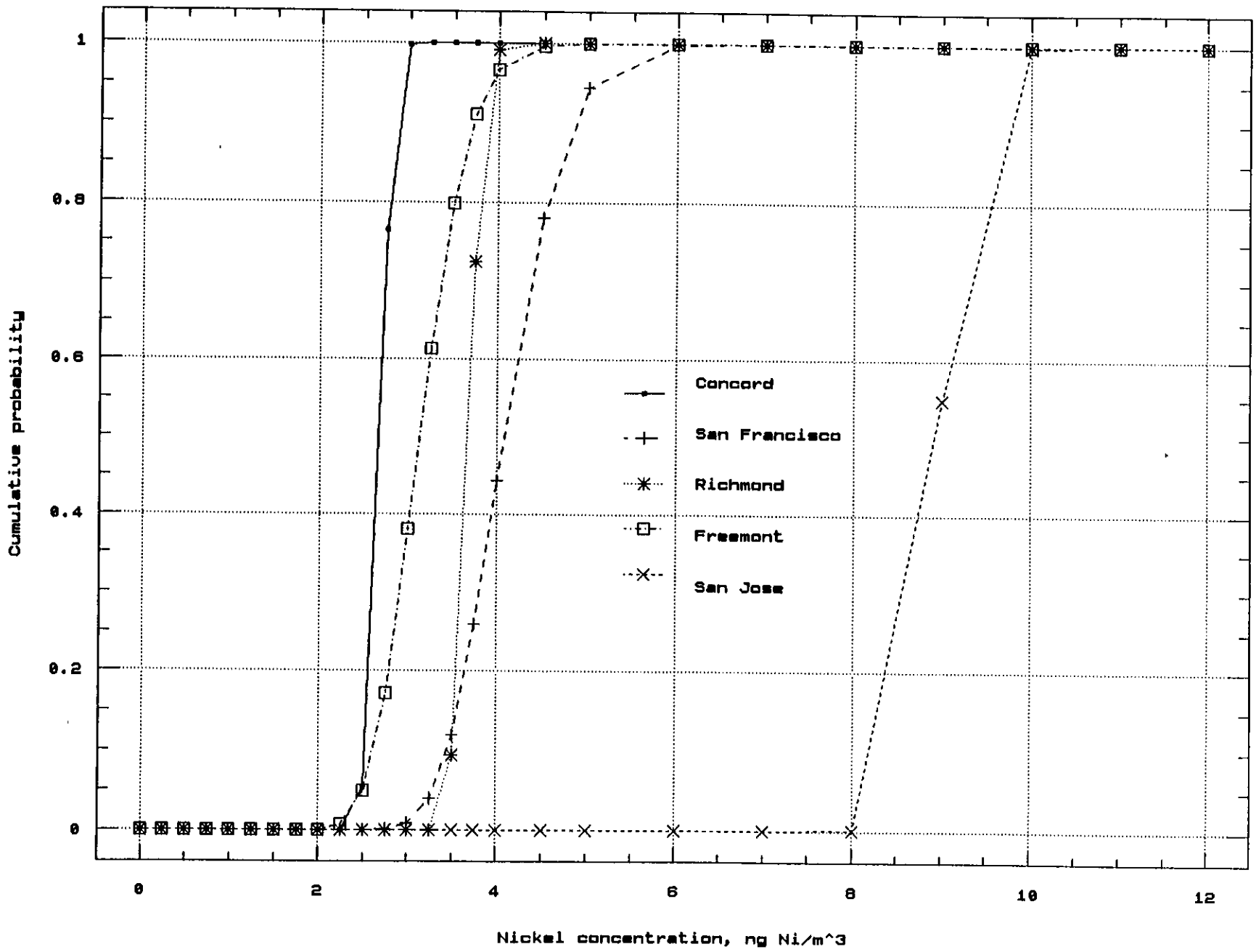
Cumulative probability of mean nickel concentrations in SFBA Air Basin
Cumulative probability
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
12
Nickel concentration, ng Ni/m^3
Concord
San Francisco
Richmond
Fremont
San Jose

FIGURE 35

APPENDIX A

THERMODYNAMIC STABILITY OF VARIOUS NICKEL SPECIES

This appendix presents a thermodynamic analysis of what chemical forms of nickel are expected to be emitted into the environment from various processes. It includes a calculation of the composition of the combustion gases inside oil-burning boilers on pages 7-11.

A chemical reaction $aA + bB \rightarrow cC + dD$ will, under favorable kinetic conditions, proceed spontaneously from left to right as written if the free energy change for the reaction is negative. This occurs when log Q is less than log K where K is the equilibrium constant and Q is the same function of activities as is K but is evaluated for a particular set of conditions that may or may not represent chemical equilibrium. The activities of pure solid or liquid phases are taken to be unity and so contribute nothing to log Q. The activities of gases are taken to be equal to their partial pressures. For example, if the reaction of interest were

$$3Ni(s) + 2SO_2(g) \rightarrow Ni_3S_2(s) + 2O_2(g)$$

then $Q=(a_{Ni_3S_2} \times P_{O_2}{}^2)/(a_{Ni}{}^3 \times P_{SO_2}{}^2)$

and K is the unique value of Q at which chemical equilibrium is achieved. K is a function only of temperature since we are concerned with reactions at a constant total pressure of one atmosphere.

Stoichiometric equations for 12 reactions and the related expressions for log Q are presented in Table 1. Table 2 gives values of their equilibrium constants for selected temperatures (expressed in degrees Kelvin) ranging from 25°C to about 1225°C. Table 3 gives values of log Q for each reaction for five different conditions. The first

of these is for ambient environmental conditions. The other four values of log Q are those calculated to result from the combustion of low sulfur and high sulfur fuel oils in boilers, each with very low and very high values of excess air. Comparing log Q with log K for a given reaction indicates whether the reaction proceeds from left to right (log Q > Log K) or from right to left (log Q < log K) at the given temperature. Thus one can determine whether the products or the reactants are stable under the given conditions.

Comparing log Q for reaction 1 in ambient air with log K for reaction 1 shows that metallic nickel is unstable with respect to nickel oxide over a very wide range of temperatures. Thus the metallic nickel found in dusts from high temperature metallurgical operations was probably unoxidized for kinetic reasons; a protective layer or patches of oxide may have formed and prevented complete oxidation of the metal; or it may have been cooled before the oxidation was complete. Comparing log K for reaction 1 with values of log Q pertaining to boiler operations again shows nickel oxide to be the stable form. Metallic nickel is unlikely to be found in dusts from combustion processes because the nickel does not start out as metal as it does in the metallurgical processes.

Data for reaction 2 shows that metallic nickel is unstable relative to the sulfate except at 1200 K. Since dusty gases are not quenched from temperatures this high, sulfate should form at the expense of metal. However, one usually does not have sulfur in metallurgical operations or metallic nickel in combustion processes, so reaction 2 is of academic interest.

Reactions 3 and 4 were analyzed to show that nickel metal is <u>not</u> converted to Ni_3S_2 or NiS. This is because sulfur pressures are too small to bring about this reaction

even where a high sulfur oil is being burned with very little excess air. The other nickel sulfides are even less stable than Ni_3S_2 under the conditions of interest.

Data for reaction 5 indicates that nickel sulfate decomposes to nickel oxide under all four combustion scenarios at temperatures of 1000 K and above; thus the nickel sulfate observed in particulate from combustion sources must be formed in the cooler regions of the equipment. Log Q is smaller for the situations with more excess air. This agrees with observations that sulfate formation increases with increased excess air. The comparison of Q and K for ambient conditions shows that nickel sulfate, once formed, will not decompose to nickel oxide under ambient conditions.

Reactions 6 and 7 are presented to show that nickel oxide tends to react with other solid phases to form complex metal oxides and silicates. This probably occurs whenever there is an abundance of other metal oxides, silicates, etc. relative to the amount of nickel present. This is usually the case in combustion processes.

Log Q for reaction 8 is always greater than log K, showing that the conditions studied are not sufficiently sulfidizing to form Ni_3S_2 from nickel oxide.

Reactions 9 and 10 proceed to the right except at 1000 and 1200 K. Thus complex oxides and silicates are unstable with respect to nickel sulfate in the cooler sections of combustion equipment.

Reactions 11 and 12 show that nickel sulfate does not decompose or react with nickel oxide to form Ni_3S_2 (and hence any of the other nickel sulfides) under any of the conditions studied.

Table 1: Reactions Involving Various Chemical Forms of Nickel

Reaction	Stoichiometric Equation	Expression for log Q*
1	$Ni(s) + 0.5\ O_2(g) \rightarrow NiO(s)$	$-0.5 \log P_{O_2}$
2	$Ni(s) + O_2(g) + SO_2(g) \rightarrow NiSO_4(s)$	$-(\log P_{O_2} + \log P_{SO_2})$
3	$3Ni(s) + 2SO_2(g) \rightarrow Ni_3S_2(s) + 2O_2(g)$	$2 \log P_{O_2} - 2 \log P_{SO_2}$
4	$Ni(s) + SO_2(g) \rightarrow NiS(s) + O_2(g)$	$\log P_{O_2} - \log P_{SO_2}$
5	$NiO(s) + 0.5\ O_2(g) + SO_2(g) \rightarrow NiSO_4(s)$	$-(0.5 \log P_{O_2} + \log P_{SO_2})$
6	$NiO(s) + Fe_2O_3(s) \rightarrow NiFe_2O_4(s)$	0
7	$2NiO(s) + SiO_2(s) \rightarrow Ni_2SiO_4(s)$	0
8	$3NiO(s) + 2SO_2(g) \rightarrow Ni_3S_2(s) + 3.5O_2(g)$	$3.5 \log P_{O_2} - 2 \log P_{SO_2}$
9	$NiFe_2O_4(s) + 0.5O_2(g) + SO_2(g) \rightarrow NiSO_4(s) + Fe_2O_3(s)$	$-(0.5 \log P_{O_2} + \log P_{SO_2})$
10	$Ni_2SiO_4(s) + O_2(g) + 2SO_2(g) \rightarrow 2NiSO_4(s) + SiO_2(s)$	$-(\log P_{O_2} - 2 \log P_{SO_2})$
11	$3NiSO_4(s) \rightarrow Ni_3S_2(s) + 5O_2(g) + SO_2(g)$	$5 \log P_{O_2} + \log P_{SO_2}$
12	$2NiSO_4(s) + NiO(s) \rightarrow Ni_3S_2(s) + 4.5O_2(g)$	$4.5 \log P_{O_2}$

*Since all solid phases are assumed to be pure, their activities are taken to be unity and thus contribute zero to log Q. Since reactions 6 and 7 involve only solids, log Q is always zero for them.

Table 2: Equilibrium Constants* for Reactions Involving Various Chemical Forms of Nickel at Several Selected Temperatures

Reaction	log K				
	298.15 K	500 K	1000 K	1200 K	1500 K
1	37.069	20.159	7.802		3.727
2	80.984	40.296	10.547	5.682	
3	-68.009	-41.332	-20.855		
4	-36.823	-22.310	-11.388		
5	43.915	20.137	2.745	-0.076	
6	0.894	0.568	0.315		0.261
7	2.13	1.01	0.17		0.03
8	-179.216	-120.954	-46.812		
9	43.021	19.569	2.430	-0.358	
10	85.700	39.264	5.320	-0.242	
11	-310.961	-162.220	-52.496		
12	-267.04	-142.10	-49.74		

*Data were taken from **Contributions to the Data on Theoretical Metallurgy, XVI Thermodynamic Properties of Nickel and its Inorganic Compounds;** Mah, A.D.; Pankratz, L.B.; U.S. Bureau of Mines Bulletin 668, 1976.

Table 3: log Q for Reactions Involving Various Chemical Forms of Nickel in Different Environments

	log Q				
		Combustion of 3.5% S oil		Combustion of 0.7% S oil	
Reaction	Ambient* Air	0.5% excess air	30% excess air	0.5% excess air	30% excess air
1	0.339	1.500	0.670	1.500	0.672
2	6.678	5.658	4.110	6.398	4.867
3	10.644	-0.685	2.859	0.796	4.358
4	5.322	-0.342	1.430	0.398	2.179
5	6.339	4.158	3.440	4.898	4.195
6	0	0	0	0	0
7	0	0	0	0	0
8	9.628	-5.185	0.849	-3.704	2.342
9	6.339	4.158	3.440	4.898	4.195
10	12.678	8.315	6.879	9.796	8.390
11	-9.389	-17.658	-9.470	-18.398	-10.242
12	-3.050	-13.500	-6.031	-13.500	-6.048

*Based on P_{O_2} = 0.21 atm and $P_{SO_2} = 10^{-6}$ atm, i.e. 1 ppm by volume.

The foregoing calculations required knowledge of the partial pressures of sulfur dioxide and oxygen in an oil-fired boiler. These were calculated as described below.

Selection of a Fuel Oil Composition

Steam/its generation and use (38th edition) by The Babcock & Wilcox Company, 1972 states on p.5-18 that "...No. 6 fuel oil is the most widely used for steam generation." In Table 25 on p.5-19, it gives a range of analyses for fuel oils. That for No. 6 is as follows: 0.7-3.5 S, 9.5-12.0 H, 86.5-90.2 C, water and sediment 2%.

Each %C requires 2.67 units of oxygen while each %H requires 7.9365 units of oxygen. Thus for a given sulfur content, a fuel rich in hydrogen and relatively poor in carbon will produce a greater volume of off-gases and thus a lower partial pressure of SO_2 than will an oil poorer in hydrogen and richer in carbon. Two hypothetical compositions of No. 6 oil were therefore postulated to give the greatest possible variation of SO_2 partial pressures and still stay in the ranges given above.

Case I:	3.5 S	9.5 H	86.5 C	0.5 H_2O
Case II:	0.7 S	12.0 H	86.5 C	0.8 H_2O

Stoichiometric Calculations

The calculation of the amount of air required for theoretically complete combustion was carried out as described in Chapter 6 of **Steam/**. The calculations were based on 1 kg of oil. For the high sulfur oil in Case I:

Element	%	Moles	Moles O_2 required
S	3.5	1.0915	1.0915
H	9.5	94.246	23.5615
C	86.5	72.0833	72.0833
			96.7363

There are 4.76 moles of air/mole O_2 so the air required for 100% combustion is 4.76 x 96.7363 = 460.465. This amount of air contains 363.73 moles N_2 and 460.465 x 29 x .013/18 = 9.6442 moles H_2O. There were also 0.2778 moles of H_2O in the oil to begin with. Thus in the exit gas (at 0% excess air) we have the following species (expressed in moles):

SO_2 = 1.0915
H_2O = 47.123 + 9.6442 + 0.2778 = 57.045
CO_2 = 72.0833
N_2 = 363.73

However, real boilers require some excess air (EA); that is, air in addition to the theoretical requirement. The amount of this air is expressed as a percentage of the stoichiometric requirement which, in this case, is 460.465 moles. Thus there will be "excess" N_2, H_2O and some free O_2 in the exit gases.

$$N_2 = 460.465 \times \frac{EA}{100} \times .79$$

$$H_2O = 460.465 \times \frac{EA}{100} \times 29 \times .013/18 = 460.465 \times \frac{EA}{100} \times .0209$$

$$O_2 = 460.465 \times \frac{EA}{100} \times .21$$

Adding these to the quantities for stoichiometric combustion gives:

SO_2	=	1.0915
H_2O	=	57.045 + 0.0964 x EA
CO_2	=	72.0833
N_2	=	363.73 + 3.6377 x EA
O_2	=	0.967 x EA
Total		493.95 + 4.7011 x EA

$$\%SO_2 = \frac{109.15}{493.95 + 4.7011 \times EA} \qquad \%O_2 = \frac{96.7 \times EA}{493.95 + 4.7011 \times EA}$$

Repeating the calculation for the low sulfur oil of Case II gives the following results:

$$\%SO_2 = \frac{21.83}{526.2447 + 4.96 \times EA} \qquad \%O_2 = \frac{102.02 \times EA}{526.2447 + 4.96 \times EA}$$

On page 7-6, **Steam/** says it is possible to operate most oil-fired boilers with as little as 5 to 7 per cent excess air at full load and that a few have run as low as 2.5 per cent. As the load drops, the excess air will normally increase. Bennet and Knapp (1978) of the EPA report observing excess **oxygen** values as low as 0.1 - 0.7% and 0.2 -1.1%. These would correspond to excess air values of about 0.5 - 3.3 and 1 - 5.2% respectively. The highest values observed by Bennet and Knapp corresponded to excess air of 14.3 - 28.6%.

The formulae for Case I and Case II were evaluated for several values of EA ranging from 0.5 to 30%.

Table 4: SO_2 and O_2 Pressures in Exit Gases from an Oil-fired Boiler

	Case I		Case II	
EA, %	SO_2,%	O_2,%	SO_2,%	O_2,%
0.5	0.22	0.10	0.04	0.10
2.5	0.22	0.48	0.04	0.47
5.0	0.21	0.93	0.04	0.93
7.5	0.21	1.37	0.04	1.36
30	0.17	4.57	0.03	4.53

An analysis of the pressure drops through a boiler indicates a pressure about 1% less than atmospheric in the region where the temperatures are of interest; i.e. high enough to provide favorable kinetics yet low enough that the equilibrium phase composition is not radically different from what would be expected at ambient temperatures. Thus with little error, the volumetric concentrations of O_2 and SO_2 can be taken to equal their partial pressures. The values from Table 4 were substituted into the formulae for log Q in Table 1 to give the values for log Q in Table 3.

The partial pressures of SO_2 are the maximum possible values because, in practice, some of this sulfur would be tied up as SO_3 and as sulfates as it made its way through the boiler. The amount of sulfur so converted is typically about 7% of the amount present. An approximate correction

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for this fact would involve taking P_{SO_2} = 0.93 x % SO_2/100 and P_{O_2} = % O_2/100 - 0.035 x % SO_2/100 where the % SO_2 and % O_2 come from Table 4. Calculating log Q from these corrected partial pressures doesn't change the conclusions about which phases are stable. It shows, however, that the nickel sulfides are even less likely to form than the uncorrected calculations indicate.

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APPENDIX B

CHEMICAL SPECIATION OF NICKEL PHASES IN INDUSTRIAL DUSTS

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JRGRL, May 3, 1990

(Supersedes the draft of January 13, 1989)

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SPECIATION OF NICKEL PHASES IN INDUSTRIAL DUSTS

1990-05-03 JRGRL, V.J. Zatka

OUTLINE

Individual nickel phases are extracted from the dust sample (-400 mesh, <0.037 mm) by sequential selective leaching. Four phase categories can be determined:

1) soluble nickel - water soluble normal nickel salts;

2) sulfidic nickel - besides Ni_3S_2 and NiS also dissolved are arsenides NiAs and $Ni_{11}As_8$, and selenide NiSe; phases, such as Ni_5As_2 and NiTe, yield more slowly and, as the rate is particle size dependent, may require longer leaching time than specified in this procedure;

3) metallic nickel - free or alloyed with iron (ferronickel);

4) oxidic nickel - refractory nickel oxide.

The sequential leachings are carried out in an all-Teflon filter holder fitted with a regenerated cellulose membrane filter. The test sample, a portion of bulk dust or a dust-loaded 37 mm membrane or an areal portion of a loaded high-volume fiber filter, is transferred onto the cellulose filter and the individual nickel phases are selectively leached. The 37 mm membrane can be held in place by a glass tripod, and so prevented from floating. Each leach solution is evaporated to dryness and the residues are wet-ashed with nitric and perchloric acids. The leached sample residue and filter(s) are also dissolved in nitric and perchloric acids. Each leach solution is analyzed for nickel by conventional atomic absorption (or plasma emission, if available).

To simplify the final wet-ashing, it is recommended to have the airborne dusts collected on PVC acrylic copolymer filters, such as the Gelman DM Metricel membranes, rather than on plain PVC. Quartz fiber filters, due to their very small surface alkalinity, are preferred to glass fiber filters in hi-vol sampling. High alkalinity of glass fibers has been linked to secondary chemical changes in sampled dusts and to possible formation of basic nickel salts.

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Soluble nickel phases, mostly as the normal nickel sulfate, are generally leached at pH 4. Leaching of basic nickel salts at this pH, however, is very slow and, without being completed, may still continue in the next sulfidic group causing false nickel finds. If the sample to be analyzed is known to contain basic nickel salts, leaching of the soluble nickel phases should be done at lower pH of 2.1 (0.1M citric acid solution). This approach ensures dissolution of all nickel salts including the basic salt component, and sulfidic nickel artefacts are so avoided. Surface Ni(III) from black nickel oxide, and nickel hydroxide, if present in the sample, may be leached to a various extent.

REAGENTS

AMMONIUM CITRATE, 0.1M SOLUTION (pH 4.4)

Dissolve 8.5 g of diammonium citrate, $(NH_4)_2HCit$, and 2.6 g of citric acid monohydrate, $H_3Cit.H_2O$, in distilled water and dilute to 500 mL. Check pH with a meter and adjust, if necessary, to 4.4 with ammonia or citric acid.

CITRATE WASH SOLUTION

Dilute 100 mL of the 0.1M ammonium citrate solution to 500 mL and mix.

PEROXIDE-CITRATE LEACH SOLUTION

Mix two volumes of 0.1M ammonium citrate solution (pH 4.4) and one volume of 30% hydrogen peroxide. The mixed solution should have pH 4.0-4.2. Adjust, if necessary, with ammonia or citric acid. Prepare fresh before use.

STANDARD NICKEL STOCK SOLUTION (1 g Ni/L)

Dissolve 1.00 gram of nickel metal in a minimum of 8M nitric acid. Add 15 mL of sulfuric acid (1+1) and evaporate to dryness. Cool and dissolve the salts in 100 mL of 6M hydrochloric acid. Transfer to a one litre volumetric flask, dilute to volume with water and mix.

DILUTE STANDARD NICKEL SOLUTION (100 µg Ni/mL)

Pipet 50 mL of the 1 g/L standard nickel solution into a 500 mL volumetric flask. Add 25 mL of concentrated hydrochloric acid, dilute to volume with water and mix.

NICKEL WORKING STANDARDS

Prepare 0.5, 1.0, 2.5, 5.0, and 10.0 µg Ni/mL standards by pipetting 1.0-, 2.0-, 5.0-, 10.0-, and 20.0-mL aliquots of the 100 µg/mL dilute standard nickel solution into 200 mL volumetric flasks. Add 8 mL of concentrated hydrochloric acid to each, dilute to volume with water, and mix.

A separate set of working standards with a sodium and calcium matrix is required for the measurement of oxidic nickel in hi-vol dust samples collected on glass fiber filters. The matrix must match the sodium and calcium contribution from the areal portion of the filter used. No matching matrix is required in the analysis of quartz fiber filters.

APPARATUS

TEFLON (PFA) FILTER HOLDER, 47 mm (Savillex No. 4750-47-6) with a rubber stopper and a 500 mL suction flask (Fig. 1). The top funnel of the filter holder should be cut to a height of 30 mm.

SUPPORTING REGENERATED CELLULOSE MEMBRANE, 47 mm, such as the Sartorius SM116-07, 0.2 µm pore size. This type of filter material is required as it is alcohol and bromine resistant. Cellulose ester filters are not suitable.

GLASS TRIPOD, about 34 mm wide, round or triangular, made of a glass rod, about 3 mm in dia.; leg height 7-10 mm.

FLARED GLASS ROD ("Willstätter needle"), 3 mm max. in dia. (Fig. 1), slightly longer than the Teflon outlet tube of the filter holder. The flared top of the rod rests on top of the outlet tube.

DETERMINATION OF NICKEL BY ATOMIC ABSORPTION

Measure the absorbance of each leach solution (Note) and of the working standards at wavelength 232.0 nm using conventional flame atomic absorption spectrometer. Make sure that all solutions are 5% v/v in hydrochloric acid.

Construct a calibration graph of absorbance versus concentration. From the graph obtain the nickel concentration found in each leach solution, correct it for the reagent blank, and calculate the nickel content in the used dust portion or the dust load on the filter.

NOTE - The procedure calls for final volumes of 10 mL each. To measure the very small nickel levels usually found in environmental samples, the AA spectrometer, set in the µg/mL concentration mode, must be calibrated to read to two decimal places. For a satisfactory readout stability of ±0.01 µg/mL, the hollow

cathode lamp and the burner assembly have to be at thermal equilibrium. Integration time of 3 sec is recommended. Under these conditions, a limit of determination of 0.02 µg Ni/mL (0.2 µg Ni abs.) can readily be achieved. Only the first two of the working standard solution set may then be needed.

REAGENT BLANK

Carry a blank cellulose filter membrane and a sampling filter blank, if necessary, through the procedure using all scheduled leaching steps. Use the prescribed volumes of all leach solutions and acids. Wet-ash the leached filters. Analyze each final solution for nickel. Special attention should be paid to blanks of fiber filter portions used.

PROCEDURE

Set up the filtering system so that mild suction can be turned on and off at short intervals as necessary. To collect the filtrates, place a test tube 20x150 mm into the suction flask. It is advisable to make a small spout in the test tube rim. Adjust the length of the Teflon holder outlet tube so that it would reach into the test tube. Place the flared glass rod into the tube as shown in Fig. 1 to prevent the outlet tube to stay filled with aqueous filtrates. Fit the Teflon holder with the regenerated cellulose membrane. The filtering system is now ready for use.

To analyze hi-vol samples, only an areal portion, such as a 2x8in. strip, of the 8x10in. fiber filter sheet should be used. Fold the strip onto the supporting cellulose membrane, cover it with the leach solution and, with a glass rod, squeeze out all air bubbles.

Washing and complete removal of the dissolved nickel at each leaching stage is of utmost importance to avoid nickel carryovers between the phase categories, most significantly between the "soluble" and the "sulfidic" groups. Filtrate which tends to accumulate under the filter-supporting disc must always be removed before a new portion of the wash solution is added. With the suction on, use rocking and tapping of the tilted flask to drain all filtrate into the test tube. Special attention has to be paid to washing of folded fiber filters. The technique which appears to serve best involves squeezing the folded filter with a glass rod and holding for a couple of seconds while the suction is on. Solution squeezed out is then rapidly drawn through the filter. First, the whole surface area of the folded filter has to be treated in this manner. Later, when most of the filter fibers are broken, the original stiffness disappears and the fiber material begins to spread over the supporting membrane filter. Complete removal of the solution by suction then becomes easier. Turn suction off between the washes, cover the fiber layer with 5 mL of wash solution, and work the layer carefully with the glass rod to get all fibers well soaked. Turn suction on and drain all solution, including that from underneath the support disc, to the test tube. Repeat the wash three times.

WARNING. The procedure involves wet-ashing of organic matter by perchloric acid. The fuming acid is a powerful oxidant and has to be handled with great caution. Organic matter must first be decomposed by conc. nitric acid before it is fumed with perchloric acid. If the hot perchloric acid solution turns dark, add a drop of nitric acid to fully oxidize the carbonaceous material. The evaporations must be carried out in fumehoods specially designed for the use of perchloric acid.

DETERMINATION OF SOLUBLE NICKEL

Weigh differentially approx. 10 mg of the sample dust (-400 mesh, <0.037 mm) and transfer it onto a moistened supporting cellulose membrane in the filter holder (Note). Alternately, use filter, or a part of it, loaded either in a personal filter pump cassette or in a hi-vol sampler. A glass tripod can be used to hold the 37 mm membrane filter in place. Moisten the sample with a few drops of methanol and add 15 mL of 0.1M ammonium acetate solution. Cover the filter funnel and allow the sample to leach for 90 min (Note). Swirl the solution at times or squeeze the filter folds under the leach solution. Apply gentle suction and pass all solution through the filter. Wash the filter thoroughly with the citrate wash solution making sure that all filtrate is fully drained from the bottom of the filter holder before the next wash portion is added. Follow the procedure of washing the folded fiber filter as described earlier. Transfer all filtrates to a 100 mL beaker and evaporate to dryness. Moisten the residue with 1 mL each of conc. HNO_3 and conc. $HClO_4$, and wet-ash by digesting in the covered beaker. If a dark spot developed, add one drop of conc. HNO_3. When contents of the beaker become colorless, evaporate to dryness. Dissolve the warm residue with 1 mL of HCl (1+1) and transfer the solution to a 10 mL volumetric flask. Dilute to volume with water and mix. Reserve the solution for analysis. Return the rinsed empty test tube to the suction flask.

NOTES - Before transferring the bulk sample portion, the cellulose membrane should be moistened with the leach solution to minimize static effects.

- During the 90-min period, a portion of the leach solution may pass through the supporting filter membrane. Since the sample must remain covered with the leach solution throughout the operation, return accumulated filtrate onto the filter as necessary.

DETERMINATION OF SULFIDIC NICKEL

To the moist sample from which soluble nickel phases have been leached add 15 mL of the peroxide-citrate leach solution. Cover the filter holder with a watch glass, and allow the dust sample to react for 60 minutes. Keep the sample covered with solution by recycling the filtrate if some has passed through the filter. When finished, apply mild suction and draw all leach solution through the filter. Wash the filters with the citrate wash solution. Remove water from the washed filters by rinsing them twice with methanol (Note). Apply suction and draw all liquid into the test tube. Transfer the filtrates to a 100 mL beaker and evaporate to dryness. Moisten the dry residue with 1 mL each of conc. HNO_3 and conc. $HClO_4$, and wet-ash by digesting in the covered beaker. When contents have turned colorless, evaporate to dryness. Dissolve the warm residue with 1 mL of HCl (1+1) and transfer the solution to a 10 mL volumetric flask. Dilute to volume with water, mix, and reserve the solution for analysis. Return the rinsed empty test tube to the suction flask.

NOTE - Turbidity may occasionally develop in the filtrate after the methanol wash. Produced by leached, water-insoluble organic matter, the turbidity is no cause for concern.

DETERMINATION OF METALLIC NICKEL

To the methanol-washed sample filter(s) from which sulfidic nickel has been leached add 10 mL of anhydrous methanol containing 0.2 mL of bromine (Note). Cover the filter holder and let stand for 5 sec (Note). Apply suction to have the solution slowly pass through the filter. Wash the filter with methanol until bromine-free. Transfer the filtrates to a 100 mL beaker and evaporate to dryness. Moisten the residue with 1 mL each of conc. HNO_3 and conc. $HClO_4$, wet-ash, and slowly evaporate to dryness. Dissolve the warm residue with 1 mL of HCl (1+1) and transfer the solution to a 10 mL volumetric flask. Dilute to volume with water and mix. Reserve the solution for analysis.

NOTES - The bromine solution must be prepared shortly before use to prevent formation of hydrobromic acid and avoid premature dissolution of some nickel oxides. For the same reason, moisture must be excluded from the bromine-methanol system by using anhydrous alcohol and by avoiding unnecessary contact with moist atmospheric air.

- The leach duration should be kept to the minimum especially in samples suspected of the presence of basic nickel salts. The short reaction time does not inhibit complete dissolution of the metallic phase.

DETERMINATION OF OXIDIC (REFRACTORY) NICKEL

Transfer the leached sample residue and filter(s) to a 150-200 mL tall beaker. Wipe the bottom and inner walls of the Teflon funnel with moist filter paper (Whatman #41) and add it to the beaker. Add 5 mL of conc. HNO_3, cover the beaker and digest on a hot plate until the filters disintegrate. Add 4 mL of conc. $HClO_4$ and continue the digestion to wet-ash the organic matter.

When analyzing a glass or quartz fiber filter strip (hi-vol sample), transfer all filters to a 400 mL heatable Teflon beaker with a graphite base (Nalge P/N 1550). Wipe the bottom and inner walls of the Teflon funnel with moist filter paper (Whatman #41) and add it to the beaker. Add a mixture of 5 mL each of conc. HF and conc. HNO_3. Heat to dissolve the siliceous fibers and the cellulose membrane. Add 5 mL of conc. $HClO_4$ and evaporate to heavy perchloric acid fumes (max. permissible hotplate temperature 280 °C), cool, rinse the beaker walls and the cover with water, and evaporate to heavy fumes again. Repeat the rinse and evaporation to allow for full elimination of the hydrofluoric acid before the perchloric acid is volatilized (Note).

Continue digesting the perchloric acid solution in the covered beaker until all sample particles are dissolved (Note). If the solution darkens, add a few drops of conc. nitric acid to oxidize the residual organic matter. Volatilize the perchloric acid completely and dissolve the warm residue in 1 mL of HCl (1+1). Transfer the solution to a 10 mL volumetric flask, dilute to volume with water and mix (Note). Analyze the solution for nickel using appropriate working standard solutions.

NOTES - An excess of free perchloric acid is required to effect complete volatilization of hydrofluoric acid. More perchloric acid may be added if it happened to evaporate prematurely.

- To dissolve completely, refractory nickel oxide requires fuming with conc. perchloric acid. Hotplate temperatures of less than 210-240 °C will result in low nickel recoveries. It is recommended to check the hot solution for undissolved sample particles before the perchloric acid is finally volatilized. Addition of 1-2 drops of HF may assist the dissolution of residues high in silica.

- In the analysis of hi-vol samples, a complete removal of hydrofluoric acid will produce a clear final solution in the volumetric flask.

J. Stuart Warner
Vice-President
Occupational & Environmental Health
(416) 361-7866

September 5, 1990

Ms Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
Attention: Nickel
1219 K Street
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma:

I am pleased to submit a copy of Inco Limited's Recommendations and Comments on the Part B Report. This, together with our Recommendations and Comments on the Part A Report, which I handed to you on August 15, 1990, constitutes Inco's response to the Technical Support Document for the Proposed Identification of Nickel as a Toxic Air Contaminant.

The TSD compared very favourably with other first draft documents on nickel that we have reviewed over the years. Nevertheless, any document of this size and scope can be improved. Many of my recommendations and comments are intended to help ARB/DHS do better some things it had already decided to do. However, there are other areas where I believe with the proposed actions are incorrect or inappropriate. Now that these areas of disagreement have been identified, I hope we can work together to resolve them.

If I can be of further assistance during your review of the TSD, please don't hesitate to call on me.

Sincerely,

Stuart Warner

att.

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RECOMMENDATIONS AND COMMENTS ON

THE PART B REPORT OF THE

TECHNICAL SUPPORT DOCUMENT

titled

PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT

Submitted to
California Air Resources Board,
Stationary Source Division

by

J. Stuart Warner, Vice-President
Occupational and Environmental Health
INCO LIMITED

on

September 5, 1990

000303

RECOMMENDATIONS FOR IMPROVING THE PART B REPORT OF THE TECHNICAL SUPPORT DOCUMENT "PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT"

1. Look for epidemiological and toxicological information on nickel-containing substances like those in ambient air

This recommendation is the corollary to Recommendation 1 in our submission on Part A of the TSD. However, DHS cannot follow it until ARB develops specific information on the forms of nickel that exist in California ambient air. Even when ARB does that, DHS might find that there is no information in the literature on forms of nickel that resemble to the forms that exist in ambient air. It may become necessary to collect some nickel-containing species at emitting sources and to conduct tests of bioavailability and toxicity. Inco would be prepared to contribute to such an effort. Although I can't speak officially for NiPERA, I believe it would consider helping to sponsor toxicity tests of nickel-containing species found in the ambient air because it is interested in environmental matters as well as in occupational concerns.

2. Rethink the definition of "threshold"

DHS should also consider non-genotoxic mechanisms of carcinogenesis. There is a growing body of literature on nickel that involves such mechanisms. These are particularly important when doses are being extrapolated over six or seven orders of magnitude.

There is also a great deal of epidemiologic information on nickel-exposed workers. The cancer risk was confined to a few workplaces in the nickel-producing industry and has not been detected in the nickel-consuming industry. DHS should examine this information in more detail to see where practical thresholds exist. After all, environmental regulation should be practical, not based on mathematical models that are increasingly called into question by the experts.

I note that the Concluding Remarks of the ICNCM (1990) report include the following comment:

> *"The evidence from this study suggests that respiratory cancer risks are primarily related to exposure to soluble nickel at concentrations in excess of 1 mg Ni/m^3 and to exposure to less soluble forms at concentrations greater than 10 mg Ni/m^3. With excess risks being confined to these high levels of exposure and the absence of any evidence of hazard from metallic nickel, it can be concluded that the risk to the general population from exposure to the extremely small concentrations (less than 1 µg Ni/m^3) to which it is exposed in ambient air is minute, if indeed there is any risk at all."*

3. *Deal explicitly with the uncertainties in the unit risk estimate and in estimated risk*

I apologize for repeating Recommendation 5 from Part A but it cannot be said too many times. I assume one of DHS's primary objectives is to produce a unit risk estimate. The major uncertainty is whether the estimate is relevant to the species of nickel found in the ambient air. (If it isn't, using such an estimate for risk assessment is like looking for your cars keys under the lamppost because the light is better there than where you dropped them.)

Assuming the major uncertainty can be avoided, there will still be uncertainties associated with the data and models needed to calculate the unit risk estimate. These should be dealt with specifically so that the risk manager can associate a probability with **any value** of the estimate, not just the upper 95% confidence limit. When the estimate is combined with the population exposure estimate, the uncertainties in each of these estimates should be combined to provide an associated probability for the estimated cancer incidence.

4. *Make use of more recent information*

Part A of the TSD did not use all of the data available to ARB on the concentrations of ambient nickel in California. Part B also seems to be somewhat dated in that few references after 1986 are employed. In my Comments, I have pointed out a number of papers, old and new, that should be of use to DHS. However, no one person can be familiar with all of the literature so I urge DHS to revisit the literature on nickel and its compounds.

Many of the experimental studies described in Part B are less than perfect; e.g. the form of nickel tested was not well-described; too few animals were used; routes of exposure were irrelevant to humans exposed environmentally; inhalation exposures were not continued long enough and/or follow-up after exposure was too short; etc. I urge DHS to take advantage of the ongoing NTP bioassays of nickel sulfate, nickel subsulfide and green nickel oxide. The exposures to the first and last of these have been completed and the subsulfide will be completed in the next month or two. The three compounds represent a wide range of solubilities and the sulfate may well be a reasonable surrogate for some ambient forms of nickel. The studies have used large numbers of animals and both sexes of two species. Numerous peripheral studies are being conducted at the same time, within and without the NTP program.

For instance, NiPERA is sponsoring a program for determining the rate of clearance of these compounds from the respiratory tracts of the test animals and from non-human primates. The purpose is to be able to model various aspects of the delivered dose and thus assist in the interpretation of the results of the bioassay.

I strongly urge DHS to do whatever is necessary to obtain access to this information before it completes its review of the Part B report. I think these studies are the first and the last good inhalation studies to be done on nickel compounds.

COMMENTS ON THE PART B REPORT OF THE TECHNICAL SUPPORT DOCUMENT "PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT"

If references cited below cannot be found in the References section of Part B of the Technical Support Document ("TSD"), they will be listed in the References section of these comments.

p.1, Summary: To minimize repetition, I generally will not repeat here comments made in later sections, where the topics were treated in detail.

p.1, para.2: The "attribution" of various symptoms in welders of high-nickel alloys to nickel metal aerosols was made by DHS, not by the authors. In any event, the metals in welding fume are almost always completely oxidized.

p.3, para.2: Only 266 of the 1855 men in one of the West Virginia cohorts were classified as "refinery workers".

p.3, para.2: The **average** exposure concentrations in the Ontario cohort ranged from about 30 to about 250 mg Ni/m^3.

p.4, para.4: If ARB analyzed all its nickel data, it would find that the highest mean nickel concentration in California is currently about 10.5 ng Ni/m^3. DHS should be multiplying the unit risk estimate by the **lifetime exposure** concentration but ARB has not yet taken account of the duration of Californians' exposures to ambient nickel.

p.4, para.5: There seems to be a discrepancy between this presentation and that on p.117, para.4. Page 4 seems to be saying that the risk will be based on exposure to **total** nickel while page 117 says it will be based on **insoluble** nickel. The encouraging statement in this paragraph is: "However, it is more likely that information on the speciation of nickel compounds in ambient air will be substantially improved." I fervently hope so!

p.5, items I B2 & B3: DHS has reported neither the full story nor the latest story of IARC's classification of nickel and nickel compounds.

In Supplement 7, IARC classified nickel and nickel compounds in Group 1. However, IARC footnoted this conclusion as follows: "This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group." IARC introduced this caveat because it had grouped a number of substances under a common heading even though relatively few members of the

group had been bioassayed for carcinogenic activity or studied epidemiologically. IARC also stated (p.265, para.7): "It is still not possible to state with certainty which specific nickel compounds are human carcinogens, and which are not."

IARC decided to re-evaluate nickel as soon as the ICNCM (1990) report was available. It did so in June 1989. I was an observer at the meeting. Although the relevant monograph has not yet been published, the conclusions have been made public. Nickel compounds are still listed as Group 1 carcinogens but metallic nickel was downgraded to Group 2B; i.e. possibly carcinogenic to humans. After the overall evaluation had been agreed upon, the IARC secretariat asked the working group to provide a rationale for grouping all forms of nickel. The working group was unable to do so! It will be very interesting to see if the IARC secretariat has prepared a defensible rationale for inclusion in the monograph.

p.5, item II A2: Wouldn't it be more accurate to say that "DHS found a linear relationship between the SMR for lung cancer and adjusted duration of exposure in an occupational cohort."? The present wording says that **more than one** occupational study was found to be consistent with a linear relationship. Furthermore, I fear the "linear relationship" may be taken to be a **linear extrapolation** to ambient levels of nickel.

p.5, item II E: The epidemiology of occupationally-exposed cohorts reveals practical thresholds for carcinogenicity at concentrations of nickel greatly in excess of ambient concentrations. DHS should explain what kind of information it would accept as evidence of a threshold.

P.5, item III A1: Is it DHS's intent to report the **range** of observed concentrations of ambient nickel or the **mean** of the observed concentrations? The words indicate the former but the higher figure suggests the latter. Inco's Recommendations and Comments on Part A indicate that the mean concentrations range from 2.4 to 10.5 ng Ni/m^3.

p.6, IV.C: The meaning of the first sentence is not clear to me. In any event, DHS has no basis for comparing the forms of nickel involved in occupational and ambient exposures because ARB has not identified the forms of nickel in ambient air. Simply finding that some of them are water-insoluble does not prove that they are the same species as the water-insoluble species that were present in the occupational settings that have been studied epidemiologically.

It is not appropriate to use ambient levels of nickel to estimate a human lung cancer risk. Such a calculation must be based on a **dose**. See Recommendation 5 in Inco's submission on Part A.

p.7, para.3: An absorption "rate" without a time dimension is meaningless.

p.8, line 8: DHS must be careful to distinguish between insolubility in water and insolubility in biological fluids because the former is not always a good predictor of the latter. For example, while nickel subsulfide has a dissolution half-time of 10.4 years in water, its dissolution half-times in rat serum and in rat renal cytosol are only 34 days and 21 days respectively. In sharp contrast, the dissolution half-time of nickel oxide in all three media is greater than 11 years (Kuehn and Sunderman, 1982). Thus the solubility of nickel subsulfide in biological fluids is much closer to that of the water-soluble nickel salts such as sulfate, chloride and nitrate than it is to that of nickel oxide. Furthermore, the NTP inhalation studies (Dunnick et al. 1988, 1989) have confirmed that the subsulfide is more like the sulfate than the oxide with respect to toxicity to the respiratory tract. Thus, solubility in water is not an adequate criterion for assessing risk associated with ambient exposure. It is essential to know what species are actually present in California's air.

p.8, line 6: Torjussen and Anderson did not attempt to speciate the nickel present in the nasal mucosa. Although I have not reread the paper word for word, I do not believe any mention was made of observing particles in the mucosa. How then does DHS conclude that the nickel which was slowly removed from the nasal mucosa was present in an insoluble form? How can DHS rule out the possibility that it was originally present as soluble nickel?

p.8, para.4: It is clear throughout Part B that DHS is primarily concerned with the possibility that inhaled ambient nickel could cause cancer. It should therefore note that the cancers associated with nickel exposure in certain obsolete nickel refining operations were those of the sinonasal cavity and of the bronchial region; i.e. where coarser particles deposited. Thus the deposition fraction in rat **lung** does not seem to be relevant to DHS's concerns. DHS should, however, ask ARB to provide information on the size distribution of nickel-containing particulate in ambient air to see where it is likely to deposit in the respiratory tract.

p.8, last para.: Menzel et al. (1986) studied the clearance of **inhaled** nickel chloride aerosol from rat lung and concluded it was governed by Michaelis-Menten kinetics based on the shape of the observed clearance curve. I encouraged Menzel to see if his model could fit the NTP data for nickel sulfate but he was not interested in trying.

p.12, item 3: Comment below will indicate that English et al. tested a substance that is very unlike most of the "nickel oxides" reported in the literature or that might have existed in the nickel refineries. It is therefore of little relevance for risk assessment.

Table 3.1: Shouldn't some data be given for metallic forms of nickel? Muhle et al. (1988) studied the decrease in lung burden of nickel powder and Ni/Cr stainless steel grinding dust instilled into Syrian golden hamsters. (Since the conference volume has not yet been published, a copy of Muhle et al. (1988) is included as Appendix A.) The powder and dust were instilled in twelve doses at two-week intervals. The total dose

of the nickel powder (MMAD=9 μm) was 9.6 mg while the Cr/Ni stainless steel grinding dust (MMAD=3-5 μm) was instilled at total doses of 36 and 108 mg. Two hamsters of each sex were sacrificed at 14 days and at six and 12 months after the last instillation for determination of the lung nickel burden. An exponential curve was fitted to the pooled lung nickel burdens of the males and females for the three sacrificial dates. The clearance half-time for nickel powder was estimated to be about 150 days while that for the Cr/Ni grinding dust was estimated to be about 450 days.

p.13, item 3: As pointed out on p.16, the Benson et al. data for instilled Ni_3S_2 indicate slower clearance than do other studies. I do not believe these results. No other work, including several subsequent inhalation studies conducted by Benson et al., has suggested that Ni_3S_2 would be cleared more slowly than NiO. There must have been some error in the sampling and or analysis.

p.16, para.3: DHS has noted that the absorption reported by English et al. for NiO was different from that reported by Wehner and Craig and by Kodama et al. DHS suggests the difference is due to different routes of administration; i.e. instillation vs. inhalation. This may contribute to the difference but DHS should also consider that the different result may have been due to the fact that three different substances were tested under the rubric "nickel oxide".

DHS has made a mistake that is commonly made by those new to the chemistry of nickel. It has assumed that nickel oxide (NiO) is a unique compound. It is not. "Nickel oxide" describes a family of substances with stoichiometry and XRD patterns close to those of NiO and Bunsenite respectively but in which subtle differences in composition and structure can make large differences in physico-chemical and biological properties. Appendix B is a report of some research sponsored by NiPERA that makes this point in more detail for "nickel oxide" and for certain other families of nickel compounds. It is unfortunate that the biological research community was unaware of the varied nature of "nickel oxide" until the early 1980s; some researchers are still unaware of it. As a result, it is very difficult to make sense of the literature on "nickel oxide".

As pointed out in Appendix B, the properties of a particular sample of "nickel oxide" depend on what nickel species it was made from and the conditions under which it was made. Temperature is the most important determinant of the oxide's nature but the partial pressures of oxygen and water vapour during its formation are also important. Impurities can play a major role in its catalytic properties. Thus, it is not surprising that the "nickel oxides" tested by Wehner and Craig, Kodama et al. and by English et al. are not the same substance. Kodama sent Inco a sample of the oxide he used. Selective leaching and XRD indicate that it was made by oxidizing metallic nickel powder at high temperatures. J.T. Baker Chemical Company would not reveal the starting material nor the temperature it used to make the black nickel oxide tested by Wehner and Craig. However, the fact that it was a black oxide suggests

that it was produced at temperatures lower than the oxide used by Kodama at al. In contrast, the "NiO" produced by English et al. was least likely to resemble the kinds of nickel oxide found in nickel refineries. It was made by calcining nickel hydroxide at a very low temperature (250 C) for a very short time (45 minutes). English et al. reported that IR spectroscopy and x-ray diffraction revealed some nickel hydroxide in the final product. This material should **never** be referred to as nickel oxide.

It should be possible to glean some information on the clearance of high-temperature green nickel oxide from the lung by modeling the lung burdens after two-week and 13-week inhalation exposures (Dunnick et al.,1988; Dunnick et al.,1989). Lung nickel burdens never reached steady state.

p.16, para.3: Tanaka et al. (1985) published a follow-up to the Kodama et al. (1985) paper. The authors modeled the lung clearance of green nickel oxide and concluded that the half-time was 11.5 months for fine particles (MMAD=1.2 μm) and 21 months for coarser particles (MMAD=4 μm). They suggested that finer particles were more easily transported to lymph nodes and, because of their greater specific surface area, were more rapidly solubilized in the lung. They also showed that while the nickel content of the lungs and kidney decreased during the clearance period, the nickel content of the liver and spleen increased.

In two other papers, Tanaka et al. (1986, 1988) developed a more realistic model, one that recognized that clearance was going on continuously, even during the deposition period. The nickel exposure was to fine (MMAD=0.6 μm) green nickel oxide at modest concentrations (0.3 and 1.2 mg/m^3) for periods up to 12 months. The half-time for clearance of this fine oxide was said to be 7.7 months. Information on the nickel content of several organs was reported after each sacrifice and after eight months following the 12-month exposure.

p.16, para.3: Kodama et al. (1989) exposed rats by inhalation to green (MMAD=4.1 μm) and black (MMAD=3.6 μm) nickel oxides and nickel subsulfide (MMAD=2.6 μm) for six months followed by a 12-month clearance period. The authors concluded, in an unsophisticated treatment of the data, that about 1% of the inhaled dusts was deposited and that 82%, 73% and 98% respectively of the green and black oxides and of nickel subsulfide were cleared in the year following cessation of exposure. This is a little surprising as black nickel oxide is normally much more reactive than is green oxide. The nickel contents of several organs were reported after one year and after 20 months. I believe the Kodama work has been published but, since I do not have a literature reference, I am providing DHS with a copy of his final report to NiPERA as Appendix C.

p.16, para.4: Muhle et al. (1988) instilled 12 doses of 0.1 mg Ni_3S_2 (MMAD=5 μm) into Syrian golden hamsters at two-week intervals. Two hamsters of each sex were sacrificed at 14 days and at six and 12 months after the last instillation for

determination of the lung nickel burden. An exponential curve was fitted to the pooled nickel burdens of the males and females for the three sacrificial dates. The clearance half-time was less than 14 days. Thus there are dramatic differences in clearance half-times for subsulfide, metal, alloy and black and green oxides, all of which are insoluble in water.

Although DHS is technically correct in stating that removal of Ni_3S_2 from the lung has been studied only following instillation, Benson et al. (1987) and Dunnick et al. (1988) reported the lung burden of nickel in rats and mice after two weeks of inhalation exposure to Ni_3S_2. The lung nickel burdens (expressed as μg Ni/g control lung) increased linearly with exposure concentration in both species. However, Dunnick et al. (1989) reported that the lung nickel burdens reached a steady state during 13-week inhalation exposures. Sufficient information is provided so that DHS could probably estimate the clearance half-time by fitting a simple model to the data.

p.16, para.5: More complete data are available than DHS has reported. The lung burden of nickel after two-week and 13-week inhalation exposures to nickel sulfate was reported by Benson et al. (1988) and by Dunnick et al. (1989). As expected, the nickel was rapidly cleared from the lung. Benson et al. (1988) found that the quantity of nickel in rat kidneys increased in proportion to the exposure concentration and concluded that a major portion of the nickel leaving the respiratory tract was taken up by the kidney.

Also Medinsky et al. (1987) studied the clearance of instilled nickel sulfate from rat lung. It was a very thorough study.

p.16, para.6: In 1980, Wehner et al. revised the Wehner et al. (1979) conclusion that fly ash was cleared slowly from the lung. In 1980, they reported the fate of neutron-activated fly ash up to 99 days after a single, nose-only exposure. During this period, the lung burden of fly ash decreased to about 10% of its initial value. The authors estimated clearance half-times of 2.6 and 34.5 days for fly ash deposited in the airways and deep lung respectively. The authors preferred the results of this study to the earlier one reported by DHS because it involved many more animals. Analyses indicated that particulate fly ash was found in the lungs, carcass, head, pelt, GI tract and feces. Wehner et al. (1980) did not review the earlier conclusion that nickel was not selectively leached from nickel-enriched fly ash.

p.17, para.6: DHS should pay closer attention to the conclusion it offered at the beginning of section 3.1.1.2 ; i.e. "The degree of absorption depends largely on chemical form." Even though the Kirchgessner study is a feeding study, it would still be useful to know what **form** of nickel was incorporated into the rats' diets.

p.18, para.2: DHS should review the paper by Sunderman et al. (1989). Like Solomons et al. (1982), it shows that the absorption of nickel from food is very much less than the absorption of nickel from water drunk after fasting. It is unfortunate that the absorption of nickel from water drunk after fasting was not determined when followed immediately or soon thereafter by a normal meal.

p.18, para.5: It is important to note that there is a significant difference in the rates at which two extremely **water-soluble** nickel compounds penetrate human skin. This fact raises again the question as to the reasonableness of attributing comparable biological behaviours to different forms of nickel just because they have similar solubilities in water; e.g. nickel subsulfide and nickel oxide.

p.19, para.5: Because nickel carbonyl can pass through biological membranes without first being metabolized, it is a poor model for the distribution of nickel inhaled as inorganic particulate.

p.21, para.1: English et al. (1981) tested a very unusual form of oxidic nickel. It should not be referred to as nickel oxide.

p.24, para.6: Why is nickel carbonyl classed with nickel chloride and nickel sulfate as "soluble" compounds? Its solubility in water is thousands of times less than that of the other two compounds. Nickel carbonyl should be treated separately, if it is to be treated in the TSD at all.

p.24, para.7: Grouping the moderately soluble nickel subsulfide with the highly insoluble nickel oxide results in misleading generalizations. Lung-removal half-times for the oxide may be measured as months or longer but the half-times for nickel subsulfide should be characterized as weeks.

Is it not possible that the higher "absorption" following instillation is due at least in part to coughing up the dose and/or mucociliary clearance to the GI tract?

p.31, para.2: The reference to occupational asthma occurring in workers exposed to low levels of nickel is probably incorrect. Details are given below.

p.31, para.3: Sunderman et al. (1988) reported a dramatic demonstration of the relatively low acute toxicity attending the ingestion of nickel salts. Electroplating workers drank sufficient soluble nickel from a contaminated fountain to raise urinary nickel levels to as high as 12,000 μg Ni/g creatinine yet symptoms lasted only a few hours in most workers and no longer than three days in any worker.

p.32, para.3: DHS says of the Akesson and Skerfving (1985) study that "Nickel aerosol was thought to be the cause of the reactions." In fact, the authors did not draw any such conclusion. They wrote: "**Of course**, our results do not allow

conclusions on the specific etiology of the high-Ni alloy associated complaints." After considering several possible causes, the authors speculated "...the Ni aerosol itself **may** be the cause." (Emphasis added.) There are other possible causes the authors should have considered.

First, it appears that the men had just returned from four weeks of vacation when they began to weld high-nickel alloys. Their **subjective** complaints might be taken more seriously if they had just completed four weeks of welding stainless steel.

Second, the fume generated in manual metal arc welding comes mainly from the welding rod, not from the substrate. Rods of the composition described by the authors are commonly used for welding stainless steel as well as for high-nickel alloys. One wonders therefore why the welders perceived a different response to what was probably a very similar fume. Could it have been due to four weeks of fresh air and imperfect recall of their perceptions when they last welded stainless steel?

p.39, para.1: Why not report oral lethality? DHS reported inhalation lethality for nickel carbonyl. Furthermore, such information would seem to be more relevant to DHS's purpose than are data related to parenteral routes of exposure or to subclinical effects produced by any route of exposure. Mastromatteo (1986) presents oral LD_{50} data. The paper unfortunately published the results for $NiCl_2 \cdot 2H_2O$ as "$NiO_2 \cdot 2H_2O$".

p.39, para.3: Spiegelberg et al. (1984) is only one of a group of researchers who have used an unusual method of generating a "nickel oxide" aerosol at the Fraunhofer-Institut fur Umweltchemie und Okotoxikologie. It involved the atomization of a solution of nickel acetate followed by decomposition at a temperature (550 C) which produced an aerosol having the approximate nickel content of NiO. In general, those using this apparatus have found effects of various kinds at much lower concentrations of aerosol than have others who used more traditional methods of aerosol generation. This might be due to the fact that the atomization method produced a very fine aerosol, (MMAD = 0.34-0.42 μm). (A sample of the oxide supplied to Inco was so fine that it did not produce an XRD pattern!) The effects might also be due to the decomposition products of the acetate - e.g. acetanhydride? - which were passed directly to the animals. It is interesting to note that when the decomposition furnace was run at temperatures above 550 C, the nickel content of the aerosol began to decrease substantially. Reduction of the oxide by organic species would increase the nickel content and the conditions are not sufficiently oxidizing to form a trivalent nickel oxide. Hence the lowering of the nickel content would seem to be due to some byproduct of the acetate decomposition. I asked scientists at the Fraunhofer-Institut if they had ever exposed animals to a nuisance oxide generated in a similar manner to see if the combination of fine particles and decomposition products of the acetate might have produced the same kinds of effects that are being attributed to "nickel oxide". No such control experiments were ever

done. It is my opinion that the results of Spiegelberg et al. as well as those of all the other researchers who used this same system cannot be accepted without reservation.

p.39, para.5: In the absence of references, I can only assume the effects produced by oxide at low doses were attributed to the oxide produced by the low-temperature decomposition of nickel acetate. It is interesting to note that Dunnick et al. (1988, 1989) rated nickel oxide as **less toxic** than nickel subsulfide or nickel sulfate after 12-day or 13-week inhalation exposures. This nickel oxide (MMAD=2.8 μm) was produced at high temperatures and re-suspended in clean air before being admitted to the exposure chambers.

p.40, item 2: The results refer to an oxide produced by low-temperature decomposition of atomized nickel acetate.

p.43: It is interesting to note that Benson et al. (1988) were unable to find an effect of **inhaled** nickel sulfate on NK cell-mediated toxicity. This information should appear in Table 5.2 to provide some perspective for the findings of Smialowicz et al., who used parenteral routes of administration.

p.44, item 2: Why did this four-month exposure also appear in Table 5.2? The results refer to an oxide produced by low-temperature decomposition of atomized nickel acetate.

p.46, para.1: The results for low-level exposure to an oxide refer to one produced by low-temperature decomposition of atomized nickel acetate.

p.46, para.4: The results obtained by each of the cited researchers refer to an oxide produced by low-temperature decomposition of atomized nickel acetate.

p.47, item 3: The results refer to an oxide produced by low-temperature decomposition of atomized nickel acetate.

p.48, item 1: What was the mortality of the control group?

p.51, para.3: DHS gives too much credence to the relation between nickel exposure and occupational asthma or chronic respiratory tract infections.

DHS should review the paper by Kilburn et al. (1990) in which 31 welders from a stainless steel fabricating plant were studied by pulmonary function tests and by analyzing serum and urine for chromium and nickel in a cross-shift investigation. The authors concluded: "Although cross-shift decreases in pulmonary function had been anticipated from the reports (Keskinen et al., Malo et al., Novey et al.) of occupational asthma during stainless steel welding, there is little evidence for chronic adverse

effects on pulmonary function caused by nickel." Similarly, Akesson and Skerfving (1985) found no change in pulmonary function in 11 men who welded high nickel alloys for four days.

It is distressing to see that DHS has not reported the Davies (1986) paper accurately. One hopes this is an isolated fault. Davies found only **one case** of asthma among 53 **current** employees of the catalyst plant and that was in "a manager who had a long well-established history of non-occupational asthma." In a review of **past** catalyst plant workers, Davies found three cases of occupational asthma for which there was "strong **circumstantial** evidence" for their relation to exposure to nickel sulfate. Furthermore, one of these three cases worked in the old, presumably dustier, catalyst plant and the other two had left the new plant in 1971 and 1979 respectively. Thus, it is not at all clear that these men were exposed to the range of nickel concentrations reported by Davies. It is clear that the 53 people **without** occupational asthma **were** exposed to these concentrations. DHS should consider why, as Davies pointed out, there are so few cases of occupational asthma that have been attributed to exposure to nickel salts when thousands of people are occupationally exposed to them and the symptoms would be difficult to overlook.

The findings of the Bencko et al. (1986) research is recognized in the next paragraph as having only a **potential** effect on **susceptibility** to infection. This is a more tentative statement than DHS has used; i.e. "...increased risk for chronic respiratory tract infections can also result from nickel exposure."

p.51, Summary of Noncancer Health Effects: I won't repeat my earlier comments, many of which refer to items repeated in the table. However, DHS should be sure to refer to the specific forms of nickel associated with a given health effect, NOEL, LOEL, etc. For instance, it is pointless in (3)(i) to refer to overt toxicity at an "air concentration over 50 mg/m^3" without stating that the concentration refers to nickel carbonyl.

p.53, para.3&4: What are the literature references for the effects cited here?

p.58, para.4: I agree wholeheartedly with DHS's caveat about the injection route of administration. Why was it not repeated in the discussions attending every other health effect produced by this route of administration?

p.58, para.5: This paragraph sounds like instructions to the consultant. Why is it in the TSD? If it is meant to be here, similar caveats should be inserted for every health effect.

p.70 & 71, Section 6: In this section, DHS has nearly abandoned the desirable practice of providing citations to the literature in support of the information provided. This makes it impossible for a reader to critically review Section 6.

p.71, Conclusions: It is clear that certain nickel compounds have the potential for genotoxicity. However, as shown on the next page, other metals have similar genotoxic potential and yet are not generally considered to be carcinogenic. Thus, genotoxic potential by itself does not seem to be adequate to explain why some substances are carcinogenic and others are not.

Why has DHS not considered non-genotoxic mechanisms by which certain forms of nickel might cause cancer? Since many forms are cytotoxic, why not consider enhanced cell proliferation as a possible mechanism? Since some forms of nickel are renowned for their ability to catalyze oxidative processes, why not consider the role of oxygen radicals in carcinogenesis? Since many of the refineries where there were respiratory cancer problems were extremely dusty, why not consider particle overload of the lung as a possible mechanism? These mechanisms are being considered seriously by many experts. Why then has DHS read the literature so narrowly?

p.72, para.1: The list of nickel compounds alleged to have produced genotoxic effects must be examined closely for accuracy. The great variability in what is reported as "nickel oxide" has already been noted. Appendix B also demonstrates that few if any researchers are likely to have actually studied "nickelic oxide" and none has studied "nickel carbonate".

As is the case with many metallic compounds, simple-minded concepts of valence cannot be applied to nickel subsulfide. Whatever "valence" one would like to use to describe the nickel in nickel subsulfide, it must be the same for every nickel atom in the structure because they are crystallographically equivalent and have the same local coordination polyhedra.

For the reasons given in Appendix B, it is unlikely that an oxide with an appreciable amount of trivalent nickel has ever been studied.

p.72, para.2: The work at the University of Connecticut dealt with a wide variety of nickel oxides. The work involved not only carcinogen bioassays by intramuscular injection but also determinations of solubility in biological fluids and the ability to produce erythropoiesis after intrarenal injection. I think Dr. Sunderman would now agree that there is no **unique** nickel oxide.

p.74 & 75, Sunderman studies: The very poor survival of the controls should be noted in the table.

COMPARISON OF *IN VITRO* EFFECTS OF Ni(II) WITH THOSE OF OTHER DIVALENT METAL IONS

(based on data reported by Sunderman, F.W. Jr., Ann. Clin. Lab. Sci. 14:93-122, 1984)

Metal ion	Mutagenicity[a]	SCE[b]	Morph. Trans.[a]	Strandbreaks/ Crosslinks[a]	DNA Conf. Changes
Cu (II)	+	NR[d]	+	+	+
Zn (II)	+	NR	+	NR	+
Fe (II)[c]	+	NR	+	NR	+[e]
Mn (II)	+	+	+	+/−	+
Co (II)[c]	+	+	+	+	+
Pb (II)[c]	+	+	+	NR	+
Hg (II)	+	+	+	+	+
Ni (II)[c]	+	+	+	+	+

a. Mammalian cells
b. Human lymphocytes
c. Animal carcinogens
d. Not reported
e. Fe (III)

Compiled by: Dr. E. Nieboer, Prof. of Toxicology, Dept. of Biochemistry, McMaster University, Hamilton, Ontario
Presented to the Metals Subcommittee of EPA's Science Advisory Board on March 25, 1986

p.76, Takenaka studies: DHS should remember that the "nickel oxide" used in these experiments was produced by decomposing nickel acetate at relatively low temperatures and that the animals were exposed continuously. It is interesting that the (surprisingly high) mortality was higher for the rats exposed to 0.06 mg Ni/m^3 than it was for the animals exposed to 0.2 mg Ni/m^3.

p.78: Why is an instillation study included in a table of inhalation exposures?

p.79, para.6: DHS suggests that hamsters "...may be non-responsive to nickel." Sunderman (1983) reviewed the literature on organ and species specificity in nickel subsulfide carcinogenesis and concluded that, at least for this form of nickel, hamsters' lungs do respond.

Some risk assessors are reluctant to give weight to non-positive results obtained in live hamsters, saying they are not good models for respiratory carcinogenesis. Yet these same assessors are only too willing to accept positive results using various hamster **cells** in *in vitro* assays. Such "reasoning" strikes me as nothing short of perverse. What is DHS's position with respect to non-positive results in hamsters by the inhalation and instillation routes?

p.79: DHS should also review the inhalation studies published by Kim (1969) in the form of a Master of Science thesis for the School of Hygiene at the University of Toronto. Kim employed male albino rats of the Wistar strain. One of the substances tested was fine nickel powder (97.8% < 2 μm) at a concentration of 3.1 mg Ni/m^3. The exposures were for seven or 13 months, sometimes with intervening periods with no exposure. Rats were observed for up to 21 months. Two carcinoid lung tumors and one lymphosarcoma were found in 40 rats examined. One carcinoid lung tumor was found in controls. Since the Kim thesis was not published in the open literature, a copy is included herewith as Appendix D.

p.79: Is any attention to be paid to studies employing intratracheal instillation? If so, the work of Muhle et al. (1988) and Pott et al. (1987) should be included. Muhle et al. examined histopathologically the lungs of 56 hamsters that had been instilled with a total of 9.6 mg of nickel powder in 12 equal bi-weekly doses. Only one lung tumor was found, an adeno-squamous carcinoma. Similar examinations were made of the lungs of 62 hamsters that had been instilled with a total of 36 mg (2.4 mg nickel) and of 62 that had been instilled with 108 mg (7.3 mg nickel) of Ni/Cr stainless steel grinding dust. No lung tumors were observed.

p.79-81, carbonyl studies: It is my belief that if these results were obtained today, they would be dismissed as inconclusive because of the very poor survival of both the exposed and control animals and the low incidence of tumors which only appeared late in the animals' lives. It is interesting to note that when these studies were first reviewed by an IARC working group in 1973, the group concluded

(IARC, 1973, p.145): "Two inhalation studies in rats on nickel carbonyl failed to produce conclusive evidence of pulmonary tumor development." The working group included Dr H.L. Falk and Dr. J.F. Fraumeni, Jr.

When the studies were reviewed a second time, IARC (1976) included a parenthetical statement (p.88): "[Because of the rarity of spontaneous malignancies in Wistar rats, the **authors** considered that the pulmonary adenocarcinomas were probably due to exposure to nickel carbonyl.]" (Emphasis added.) It is interesting that one of the authors was a member of the second working group.

p.81, para.1: Why does DHS say that nickel oxide "has not been well studied" when 102 animals were given lifetime exposure to such high concentrations of black nickel oxide that massive pneumoconiosis developed? While mortality did not appear to differ from the controls, body weight was lower than controls for most of the experiment.

p.81, para.4: While the form of the nickel in the fly ash was not determined, it is a simple matter to calculate its concentration in the air; 4.2 mg Ni/m^3 in the high NEFA exposure, 1 mg Ni/m^3 in the low NEFA exposure and 0.2 mg Ni/m^3 in the FA exposure.

p.81, para.5: The "nickel oxide" used in these experiments was produced by decomposing nickel acetate at relatively low temperatures and the animals were exposed continuously.

p.82, para.3: DHS should try to obtain information on the NTP bioassay of green nickel oxide. The animals completed two-year chronic exposures this past spring. This will be the definitive inhalation study of nickel oxide and even preliminary information should be very useful to DHS.

p.82, para.3: DHS should review the work of Kodama et al. (1989) who studied both green and black oxides by inhalation in rats. The animals were exposed for six months to 1.1 mg green NiO/m^3 or to 1.3 mg black NiO/m^3 then followed for one year. The authors concluded: "There was no significant difference of neoplastic growth between the exposure group and control group, in spite of an appearance of pulmonary adenocarcinoma in Run No. 4 (black NiO)." (Note: Table 5 and Photographs 13-14 indicate this tumor appeared in one of 47 rats that had been exposed to **green** nickel oxide.)

p.82, para.3: Tanaka et al. (1988) reported on rats exposed to green nickel oxide at concentrations of 0.3 and 1.2 mg/m^3 for 12 months followed for an additional eight months. Though their exposure was twice as long as that employed by Kodama et al., the authors found no malignant tumors. Unfortunately, there were only eight rats in this exposure/follow-up group.

p.82: If instillation is to be considered, the papers by Pott et al. (1987) and Farrell and Davis (1974) should be reviewed. Pott et al. reported lung tumors in 27% of 37 examined rats that had been instilled with 64 mg (6.4 mg for 10 weeks) of an unspecified nickel oxide. Another group of rats was instilled with 191 mg (19.1 mg for 10 weeks) of the same oxide but the incidence of lung tumors increased to only 31.6%. One must wonder about particle overload effects in such an experiment.

Farrell and Davis instilled a total of 120 mg of an unspecified nickel oxide (0.5 to 1 μm) into each of 50 hamsters (4 mg for 30 weeks). Only one tumor was detected and it is not clear from the paper that it was in the respiratory tract.

p.82, para.4: The exposure phase of NTP's inhalation bioassay of Ni_3S_2 is to be completed in October. DHS should try to obtain at least preliminary results from this study.

p.85, para.1: Kim (1969) employed a mixed dust in one of his experiments that contained four different species of nickel. If you work through the recipes for the dusts on p.13 of Kim's thesis and the concentrations of nickel and iron on Table 4 of p.16, it appears the dust contained in mg/m^3, 1.3 metallic nickel, 0.9 Ni_3S_2, 0.3 $NiSO_4 \cdot 6H_2O$, 0.1 NiO, 1.4 Fe_2O_3 and 1.4 FeS. Thus the concentration of Ni_3S_2 alone was nearly the same as that reported by Ottolenghi. The total concentration of nickel in all forms was nearly three times that reported by Ottolenghi! The duration of exposure was for seven or thirteen months. No long tumors were found in the 32 rats that were examined.

p.85, para.1: Kodama et al. (1989) exposed 50 rats to 0.5 mg Ni_3S_2/m^3 for six months then followed them for an additional year. No lung tumors were found in the 47 animals that were examined.

p.85, para.1: Is there to be no discussion of Fisher et al. (1986) after it was raised on p.82? If intratracheal instillation is to be considered, the papers of Muhle et al. (1989), Pott et al. (1987), Kasprzak et al. (1973), and Sunderman (1983) should also be considered.

Muhle et al. found no lung tumors in 62 hamsters that were instilled with a total dose of 1.2 mg Ni_3S_2 (0.1 mg for 12 bi-weekly instillations).

Pott et al. reported a lung tumor incidence of 14.9% in 47 rats that were instilled with a total of 1.28 mg Ni_3S_2 (0.085 mg for 15 weeks). The incidence increased to 28.9% in 45 rats when the total instilled dose was increased to 2.56 mg Ni_3S_2 (0.17 mg for 15 weeks).

Kasprzak et al. instilled a single dose of 5 mg Ni_3S_2 into 13 rats and followed them for 15 months. No lung tumors were observed.

Sunderman instilled a total of 10 mg Ni_3S_2 in four equal monthly doses into 12 hamsters but found no tumors of the respiratory tract. In a second experiment, a total of 36 mg Ni_3S_2 in 18 equal weekly doses was instilled into 15 hamsters. All the hamsters died within seven months but no neoplasms of the respiratory tract were found.

p.85: para.1: DHS should try to obtain information on the NTP bioassay of nickel sulfate hexahydrate. The animals completed two-year chronic exposures this past spring. This will be the definitive inhalation study of the sulfate and even preliminary information should be very useful to DHS.

p.88, section 7.1.3: I hope DHS is not going to put much weight on results obtained by an unrealistic route of exposure that produces tumors of a type not relevant to respiratory cancer. After a review of the IARC Monographs, Theiss (1982) pointed out that nearly half of the substances that produced only injection-site tumors (i.e. no remote primary tumors) failed to produce tumors by the routes of exposure relevant to man - inhalation, oral and dermal. Thus a flip of a coin is about as useful for predicting carcinogenicity by relevant routes of exposure as is evidence of injection-site tumorigenicity.

However, I agree (reluctantly) with DHS that the series reported here may provide a basis for comparing carcinogenic potencies. It is interesting that they vary so widely **even though the dose of nickel was held constant.**

p.88, last line: Inco synthesized the iron-nickel sulfur material for Dr. Sunderman. He used the formula Ni_4FeS_4 as a convenient way to express the composition of this material. The substance consists of at least two and probably more phases. It is **definitely not** a single phase of composition Ni_4FeS_4.

p.90, para.1: It is unfortunate that not enough of the nickel oxide used in these tests was left to allow it to be properly characterized. It was a green oxide so it was presumably prepared at high temperatures. However, other high-temperature nickel oxides tested by Sunderman at even higher nickel doses (20 mg/rat) produced different results. The results of the intramuscular injection tests of several nickel and nickel-copper oxides described in Sunderman et al. (1987) were reported at the 15th International Cancer Congress in Hamburg this August. His abstract of that presentation, shown on the next page, shows that black nickel oxide calcined at 735 C or 1045 C failed to produce injection-site tumors.

CARCINOGENESIS BIOASSAYS OF NICKEL OXIDES AND NICKEL-COPPER OXIDES BY INTRAMUSCULAR ADMINISTRATION TO MALE FISCHER-344 RATS.

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Five nickel oxides and nickel-copper oxides, with chemical compositions and physicochemical properties that were previously reported (Sunderman *et al.*, Carcinogenesis, 8:305-313, 1987), were tested for carcinogenicity by single *im* injection (20 mg Ni/rat) to groups of 15 male Fischer-344 rats. Two additional groups of 15 rats received injections of the saline vehicle (*Negative Controls*) or nickel subsulfide (αNi_3S_2, 20 mg Ni/rat, *Positive Controls*). By the end of the experiment at 104 wk post-injection, the following numbers of sarcomas had developed at the injection site: *Negative Controls*, 0/15; *Positive Controls*, 15/15; *Compound A* (INCO black NiO), 6/15; *Compound B* (NiO, calcined at 735°C), 0/15; *Compound F* (NiO, calcined at 1,045°C), 0/15; *Compound H* (oxidized Ni-Cu matte, Ni/Cu = 2.5:1), 13/15; *Compound I* (oxidized Ni-Cu matte, Ni/Cu = 5:1), 15/15. The following primary neoplasms arose at other sites: 3 pulmonary carcinomas in rats that received *Compound B* and 3 Leydig cell tumors of the testis in rats that received *Compound H*. The nickel compounds that induced sarcomas (*Compounds A, H, I,* and αNi_3S_2) had measurable dissolution rates in body fluids (serum, renal cytosol) and were positive in an erythrocytosis stimulation assay (Sunderman *et al., op cit*), while the nickel compounds that did *not* induce sarcomas (*Compounds B and F*) were insoluble in the body fluids and did not stimulate erythrocytosis. These findings suggest that the bioavailability of nickel influences the relative carcinogenic activities of such nickel compounds.

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Abstract submitted to the 15th International Cancer Congress, to be held in Hamburg, FRG in August 1990

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p.90, para.5: In 1988, Skaug informed attendees at the Fourth International Conference on Nickel Metabolism and Toxicology in Helsinki, Finland that he had **not** been able to reproduce the high incidence of pleural tumors reported in Skaug et al. (1984). The abstract of this presentation is included on the next page.

p.90, para.6: DHS should remember that NTP completed its chronic exposure of rats and mice to nickel sulfate hexahydrate this past spring.

Neither Kim (1969) nor Kodama et al. (1989) found an increased incidence of lung tumors in rats exposed by inhalation to Ni_3S_2.

DHS notes that "only" nickel sulfate, a water-soluble compound, has been adequately evaluated for oral carcinogenicity. Does DHS think that an insoluble form of nickel is more likely to be carcinogenic by ingestion?

p.91, para.1: Nickel subsulfide is a consistent experimental carcinogen by parenteral routes of administration but has not been as consistent by inhalation and intratracheal instillation. As pointed out earlier, "nickel oxide" has not been a consistent experimental carcinogen by parenteral routes. DHS has pointed out that inhalation studies on "nickel oxide" have been negative or inconclusive. It is thus premature to draw conclusions about the relative carcinogenicity of one compound and one family of compounds.

p.91, para.2: If ARB were to regulate insoluble nickel compounds as a group, it would be grouping substances that are experimental carcinogens with others that have not even been bioassayed. Instead, ARB should try to identify the forms of nickel in ambient air and DHS should see which, if any, of the substances that have been tested experimentally they most resemble. I believe such an approach would be seen as reasonable by the regulated community.

p.92, section 7.1.5.1: The techniques of risk assessment have been changing rapidly in recent years. DHS should use the best methodology, rather than adhering to the status quo of the early 1980s. For instance, what is the reasoning behind the assumption that weight/surface area/day is an equivalent dose between species? EPA says in its Health Assessment Document for Nickel and nickel Compounds ("NiHAD") (p.8-179) that the concept "...is virtually without experimental verification regarding carcinogenic response." In any event, it would seem that the only reasonable surface area to be used for interspecies extrapolation would be that of the respiratory tract. Even then there are questions as to what relation between dose and surface area is relevant for bronchogenic lung cancer; e.g. is it the average surface concentration, the maximum surface concentration, the average rate of clearance, etc. To answer them with any certainty would require a better knowledge of the mechanism of the carcinogenic process.

VI 5.

TUMOR INDUCTION IN RATS AFTER INTRAPLEURAL INSTILLATION OF VARIOUS NICKEL OXIDES

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Nickel compounds which are closely related in chemical composition differ substantially in their carcinogenic activity in experimental animals. In a previous paper we have demonstrated that nickel oxide (NiO Merch PA - Joint Committee on Powder Diffraction Standard file no. 4-835) induces rhabdomyosarcomas in the pleural cavity in rats at a rate corresponding to that of nickel subsulfide (Skaug et al. in Progress in Nickel Toxicology, Blackwell Sci. Publ. pp. 37-41).

Ten different nickel oxides or nickel-copper oxides (Nickel Producers Environmental Research Association - NiPERIA) were instilled in the pleural cavity of 10 groups of 20 rats each. Nickel oxide (Merch-PA) was used as a positive control and physiological saline as a negative control making a total of 12 groups of rats in the experiment.

After 27 months only 8 of the total 220 nickel injected rats had developed pleural cavity tumors compared to 31 of 32 rats with nickel oxide instillation in the previous experiment. Most tumors (4) were found in the positive control group with single tumors in 4 other groups. Histology confirmed the previous diagnosis of rhabdomyosarcoma.

A number of other tumors were found, the most common being tumor of the hypophyses which was demonstrated in 73 rats of the total of 240 animals. The tumors were evenly distributed in all groups.

The discrepenancy between these and our previous results could be explained by the treatment of the particle suspension before instillation. In the first experiment the suspension was instilled immediately after mixing, but in this experiment the suspensions were stored for 3 to 6 days between mixing and use. This explanation however, has not yet been confirmed.

Taken from the volume of abstracts prepared for the Fourth International Conference on Nickel Metabolism and Toxicology; 5-9 September 1988, Espoo, Finland

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p.94: In following EPA, DHS has introduced the confusing and completely unnecessary variable i=I/W. Also, the line dividing the numerators and denominators in the last two equations should not extend under and beyond the equals sign.

p.94, section 7.1.5.2: It is interesting to note that the result obtained here is not inconsistent with the fact that Kodama et al. (1989) found no tumors in male rats exposed to 500 μg Ni_3S_2/m^3 for six months. While I don't have access to GLOBAL86 or anything like it, I can easily solve the linearized multistage model for the case where there was only a single dose group plus controls. Using the Ottolenghi et al. data (1975) for males only leads to a value of 0.0093 for the constant term Q_0 and 0.147883 for the product of Q_1 and d, the dose. (This leads to a maximum likelihood estimate for continuous human lifetime exposure of 3.2E-03, very close to the DHS value of 3.05E-03.) Since Kodama et al. (1989) used the same exposure regime as did Ottolenghi et al. but for only 26 weeks instead of 78, the Q1*d term has to be multiplied by 500*26/(970*78). Solving the multistage equation for this dose leads to a probability of 3.4% for observing lung cancer. Since Kodama et al. sacrificed only 47 hamsters 12 months after the cessation of the six months exposure, he might have expected to see only 1.6 rats with lung cancers. Unfortunately Ottolenghi et al. do not provide any time-to-tumour information which would help to judge whether tumours were not seen by Kodama because of insufficient latency, rather then insufficient exposure. In any event, the discrepancy is not large.

However, that was not the case when the Ottolenghi data for rats exposed to nickel subsulfide were extrapolated to other rodents and to another form of "insoluble nickel" (nickel oxide) and to a material expected to contain both soluble and insoluble forms of nickel (nickel-enriched fly ash). The Ottolenghi data vastly overestimated the observed incidence of lung tumors in these animals. A copy of this comparison, which was presented to EPA's Science Advisory Board in 1983, is included as Appendix E. It is not clear whether the discrepancy is due to different carcinogenic susceptibilities of the two rodent species or to different carcinogenic potentials of these other forms of nickel when administered by inhalation or, more likely, both. DHS can avoid one source of error by not relying on animal data for its risk assessment. It can minimize the possibility of the second kind of error by avoiding the assumption that different forms of nickel have similar carcinogenic potencies even if they share some common physicochemical property, such as solubility in water.

p.96, para.1: DHS is aware of the publication of the Report of the International Committee on Nickel Carcinogenesis in Man (ICNCM, 1990). While the cohorts reported on in this document were known to EPA, the vital status of each of the cohorts was updated for the ICNCM analysis. The updating alone makes it worthwhile for DHS to review this document carefully.

p.96, para.2: The vital status of this cohort is updated in the ICNCM report. With respect to the exposure information, DHS should note the estimated breakdown of nickel by species in Table 10 of the ICNCM. Unfortunately, high concentrations of nickel existed only where there were high concentrations of nickel subsulfide. Enterline and Marsh (1982) ignored this fact when looking for a dose-response relationship. Also, it is generally overlooked that the authors announced that they had gerrymandered the dose groups to try to strengthen the relationship.

p.96, para.3: It would be preferable to refer to the Copper Cliff sinter plant ("CCSP") cohort as something other than the "Ontario cohort". That name should be reserved for the cohort of 54,509 men who worked in Inco Limited's Ontario Division and have been the subject of a thorough epidemiological study. Updated studies of the Ontario cohort can be found in the ICNCM report and in two publications by Roberts et al. (1989a, 1989b). The CCSP cohort is part of Inco's Ontario cohort. The Roberts et al. reports provide much more timely and complete data than does Chovil et al. If DHS persists in using this cohort for risk assessment, it should use the latest available data.

Incidentally, there is some misunderstanding of the service requirement for entry to the Chovil cohort. Chovil's cohort consisted of men who had "...five or more years of **total** service, including some sinter plant service." In view of the CCSP experience, Roberts et al. included men with **any** recorded CCSP service in the CCSP cohort. Current thinking of the epidemiologists who hold the CCSP data is that the minimum service requirement should be increased to from three but no more than six months.

p.96, para.4: Since Roberts et al. conducted follow-up to the end of 1984, it is not surprising that they have observed 62 lung cancer deaths (63 in the ICNCM report) compared with only 37 deaths observed by Chovil et al. The SMR has dropped from the 871 reported by Chovil et al to 305.

p.96, para.5: EPA expressed concern that Chovil et al. had underestimated the lung cancer risks by assuming untraced workers were alive (NiHAD, p.8-25). However, I can find no place where EPA speculated that "a large proportion of those lost to follow-up were likely to be those workers who were exposed earliest, and hence to the dustiest conditions." In any event, Roberts et al. estimate their ascertainment rate was 95% so the 25% that Chovil was unable to trace is no longer a problem.

p.98, para.2: Whatever information Roberts or Chovil had with respect to environmental conditions in the CCSP was obtained from me.

p.98, para.2: It is unreasonable for Chovil's mortality data to **constrain** one to assume anything about exposures. DHS claims to be trying to evaluate a dose-response relationship and it can't do that if it estimates exposures based on mortality data. There is no justification for a step-function change in nickel

concentrations between 1951 and 1952. Figure 1 shows the relationship between the sintering rate and the rate of metal lost from the CCSP monitors as a function of time. I believe that learning how to run the plant was the major cause of lowered dust losses and hence dust concentrations. The figure shows a dramatic but not precipitous improvement with time. There was nothing radical about the 1951-1952 period.

p.98, para.3: I was trying to make the case that the use of nickel concentrations measured at the roof monitors were probably conservative estimates of the environment at the working level. I was **not** advocating the use of still higher concentrations. The measurement of dust taken at floor level is in reasonable agreement with the monitor data when one considers all of the data and the fact that pains were taken to have the floor sample collected in the cleanest possible area under the best possible conditions. I agree that the coarse dusts recirculating at lower levels would have been of concern mainly for nasal cancer but I think DHS should be concerned about dust that is coarser than **respirable** dust because the lung cancers in the CCSP workers were in the bronchial region, not the pulmonary region.

p.98, section 7.2.1.3: The vital status of the Clydach cohort was updated in the ICNCM report.

p.99, para.5: For the ICNCM study, exposures to various nickel species were estimated for different areas of the Clydach refinery as well as for different calendar periods. In the absence of measured data, most of the estimates involved very broad ranges.

p.99, para.6: I have included, as Appendix F, some exposure estimates for the Clydach plant based on **measured data**. These are for the period from 1932 and later. I agree with DHS that these estimates are probably not relevant to the lung cancer risks in the cohort as a whole. However, when combined with information on plant improvements, they give credence to the anecdotal information that said the plants were extremely dusty on the early years. More important, they indicate that concentrations of airborne nickel were still extremely high (relative to ambient exposures) during a period when adverse health effects were not observed.

p.100, para.2: While there are many good things in the EPA NiHAD, estimating Kristiansand exposures from estimates of exposures at Clydach is not one of them! A comprehensive set of exposure estimates for the Kristiansand refinery have been included in the ICNCM report.

p.100, para.5: Not only were the nickel concentrations in air of the West Virginia plant closer to ambient levels than were those in other plants, the mix of nickel species was probably less alien also. Apart from the calciner department, the

West Virginia plant would not have had the various nickel-sulfur species common in the other refineries.

I understand DHS's concern about the lack of precision of the relative risk estimates but I do not recognize any "problems in precision of low exposure estimates". Since we are dealing with **estimates,** it would seem that the important parameter is their **accuracy**, not their precision. The estimates for the West Virginia plant are very much more likely to be accurate than are the estimates for the other plants. The West Virginia estimates are based on at least some measured data and on chemical speciation whereas the estimates for most of the other plants are simply educated guesses.

p.102, para.2: There are now estimates of exposures for the Norwegian cohort. However, mixed exposures were the norm so the interpretation of the data won't be easy.

p.102, para.3: The ICNCM report might provide enough additional deaths in men hired after 1930 to satisfy DHS'S desire for precision. However, the exposure estimates are very broad and the men had mixed exposures with respect to nickel species.

p.102, para.4: Even though they were based on measurements, the information on exposures in the CCSP should be referred to as "estimates", not as measures.

p.102, para.6: DHS has obviously given a lot of thought to the additive risk and relative risk models. Has it given any thought to the validity of assuming that either of these measures should be related to **cumulative exposure?** Anderson and Svenes (1989) published the nickel contents of the lungs of 39 autopsied workers from the Kristiansand refinery. There were 14 deaths from lung cancer among this group. The authors showed that, as a group, the workers who died of lung cancer had the same concentration of nickel in their lungs as did the men who died of other causes. Their data indicate that lung cancer may not even be predicted from cumulative **dose** of insoluble compounds.

Furthermore the increasing information on the effects of particle overload suggest that relatively short periods of high exposure may initiate irreversible processes whereas the same dose spread over a longer period of time may not.

p.103, para.3: I have no expertise whatever with respect to models of carcinogenesis so I probably shouldn't be troubled by my failure to understand the argument given here. However, DHS should consider whether it could express the argument more clearly. I can accept the premise set forth in the first sentence but the second sentence seems to use the synergistic basis for relative risk to prove the premise. It would make sense to me if the second sentence read as follows:

"Thus, if the background cancer risk **and** the risk for a particular cause both rise as the fifth power of age, the relative risk will remain constant."

I'm further confused by the appearance of "excess risk" in the second sentence. I thought this discussion was about **relative** risk.

p.103, para.5: DHS could provide a service to its readers by explaining the derivation of this "simple" model. The NiHAD does not indicate how it differs from the "exact" relative risk model.

p.105, para.1: The reason EPA changed the values of P_o is because I pointed out to EPA's Science Advisory Board that EPA had been using the background lung cancer rate for U.S. males for the year 1976 to apply to cohorts studied in other countries at other times. EPA's initial response was that the approximations in the model and the uncertainties in the data were so large that EPA didn't think it was worth the effort to calculate P_o properly. Fortunately, the SAB prevailed and EPA reported values said to be for the proper times and places.

p.105, section 7.2.3.3: It is not clear whether DHS has tried to evaluate the maximum likelihood model using data of its own choosing. If it has and the discrepancy persisted, DHS should consult with Steven Bayard of EPA's Carcinogen Assessment Group. I expect the matter could be resolved with him.

p.107, para.3: I would appreciate an explanation of why it is not best to use a model that is compatible with the actual biological situation when trying to quantify the risk.

p.107, para.4: If DHS is given access to the more complete data on the CCSP cohort that was developed by Roberts et al., age-specific person-years at risk could also be supplied. DHS might then wish to reconsider doing a risk assessment with the additive model also.

p.108, para.2: I'm sure DHS knows the difference but the wording of this paragraph may lead some readers to think that cases and deaths are being indiscriminately mixed. In any event, **Ontario** rates, not Canadian rates, should be used as background because that is what Chovil et al. used to estimate expected deaths.

p.109, para.2: It should also be pointed out that Rivedal and Sanner (1981) concluded that benzo(a)pyrene probably acted as the initiator of cell transformation while nickel sulfate probably acted as a promoter.

Maenza et al. (1971) showed that simultaneous intramuscular injection of nickel subsulfide and 3,4-benzpyrene in male Fisher rats significantly shortened the time for tumour development. Kasprzak et al. (1973) reported an increased incidence of "premalignant pathological reactions" in the lungs of rats that received a single

intratracheal injection of nickel subsulfide and 3,4-benzpyrene. Neither of these studies varied the order in which the organic and the subsulfide were administered.

Farrell and Davis (1974) administered 12 weekly sc injections of diethylnitrosamine into hamsters followed by 30 weekly intratracheal instillations of 4 mg/week of an unspecified nickel oxide. I will leave the interpretation of their results to the experts at DHS.

p.109, para.4: Why doesn't DHS discuss the Kreyburg (1978) study?

p.111, para.4: Friends at Falconbridge who visited the refinery many times over the years, were always impressed by the extent of smoking among the workforce. They particularly noted the propensity of workers to roll their own cigarettes with nickel-covered fingers in the presence of nickel-containing airborne dusts .

p.112, para.1: I'm still confused. DHS seems to be satisfied that the risk of lung cancer from nickel exposure is independent of the risk of lung cancer from background causes, principally cigarette smoking. If so, doesn't this suggest the use of an excess risk model to evaluate the risk from nickel exposure alone? Why does DHS subsequently use a relative risk model to ascertain the risk for the CCSP cohort? Since DHS has rejected biological synergism as justification for using the relative risk model, DHS should provide some evidence for its other justification for using the relative risk model; i.e. it should demonstrate that the age dependence of nickel-related lung cancer is the same as the age dependence of smoking-related lung cancer. Can this be done? Doesn't Kreyberg (1978) address this question?

p.112, section 7.2.5: I have several concerns about the risk assessment that follows. Most important, Part B of the TSD has provided ample evidence that DHS, like EPA and ATSDR, recognizes that the absorption (p.8, para.5), retention and excretion (p.20, para.5) and carcinogenic effects (p.72, para.2) vary with the form of nickel. DHS should therefore explain how it can estimate the risk of lung cancer from exposure to ambient nickel from the experience of an occupational cohort exposed to quite different forms of nickel. It is a constant source of amazement to metallurgists that toxicologists will take great pains to discriminate between individual organic compounds but, at the same time, will group all the forms of a metallic compound under one heading. For example, ATSDR plans to issue separate toxicological profiles for individual **isomers** of some organics but plans to handle all forms of a metal as a group. (It will be interesting to see how toxicologists handle organometallics if they become the subjects of risk assessments.)

Even if DHS can justify using the CCSP cohort for ambient risk assessment, it should not use the Chovil et al. study. The study by Roberts et al. is superior in every respect. However, it is not perfect as follow-up ended in 1984. The Joint Occupational Health Committee of Inco Ltd. and the United Steel Workers of America

has therefore decided to update this cohort yet again. This information may answer the burning question as to whether there was indeed a marked difference in the cancer risk between the early hires and the late hires (Muir et al.,1985; ICNCM,p.52). If there was, it would be very interesting because the concentrations of nickel were still extremely high during the later years of operation.

I will try to get the company and the union to agree to provide the Roberts et al. data in a form that would allow convenient evaluation of the dose-response relationship. If the planned update can be completed within a reasonably short time, the updated data will also be supplied to DHS.

In addition to using more up-to-date epidemiological data, DHS should use better exposure estimates than did Chovil et al. As pointed out earlier, it is too simplistic to say that exposures dropped from one level in 1951 and earlier to half of that level in 1952 and later. I am therefore including more information on the CCSP exposures.

The first question to consider is whether or not the CCSP could be treated as spatially homogeneous with respect to the concentrations of airborne nickel. DHS followed Chovil et al. and assumed that it was. However, plant operators recognized that some areas of the plant were dustier than others. The question is whether or not these differences can be quantified.

Figure 2 shows nickel concentrations for individual roof monitors. Although it is not easy to see on Figure 2, there was some pattern to the geographic distribution of nickel concentrations in the CCSP. In those cases where dust loadings were reported for individual roof monitors, it appears that the nickel concentrations were likely to be highest at monitor 4 in the early years and at monitors 1 and 2 in the later years. Nickel concentrations were invariably lowest at monitor 3. This makes some sense in terms of the process and the plant's history. As Figure 3 shows, monitors 1 and 2 were located over the area where the hot sinter fell from the sinter machines, was crushed, screened, cooled and mechanically conveyed. With the exception of the cooling operations, these are intrinsically dusty operations. Monitor 3 was located over the sintering machines. Since they received a damp feed and were under high draft, they were not particularly dusty operations. (This is where the hi-vol sample was taken.) Monitor 4 was located over the feed preparation operations. These could obviously be very dusty but, the monitor data show that, relative to the other areas of the plant, the dust control measures introduced here were effective.

The table on the next page shows konimeter data taken at various locations on the operating floors late in the CCSP's life. In general, the konimeter samples were higher than the single konimeter sample taken by the MOH and did not decrease as rapidly as did plant production. The data tend to show more temporal variability than spatial variability in the respirable dust. However, screening sinter was more likely to be dusty than was cooling sinter or mixing the charge. "Calibrated" konimeter data

KONIMETER DUST SAMPLES TAKEN NEAR NO. 3 SINTER MACHINE

Date of konimeter sample	July 1959	Feb. 1960	Feb. 1961	Aug. 1961	Mar. 1962	Sept. 1962
Number of sintering machines in use	4	4	4	3	1	1
Millions lbs Ni/month in sinter	22.0	22.5	22.5	11.0	3.2	1.8
Location of sample konimeter	particles per cubic centimeter[a]					
Feed end, operating floor	1416	1000+[b][c]	1000+	1000+	564	301
Mixer floor	2100	629	673	473	859	3[illegible]
Hummer screens	1667	458	913	976	1000+	310
Beside fines cooler	579	847	108	175	907	268

Date roof monitors were sampled	May 1959	Feb. 1960	Nov. 1960	Oct. 1961	June 1962
mg dust/m^3 at roof monitors	103	143	81[c]	69	120

Footnotes:

(a) All slides were washed in hot 50% HCl prior to counting. Isolated tests were made in which the dust was counted before and after washing. These indicated a "solubility" of 35% around the CC fluid bed roasters and from 50 to 60% around the PCNR calciners. This suggests that the above dust counts should be multiplied by about 1.7 to correct for the acid wash.

(b) 1000+ indicates the slides were so heavily laden as to be considered a health hazard. Once this condition was observed further precision was considered useless. The July 1959 counts were reported as determined, probably out of curiosity.

(c) On November 28-29, 1960 a 40-hr. gravimetric sample on the operating floor gave 46.4 mg/m^3 = 26.9 mg Ni/m^3. Konimeter sample gave 255 ppcc. Microscopic examination reported particles were "mostly 5 to 50 microns. Very few particles less than 5 microns."

are displayed on Figure 2. They agree well with the individual roof monitor data. The single hi-vol sample from the operating floor is also displayed. It is higher than some roof monitor values and lower than most of the "calibrated" konimeter samples, which were taken on the operating floor. The hi-vol does not look out of place on Figure 2.

Since most of the roof monitor data were reported as the average for all the monitors, it did not seem feasible to try to ascertain the temporal trends in nickel concentration for individual monitors, and hence plant areas. I therefore regressed the average nickel concentration for all the monitors against calendar time. The averaging process obviously obscures the true variability in the monitor data.

Although the konimeter samples were collected at different locations on the operating floor, I did not use them in the regression. First, they represented instantaneous conditions whereas the monitor samples were collected over hours. Second, the konimeter sampled only the low end ($< 5\ \mu m$) of a particle size distribution said to extend to 50 μm. In contrast, the isokinetic sampling technique used at the roof monitors should have sampled all particle sizes with high efficiency. Third, the konimeter data are reported as particles per cubic centimeter of air ("ppcc") rather than in the gravimetric units favoured by toxicologists. In order to use the konimeter data, it has to be "calibrated". I did this to construct Figure 2 using the hi-vol sample collected at the "same" time (over a 40 hour period) the konimeter was "snapped" (less than 1 second). To apply the calibration factor (mg Ni/m^3-ppcc) to other konimeter readings requires the assumption that the particle size distribution and the distribution of nickel as a function of particle size has not changed. While I think the konimeter data add to the credibility of the roof monitor data, I do not think they would add to the credibility of the regression.

Having selected the data, the next question was what model to use for the regression. My understanding of what happened in the plant to alter the nickel concentrations over time is reflected in Figure 1. This understanding suggests that a linear model is not appropriate even though it might give a reasonable fit because of the scatter in the data. I therefore tested both exponential and reciprocal models. The results are given in Figures 4 and 5, respectively. Each figure shows the data points, the mean, the 95% confidence limits of the mean and the 95% confidence limits of predicted values. The exponential model gave a slightly better fit to the data as shown by the regression statistics in Figure 6. However, I favour the exponential model because the upper confidence limits for the reciprocal model head for infinity fairly early in the game and that is not realistic.

I believe I have provided enough information to show that the single hi-vol sample taken on the working floor does not invalidate the roof monitor data as reasonable surrogates for the working environment. Nevertheless, I will revisit the issue one more time by adding the hi-vol data point to Figures 4 and 5. It is not precisely placed because of the limitations of the graphics package available to me. However, it is

close enough to show that it falls within the prediction limits of the exponential model but outside those of the reciprocal model. Thirty-five measurements have fallen inside the limits and only one has fallen outside. This is the kind of behaviour one might expect from a 95% confidence limit.

The question remains as to what exposures should be estimated for the years 1948 and 1949. Unfortunately there is only one data point for one monitor for this start-up period. It is considerably lower than the data for 1951 but Figure 1 suggests that conditions should have been even worse in the early days. The men who worked there agreed that conditions were particularly bad during the start-up period. I would therefore recommend that the mean nickel concentration for the 1948-1949 period be taken as the upper 95% confidence limit of the mean evaluated at 1950; i.e. 250 mg Ni/m^3. While this may seem high, Figure 4 shows that this average value was attained on occasion in 1950 and 1951. For 1950 on, I would use the mean nickel concentration from the exponential regression equation; i.e.

$$\text{Mean concentration (mg Ni/m}^3\text{)} = \exp(237.471 - 0.119123 * \text{Year})$$

Although I have treated the exposures as being uniform throughout the CCSP, that is clearly not the case. Some effort could be devoted to incorporating the uncertainty caused by this assumption into the dose-response relation. I would be pleased to try to assist DHS in doing so. However, there is another fact that may make such an exercise useless. All the CCSP workers were issued respirators but their wearing was not enforced. Some men wore their masks religiously. Others took pride in wearing them around their necks!

p.112, para.3: DHS spent a good bit of time trying to explain its reasons for using a relative risk model. However, when it came time to crunch numbers, it didn't provide a specific model to help the reader follow what was going on. If the calculations are based on EPA's average relative risk model $BH=P_o(R-1)/X$, why not show how DHS calculates each of the terms in that model? Table 7.12 is helpful but it would be more helpful still in conjunction with an equation.

More important, just because DHS couldn't deduce the reason for the discrepancy between the results EPA obtained with two different forms of the relative risk model is not a justification for not applying the maximum likelihood approach to the CCSP cohort. Its derivation in the NiHAD (p.8-201 to 8.204) is clear enough. As EPA points out (NiHAD, p.8-209), it uses the average relative risk model in cases where there is only one dose-response data point and where more detailed information such as time since first exposure are not available. This is not the case with the CCSP cohort, particularly if DHS makes use of the newer, more complete data from Roberts et al.

p.112, para.3: DHS will notice that the estimated nickel concentrations for the CCSP that are reported in the ICNCM are only 40% of those given by Warner (1984). This was the result of a majority decision which I opposed unsuccessfully. The majority wanted to express all exposure estimates on a common basis: the concentration one would have **expected** to obtain with a personal, "total dust" sampler (2 l/min, 37 mm filter, cassette operated in "closed face mode"). While standardization was an admirable objective, we were having enough trouble making reasonable exposure estimates without having to **estimate** conversion factors to other forms of sampling. To be meaningful, such conversion factors would have to be based on a knowledge of the size distribution of the dust and of the average windspeed in the workplace. The detailed information needed was lacking. However a single dust sample taken on the operating floor in 1960 was reported to contain particles "mostly 5 to 50 microns. Very few particles less than 5 microns." No information was provided as to whether the nickel-bearing particles were among the largest ones or not. The conversion factor of 0.4 employed in the ICNCM study was based on this scanty information and on an assumed windspeed.

By requiring the translation to the "total dust" standard, I believe the ICNCM distorted the amount of dust actually inhaled by the workers. The sampling at the roof monitors was conducted isokinetically. The monitor data should therefore provide reasonable estimates of the concentrations of the total dust. No direct determinations of the size distribution of the total dust collected at the monitors were available. However, an indirect calculation suggests that the principle nickel species in the dust sampled at the monitors would have been inhalable; i.e. they would have had **aerodynamic diameters** less than 100 μm.

The total volume of warm air leaving the four roof monitors averaged 650,000 cfm with a standard error of 20,000 cfm. The temperature of the air at the monitors averaged 32 C. The cross-sectional area of the plant was about 30,500 square feet. Thus the **average** vertical velocity of the rising air was about 0.35 feet/second. I used standard equations to determine what diameters of nickel subsulfide and nickel oxide would have terminal velocities equal to the rising velocity of the warm air. These were 25.5 μm and 22.6 μm respectively. This is equivalent to an aerodynamic diameter of about 62 μm, well within the inhalable range. This is coarse relative to respirable dust but respirable dust probably was of little consequence in the CCSP because the respiratory cancers seen were of the sinonasal cavities and of the bronchial region.

The above should not be taken to mean that there was no respirable dust present in the CCSP. Even though the Ministry of Health ("MOH") reported "Very few particles less than 5 microns.", it simultaneously reported a konimeter count of 255 particles per cubic centimeter and the table on page 30 shows even higher counts. Only particles smaller than 5 μm are included in the konimeter counts! The konimeter slides were washed in hot HCl prior to being counted. This would have readily

dissolved the nickel subsulfide and would have attacked the nickel oxide in the CCSP dust, artificially lowering the dust count. Sebestyn et al. (1987) showed that the acceptance curve of the konimeter provides a reasonable estimate of respirable dust; this is not unexpected as the konimeter was used successfully for many decades to control dusts capable of causing silicosis.

p.112, para.3: The analysis assumes either that the composition of the sinter plant dust remained constant over the life of the plant or that the airborne carcinogens all had equal potencies. I don't think that either of these assumptions is true. Since the dust losses from the plant declined dramatically as the productivity increased, it is likely that the proportion of nickel subsulfide -- the plant feed -- in the airborne dust decreased in later years. The amount of coke breeze used per unit of sinter produced also declined dramatically with the passage of time; e.g from 0.27 kg coke/kg sinter in 1948 to 0.133 in 1951-1954 to 0.099 in 1955-1959. Thus the potential for airborne PAHs also declined in later years. However, in addition to the combustion of coke breeze, oil and grease from the materials handling equipment was shoveled from the floor back onto the hot (over 500 C) sinter. One plant manager told me that there was usually a blue haze in the air even towards the end of the plant's life. The record also shows that rubber conveyor belts ignited and burned frequently in the first year or two of operation.

p.112, para.4: While using expected values as weights is prudent, it cannot eliminate the possible errors due to inadequate latency periods. Since those exposed least were most likely to be exposed in later years, it is possible that insufficient time has elapsed to permit lung cancers to develop in these exposure groups. Thus, the passage of time is likely to reduce the slope. I do not know how DHS could eliminate such a bias from the Chovil et al. data. With the planned update of the CCSP cohort, it might be possible to ensure that the various exposure groups are constructed of men with comparable latency periods.

p.115, para.1: DHS has assumed the untraced men in Chovil et al's cohort had the same proportion of lung cancer deaths as existed among those who had been traced. DHS has made another, even less justifiable, assumption. By adjusting the slope, DHS has also assumed that the hypothesized lung cancer deaths occurred in the seven exposure groups in the same proportion that they appeared among the traced workers. This is quite inappropriate as DHS has no idea how the untraced workers were distributed across the seven exposure groups. It is quite possible that, if there were undetected lung cancer deaths, they would have resulted in a smaller slope, rather than a larger one.

If DHS uses the Roberts et al. data or the results of the planned update, it will not have to be concerned about lack of ascertainment.

p.115, para.2: The estimated exposures should reflect the actual hours worked. Payroll records show that Inco's surface plant workers changed from a 7-day 60-hour workweek to a 6-day 48-hour workweek in 1935. On June 5, 1950, a 44-hour workweek was adopted; this consisted of alternating 40 and 48-hour workweeks. On June 25, 1951, the 40-hour workweek was adopted. These changes would have a substantial effect on the estimated cumulative exposures of the CCSP workers because the hours of exposure were reduced at roughly the same time the concentrations of airborne dust were most rapidly reduced.

Exposure estimates should account for the fact that the CCSP (along with all other Inco's Sudbury operations) were shut down from September 24th through December 25, 1958 as a result of a strike by organized labour.

The inhalation rates of the CCSP workers (and of Californians in Part A) should also be taken into account. I consulted with two retired individuals who had worked in the CCSP, one as the plant manager. I read to them the definitions of the activity levels used by EPA to discriminate between different inhalation rates (see p.14 of my Recommendations and Comments on the Part A Report). After reflection, they both opined that two-thirds of the workers would be classified as having "light" activity levels while one-third worked at "moderate" activity levels.

p.115, para.4: DHS arrived at a lifetime lung cancer mortality risk of 0.049 whereas EPA arrived at a rate (also stated to be for Canada) of 0.026 for the same period (NiHAD p.8-212)? These differ by a factor of nearly two!

The calculation of the lifetime lung cancer mortality risk should be based on the same rates that were used to calculate the SMRs for the CCSP workers. Both Chovil et al. and Roberts et al. employed Ontario statistics, not Canadian statistics. Also, I hope line 3 of this paragraph contains a typographic error as it would be incorrect to estimate a **lung** cancer risk by using the rates for all cancers.

I am not sure how P_o should be calculated because I have never seen an explanation of how the average relative risk model was derived from the fundamental equation for relative risk. At the time I was arguing with EPA's Carcinogen Assessment Group about its universal use of a single value of P_o, I was told that CAG calculated P_o as follows: a male child borne in the calendar year of interest was moved through successive age-groups making him subject to the risks of lung cancer and of all other causes of death, assuming that the relevant rates for that calendar year remain unchanged throughout his life. I interpreted this description to mean the following equation would give at least an approximate value of P_o.

$$P_o = \sum_{i=1}^{i=L} (LCR_i/1000) * \prod_{j=1}^{j=i-1} (1-Dr_j/1000)$$

where:

i and j are years in the subject male's life;

L is the number of years comprising a "lifetime";

LCR_i is the annual lung cancer death rate per thousand population in the five-year age-group in which year i falls;

DR_j is the all-causes death rate per thousand population in the five-year age-group in which year j falls;

The product of the $(1-DR_j/1000)$ terms is the probability that one has survived all preceding years and is thus available to die of lung cancer in the ith year.

One relevant question is over how many years should the probabilities be summed? Over all those for which LCR_i and DR_j are available? Or only for the standard 70-year life? Another question is how to calculate a value of P_o averaged over a number of calendar years. Should one simply average the final values of P_o for each calendar year or should the averaging take place during the calculation for each year of life?

I say again, I don't know if this is how P_o should be calculated but it looks reasonable to me. In contrast, it seems to me that DHS's approach could produce only a rough estimate of P_o at best.

$$P_o = \sum_{k=1}^{k=N} \text{Lung cancer deaths} \; / \sum_{k=1}^{k=N} \text{All deaths}$$

where:

the deaths were those observed in the total population for calendar year k;

N is the number of calendar years for which P_o is to be calculated.

The only rationale I can imagine for this approach is to say: (1) the probability of dying in a lifetime is 1 and (2) the probability that the death was due to lung cancer equals the PMR for lung cancer. However, such an approach would neglect the "fine structure" in age distribution of the population and in the rates. I compared the Warner/EPA approach with the DHS approach for several years of Ontario vital statistics that I had on hand. The DHS approach always gave a higher value for P_o.

DHS should explain what P_o should be and then demonstrate that its approach yields the correct number. P_o is too important a factor in the risk assessment to tolerate unnecessary uncertainty, particularly a factor-of-two uncertainty.

p.116, para.2: It is reassuring to learn that DHS has not forgotten that its unit risk factor is only applicable to men exposed to a particular mix of nearly-pure nickel compounds.

p.116, para.2: I have done more work on the nickel species believed to be present in airborne dust at the CCSP for the ICNCM study. The process did not involve "various sulfur-containing forms of nickel"; it involved only one form, nickel subsulfide. The plant products were mainly nickel oxide (NiO) and a small amount of nickel-copper oxide ((Ni,Cu)O). The nickel-copper oxide contained about 10% CuO in solid solution in NiO.

It is obvious that Ni_3S_2, NiO and (Ni,Cu)O were each represented in the airborne dust at the CCSP. The questions to be answered are the proportions of each phase and whether there were any other nickel species present.

The subsulfide was contaminated with one or two percent by weight of a metallic fraction, which typically analyzed about 75 to 90% Ni. A review of the process suggests that it is unlikely that this metallic phase or one produced by the unintended reduction of nickel oxide by coke breeze would have become airborne. Nevertheless, this possibility has been considered.

X-ray diffraction analysis of samples of rafter dust collected 13 years after the CCSP closed indicated the presence of hydrated nickel sulfate. Further laboratory work (selective leaching, SEM and microscopic examination) suggested strongly that the sulfate was formed by weathering reactions after the dusts were deposited. Other laboratory experiments have shown that prolonged heating (five hours) of nickel subsulfide at 500 C in air would have sulfated no more than 5% of the Ni_3S_2. Review of the process indicated that, even if the time and access to oxygen were provided, there is no reason to expect that the sulfate so formed could have become airborne. Nevertheless, this possibility has been considered.

Although many assays were made of the dust collected at the roof monitors, they were only for nickel and copper. These assays don't provide enough information to partition nickel among sulfur-, oxygen- and sulfate-species. I have been able to find assays for only seven samples of airborne CCSP dust that were analyzed for copper, nickel and sulfur soon after the dust was removed from the air. Six of these samples were collected from new-fallen snow on January 7, 1949. The other was the high volume sample taken on the operating floor on August 3, 1960. The snow samples were analyzed by Inco, the hi-vol sample by the Ontario Department of Mines. Thus we have samples from early and late in the CCSP's life but nothing in between.

The analyses of the rafter dust samples and a review of the process indicated that the dusts would have contained typically 5-7% of "other" material; e.g. carbon, iron oxide, refractory oxides and other metal oxides.

The limited facts, together with thermodynamic and stoichiometric considerations, were used to calculate various mixes of phases that would have been compatible with the elemental assays. The equations were "best behaved" and the results seemed most reasonable when it was assumed that the only nickel phases present would have been Ni_3S_2, NiO and $NiSO_4 \cdot 6H_2O$. Assuming the presence of metallic nickel seemed to give unstable and unrealistic results. These studies suggest that, **on the two days** for which the assays were available, about 60% of the nickel in airborne dust was present in NiO, about 35% was in Ni_3S_2 and no more than 5% was in $NiSO_4 \cdot 6H_2O$, if the sulfate existed at all. I must emphasize that these calculations can't **prove** anything but they are the best we can do to unravel the mystery of the CCSP.

The calculations described above, and common sense, suggest that the airborne nickel oxide contained some copper oxide. The contained CuO could have amounted to from about 5 to 10% of the weight of (Ni,Cu)O. The Sunderman abstract (p.20) indicates that nickel-copper oxide is a potent experimental carcinogen. It should also be noted that the Clydach refinery treated a nickel-copper oxide although the copper content began to decline dramatically after 1930 and fell to very low levels after 1937. The Kristiansand refinery always treated nickel-copper oxide. I have stated earlier that I do not expect to find nearly-pure NiO in California air. I think it is even more unlikely that a nickel-copper oxide would be found there.

Just because the CCSP was a nickel refinery doesn't automatically mean that some form(s) of nickel was the only possible explanation for the cancer hazard. As a result of the incomplete combustion of coke breeze, fuel oil, lubricating oil and, initially, rubber conveyor belts, it is very likely that PAHs were present. Combined with the very high concentrations of airborne particulates, they could have played a significant role in the incidence of respiratory cancer at the CCSP.

p.116, para.3: DHS is right with one exception. The epidemiological studies of nickel workers have had to contend with cohorts with mixed exposures to nickel compounds. This is why the ICNCM was forced to employ such an elaborate analysis. However, I believe the epidemiological studies conducted at the Oak Ridge Gaseous Diffusion Plant indicate clearly that there was no risk of lung cancer associated with exposure to fine, pure metallic nickel powder. The latest update of this cohort is presented in the ICNCM report.

p.116, para.5: Nickel oxide was **not** a consistent experimental carcinogen, even by the parenteral route. When nickel oxide **known** to be produced at high temperatures (like those used in the CCSP) was tested, it did not produce tumors by injection. Nickel subsulfide, on the other hand, was a consistently potent carcinogen by parenteral routes. It seems premature rather than prudent to equate their carcinogenic potencies, particularly when the NTP is close to completing the best inhalation experiments that will ever be done on these two compounds.

p.117, para.4: DHS recognized at the top of p.116: "Thus the risk estimates and their extrapolation apply to whatever combination of nickel species the refinery workers were exposed." Neither DHS nor ARB has provided any evidence for the similarity of ambient nickel to the combination of nickel species found in the CCSP. There is no reason to expect to find crystalline Ni_3S_2 and NiO or (Ni,Cu)O in ambient air. Referring to these compounds as "insoluble nickel species" does not solve the basic problem: the risk assessment is based on circumstances not relevant to California ambient air. Furthermore, examples provided by DHS and by me indicate the great diversity in biological behaviour of nickel compounds with similar water solubilities. Aqueous solubility is not an adequate criterion for grouping nickel compounds according to carcinogenic potential.

At the public consultation meeting on August 15th, Ms. Shiroma said that ARB needs to show only three things to justify a conclusion that a substance is a toxic air contaminant:

1. the substance is present in California ambient air;

2. there is evidence that it can cause serious health effects, at least under certain circumstances;

3. there is no evidence of a threshold in the dose-response relationship.

It seems clear that ARB/DHS has not satisfied the first requirement. It has found nickel in the ambient air and determined that some of it is relatively insoluble in water. The fact that some water-insoluble forms of nickel can reasonably be associated with an increased risk of respiratory cancer in an occupational setting or in animal experiments does not constitute even weak proof that their carcinogenic potentials are the same. Would ARB propose to regulate as a group all organic species that had similar solubilities in a particular solvent?

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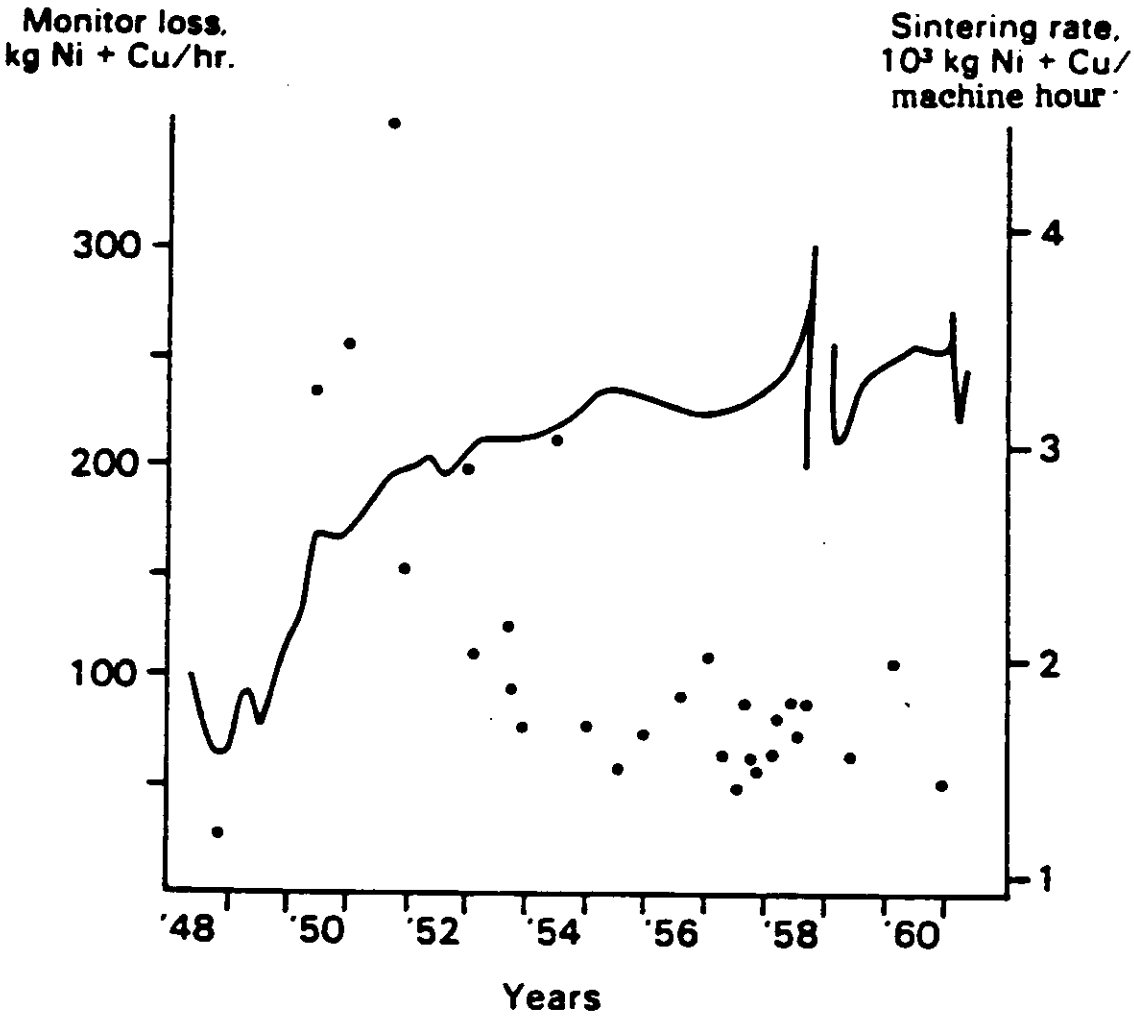
FIGURE 1

NICKEL+COPPER LOSSES AND SINTERING RATE IN THE COPPER CLIFF SINTER PLANT



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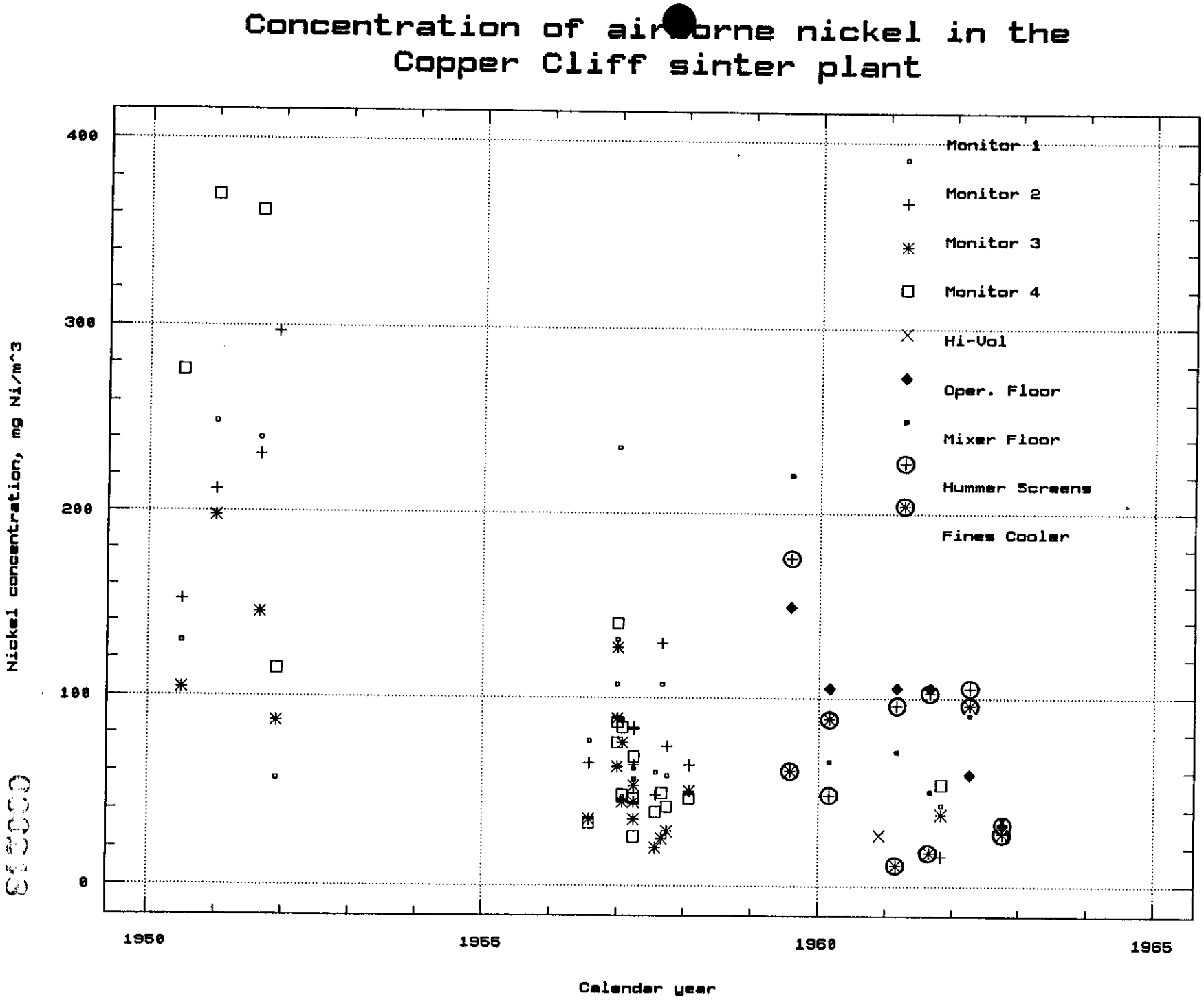
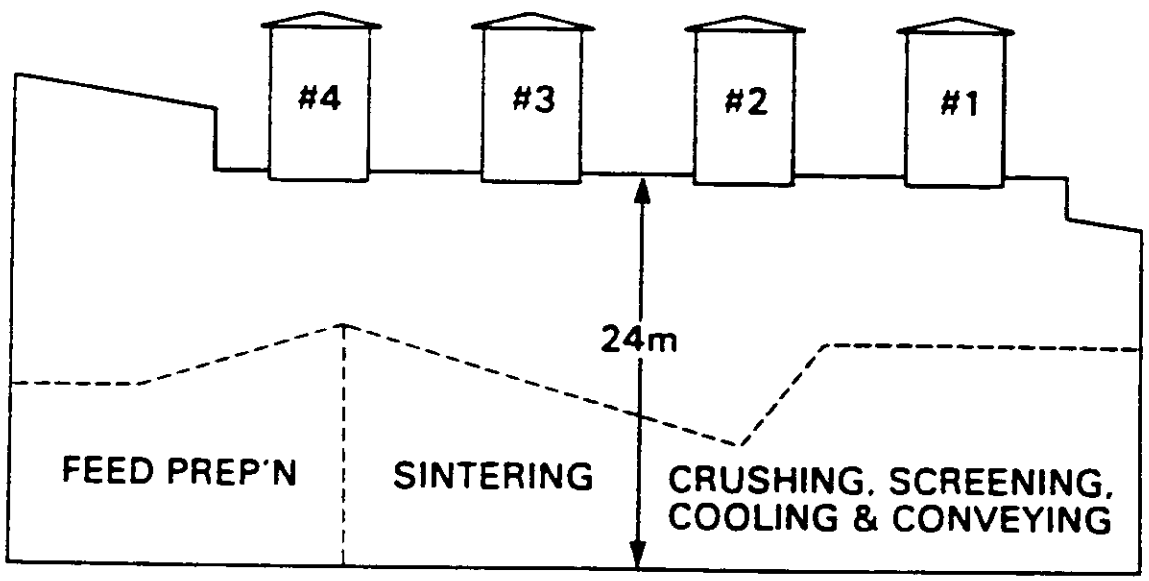

Concentration of airborne nickel in the Copper Cliff sinter plant
Nickel concentration, mg Ni/m^3
400
300
200
100
0
1950
1955
1960
1965
Calendar year
Monitor 1
Monitor 2
Monitor 3
Monitor 4
Hi-Vol
Oper. Floor
Mixer Floor
Hummer Screens
Fines Cooler

FIGURE 2

FIGURE 3

SECTION OF THE COPPER CLIFF SINTER PLANT



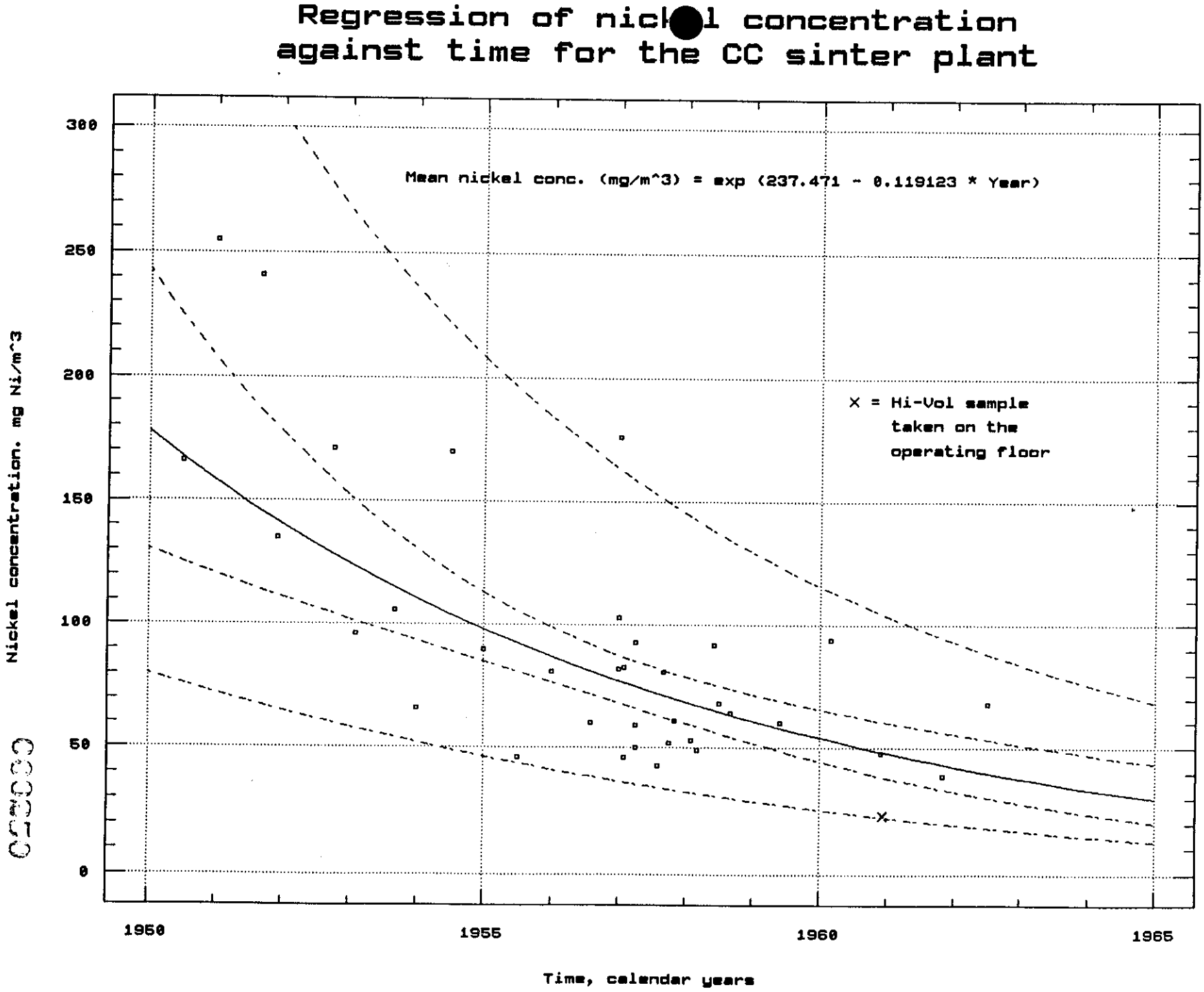

Regression of nickel concentration against time for the CC sinter plant
Mean nickel conc. (mg/m^3) = exp (237.471 - 0.119123 * Year)
X = Hi-Vol sample taken on the operating floor
Nickel concentration, mg Ni/m^3
300
250
200
150
100
50
0
1950
1955
1960
1965
Time, calendar years

FIGURE 4

Regression of nickel concentration against time for the CC sinter plant

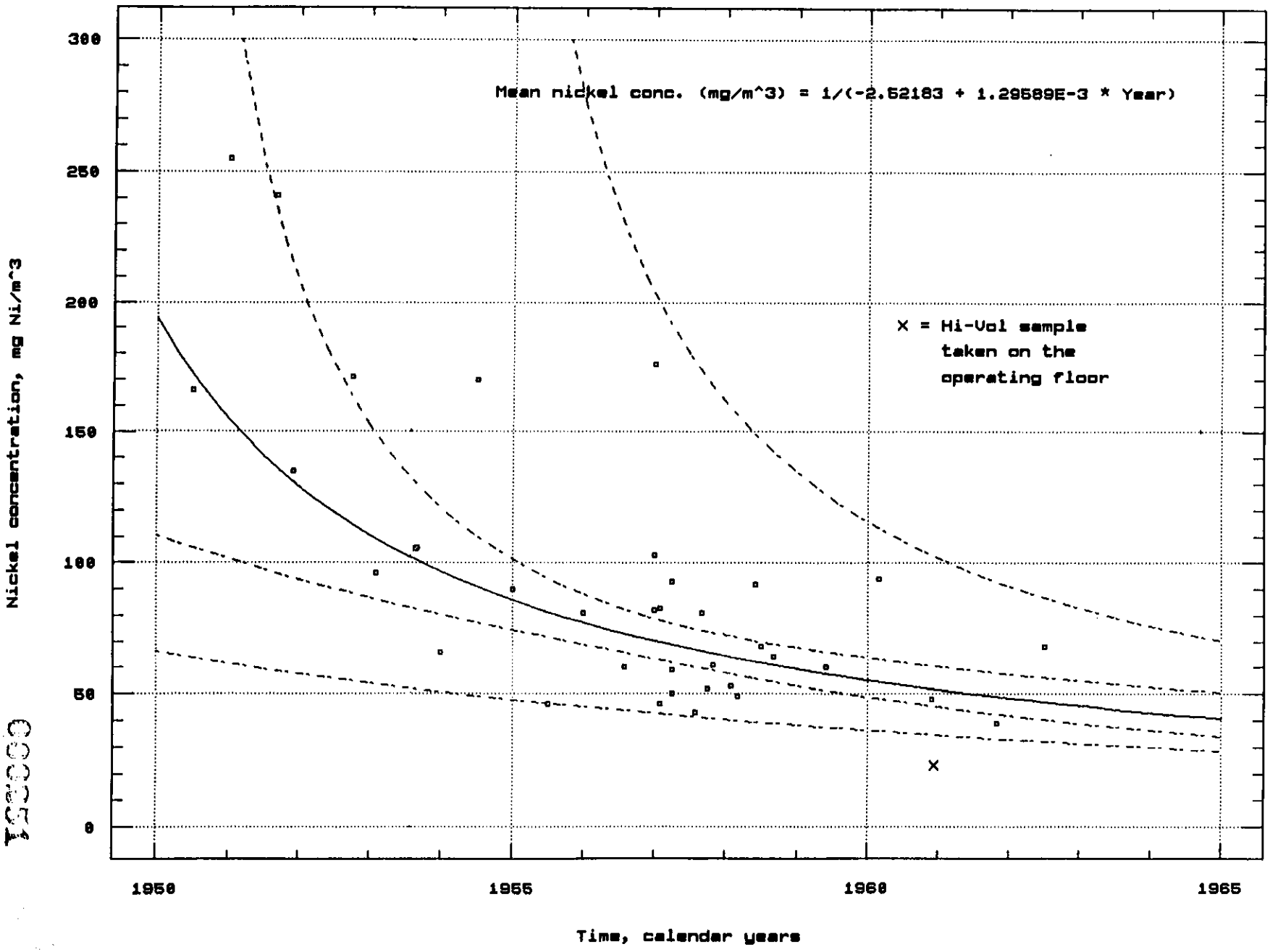


FIGURE 5

FIGURE 6

Regression Analysis - Exponential model: Y = exp(a+bX)

Dependent variable: CCSPDUST.ALLMONTR Independent variable: CCSPDUST.YEAR+CCSP

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	237.471	41.5768	5.71162	.00000
Slope	-0.119123	0.0212496	-5.60586	.00000

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	4.121051	1	4.121051	31.42571	.00000
Error	4.327498	33	.131136		
Total (Corr.)	8.448549	34			

Correlation Coefficient = -0.698414 R-squared = 48.78 percent
Stnd. Error of Est. = 0.362127

Regression Analysis - Reciprocal model: 1/Y = a+bX

Dependent variable: CCSPDUST.ALLMONTR Independent variable: CCSPDUST.YEAR+CCSP

Parameter	Estimate	Standard Error	T Value	Prob. Level
Intercept	-2.52183	0.517459	-4.87348	.00003
Slope	1.29589E-3	2.6447E-4	4.89995	.00002

Analysis of Variance

Source	Sum of Squares	Df	Mean Square	F-Ratio	Prob. Level
Model	.000488	1	.000488	24.00955	.00002
Error	.000670	33	.000020		
Total (Corr.)	.001158	34			

Correlation Coefficient = 0.64896 R-squared = 42.11 percent
Stnd. Error of Est. = 4.50699E-3

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Chronic Effects of Intratracheally Instilled Nickel Containing Particles in Hamsters

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1. Introduction

Only limited information is available concerning whether a potential carcinogenic risk is associated with an exposure to particles of nickel alloys. In a chronic study, Syrian golden hamsters were treated by intratracheal instillations to evaluate the carcinogenic potency of grinding dusts derived from stainless steel and particles from the mineral pentlandite, both containing nickel. Nickel powder and nickel subsulfide (α Ni_3S_2) were used as reference materials. In a previous study the acute and subchronic effects were investigated to determine the maximum tolerated dose (Muhle et al. 1986).

2. Material and Methods

2.1 Test Materials

A characterization of test materials nickel powder, nickel subsulfide, pentlandite and grinding dusts is given in Table 1. The diameters of particles were determined by electron microscopy. For irregular shaped particles (grinding dusts) the median geometric diameter was estimated whereas for more regular shaped particles the mass median diameter was calculated. From these data the values of the mass median aerodynamic diameters were estimated.

A respirable fraction of stainless steel grinding dust was collected in a factory in which metal pieces were ground. For the separation of coarse and fine dust a high-volume heavy-grain-load impaction sampler was used (Muhle et al. 1986, Koch et al. 1986). Animals were treated by two types of stainless steel grinding dusts, one

originating from a normal 18/10 Cr/Ni steel and the other originating from a ferritic chromium steel. The latter was used to investigate biological effects of particles with a very low nickel content (negative control). The composition of the grinding dusts is presented in Table 2.

The Cr/Ni steel dust was also investigated by powder diffraction analysis. It was composed of a phase mixture of austenite and a cubic spinel $(FeCrNi)_3O_4$. Additionally about 100 single randomly selected particles were investigated in a scanning electron microscope by energy dispersive X-ray analysis. This investigation showed no evidence for the presence of nickel or nickel oxide in pure form. The range of the nickel content per particle was 4 to 10 %.

The Cr steel dust was composed of a phase mixture of ferrite and a cubic spinel $(FeCrAl)_3O_4$

2.2 Animal Model

Syrian golden hamsters were chosen as experimental animals because in this species inflammatory reactions in the lung are less pronounced after intratracheal instillation compared to rats (Della Porta et al. 1958, Saffiotti et al. 1968, Nettesheim, 1972). Persistent inflammatory reactions may aggravate other chronic lung diseases.

Further reason for selecting the hamster was the low spontaneous tumor rate of 0.1-0.5 % (Saffiotti et al. 1968, Dontenwill et al. 1973, Mohr et al. 1984).

Syrian golden hamsters (Cpb - ShGa 51) from TNO, The Netherlands, were used. At start of the treatment animals were 10-12 weeks old and weighed about 80 g. Hamsters were randomized.

The particles were suspended in saline and intratracheally instilled 12 times every 14 days. Hamsters were under slight halothane anesthesia and placed in a vertical position during treatment. The volume per treatment was 0.15 ml. The dose is given in Table 4.

2.3 Sacrifices and Histopathology

At termination of the study hamsters were sacrificed by an overdose of ether. Tissues and organs were fixed in 10 % neutral buffered formalin and processed for routine histology (H & E stain). In animals bearing lung tumors additionally main organs were examined histopathologically to exclude metastatic lung tumors.

3. Results

3.1 Retention of Nickel Containing Particles in Lungs

In satellite groups at 14 days, 6 and 12 months after the last intratracheal instillation two hamsters of each sex were sacrificed. Excepted was the group treated by Cr steel dust. Lungs were ashed and the nickel content was analysed. Table 3 shows the used dose and the retained mass, calculated from the nickel content of the instilled particles.

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For calculation of the clearance kinetics of the particles an exponential curve was fitted to the values of the three retention dates. The half-time of the pulmonary nickel clearance was estimated as 152 days for nickel powder, < 14 days for Ni_3S_2, 120 days for pentlandite and about 450 days for Cr Ni stainless steel dust.

The number of animals for this evaluation was relatively low. Values of male and female hamsters had to be pooled.

3.2 Carcinogenicity Study

3.2.1 Study Design

At start of the study, start 30 hamsters per sex were treated by intratracheal instillation 12 times every 14 days, o.15 ml per treatment. The particles were suspended in saline. The single and the cumulative dose is shown in Table 4.

3.2.2 Clinical Observations

The number of animals which died during the treatment period of 170 days is listed in Table 4. Most of these hamsters died during the period of first two treatments. The reason for the high mortality rate in the Cr stainless steel dust group after the first treatments could be agglomerations of particles which may have caused partial airway obstruction. To prevent this effect, a more intensive ultrasonic treatment of the particle suspension was performed in the

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subsequent instillations. The mortality rate during the treatment period was larger in males (uneven group numbers) than in females (even group numbers). Beside airway obstruction acute toxic effects may have caused same mortality.

Fourteen days after the first instillation additional hamsters were added to those groups indicating losses as a result of the treatment (see Table 4). The reserve hamsters came from the same delivery as the original animals.

Animals which died during the treatment period were not included in analysis of a carcinogenic risk because of their short life span and were excluded from the calculation of the median life time. The listed life time is the period since start of treatment. For the total life time the span of 10 weeks before treatment has to be added.

Body weights of female hamsters in group 6 (Pentlandite) and group 10 (Cr/Ni stainless steel dust) were lower than to the control groups starting at about day 500 of the study. Body weights of other groups were comparable to controls.

3.2.3 Results of Histopathological Investigations

Results of histopathological investigations of the hamsters surviving the treatment period of 170 days are listed in Table 5. After treatment to nickel subsulfide particle deposition was detected in only a few animals. This is due to the low amount of mass used for the treatment and the relatively fast pulmonary clearance of this

material. In all other groups, distinct particle deposits were found. The smallest amounts were in the group treated with nickel powder. In this latter group the administered mass was also relatively low.

Granulomatous changes, which reflect inflammatory processes, were only observed in groups treated with pentlandite and stainless steel dusts. These were the groups with the highest lung burden of particles.

Bronchioloalveolar hyperplasia was detected in the groups treated with nickel powder, pentlandite, and stainless steel dusts. Squamous metaplasia was slightly increased in the nickel group.

Two primary tumors were observed: one adenosquamous carcinoma in the group exposed to nickel powder and one bronchioloalveolar adenoma after pentlandite exposure.
This means that no statistical increase in tumor rates was found.

In the groups with nickel powder and nickel subsulfide the larynx, trachea and kidneys were additionally examined histologically. There were no indications of treatment-releated effects.

4. Discussion

In this study the calculation of the half-times for the pulmonary clearance of the applied dusts was based on the retention data of nickel. For nickel subsulfide the half-time was relatively short at less than 14 days. This value was of the same magnitude as the one published by Finch et al. 1987 and Fisher et al. (1986) which was

given as 5 days for mice. The fast clearance of nickel subsulfide could be one of the reasons why little response was detected in this treatment group.

The half-times of the pulmonary clearance of nickel powder and pentlandite were 152 and 120 days, respectively. The corresponding values for Cr/Ni stainless steel dusts were about 450 days. The significant retardation of lung clearance after treatment with stainless steel dust is probably caused by an overloading of the alveolar clearance. This effect is produced by lung burdens higher than 1 mg per gram of lung and is reported also for other dusts like plastic powder (Muhle 1988 a,b) and is therefore not specific for stainless steel grinding dusts.

In this study, none of the treatment groups had a statistically significant number of tumors. Five cases of squamous cell metaplasia and one case of an adenosquamous carcinoma after nickel treatment indicate that nickel powder has only a very weak carcinogenic effect in hamsters. After treatment with pentlandite one bronchioloalveolar adenoma was observed in 60 animals.

No inflammatory reactions were observed after administration of nickel powder and Ni_3S_2. On the other hand, inflammation was visible after treatment with pentlandite, Cr/Ni steel and Cr steel dusts. This effect is mostly an nonspecific reaction of the type commonly found after application of many particulates with low solubility. The particles are phagocytosed by alveolar macrophages and induce inflammatory granulomatous changes (Saffiotti, 1986).

A ranking of the relative carcinogenic potential of nickel, nickel compounds and nickel alloys is not possible as a result of this study.

Since the beginning of the design of this study in 1982 various other carcinogenicity studies were completed in which hamsters and rats were investigated concurrently (see Table 6). These studies show that after inhalation or intratracheal instillation of various test materials rats did develop lung tumors but not hamsters. The Table 6 represents only a small section of the numerous carcinogenicity studies. A more complete overview was compiled by Pepelko (1984).

In humans, carcinogenic effects are described after exposure to coke oven exhaust. For this material, the rat is obviously a more suitable species for investigating the carcinogenic potency on humans than the hamster.

For other materials (diesel motor exhaust, cadmium and α quartz) the IARC (1987) evaluated a limited evidence for carcinogenicity in humans. In the rat, these materials and also nickel and some nickel compounds induced lung tumors. The absence of statistically significant carcinogenic effects in hamsters after treatment with nickel containing particles does not exclude a carcinogenicity of the tested substances in humans. A better knowledge on the mechanism of nickel induced tumors in various species will give a better data base for risk extrapolation.

5. Acknowledgements

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TABLE 1. Characterization of Test Materials

Test Material	Median Geometric Diameter (µm)	Mass Median Diameter (µm)	Estimated Mass Median Aerodynamic Diameter (µm)	Chem. Characterisation	Source
Ni Powder		3.1	9	Ni: 99.9 %	INCO, Clydach, GB "Experimental Nickel Powder No. 384"
Ni_3S_2		2.2	5	αNi_3S_2 72.9% Ni, 27.1% S	INCO; Grinded Sample
Pentlandite		2.2	5	Ni: 34.3 % S : 32.2 % Fe: 28.8 % Cu: 0.028 % Al_2O_3: 0.05 %	INCO
Cr/Ni Stainless Steel Grinding Dust	1.1		3-5	see Tab. 2	After Grinding Machine
Cr Stainless Steel Grinding Dust	0.8		3-5	see Tab. 2	After Grinding Machine

INCO: International Nickel Corporation

TABLE 2 Chemical Analysis of the Stainless Steel Grinding Dusts

	Cr/Ni Steel (%)	Cr Steel (%)
Fe Σ	59.2	68.0
Fe met	17.2	28.5
Cr	13.92	12.87
Cr^{6+}	<0.01	0.04
Ni	6.79	0.54
Mn	1.0	0.3
As	0.016	0.018
S	0.13	0.12
Al	2.14	1.99
Si	0.65	0.28
Zn	0.03	0.04
Pb	<0.01	<0.01
Cd	<0.01	<0.01
C	3.90	3.43
Be	<0.001	<0.001
Co	0.10	0.03
Ti	0.03	0.02
Mo	0.22	0.09

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TABLE 3. Results of Retention Measurements of Nickel in Lungs

Test Material	Cumulative Dose (mg/animal)	Lung Retention after 14, 182 and 364 Days after the Last Treatment (mg/lung)	Number of Investigated Hamsters	Estimated Half-Time of Nickel Clearance (Days)
Ni Powder	9.6 (12 x 0.8 mg)	0.367±0.172 0.195±0.094 0.075±0.029	3 4 4	152
Ni_3S_2	1.2 (12 x 0.1 mg)	0.0514±0.0196 -[a] -[a]		3 < 14
Pentlandite	36 (12 x 3 mg)	13.9±4.1 2.2±1.6 1.8±1.7	4 4 4	120
Cr/Ni Stainless Steel Dust	36 (12 x 3 mg)	21.3±4.5 14.5±6.2 12.8±2.9	4 4 4	481
Cr/Ni Stainless Steel Dust	108 (12 x 9 mg)	71.8±25.8 51.0±19.8 39.9±14.5	4 4	415

[a] Below Detection Limit

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TABLE 4. Mortality Development and Median Life Time in the Chronic Study

Test Material	Cumulative Dose (mg/animal)	Group No.	No. of Hamsters Added after 14 Days	No. of Died Hamsters till End of Treatment	No. of Hamsters after the Treatment Period	Median Life Time (weeks)
Ni Powder	9.6 (12 x 0.8 mg)	1	2	5	27	111
		2	1	0	31	100
Ni_3S_2	1.2 (12 x 0.1 mg)	3	3	3	30	114
		4	2	0	32	101
Pentlandite	36 (12 x 3 mg)	5	1	2	29	109
		6	2	1	31	91
Cr/Ni Stainless Steel Dust	36 (12 x 3 mg)	7	2	1	31	130
		8	2	0	32	102
Cr/Ni Stainless Steel Dust	108 (12 x 9 mg)	9	5	4	31	112
		10	2	1	31	96
Cr Stainless Steel Dust	108 (12 x 9 mg)	11	10	12	28	119
		12	2	4	28	90
Vehicle Control (NaCl-Solution)	-	13	0	0	30	117
		14	0	0	30	103

Groups with odd number: males
Groups with even number: females

TABLE 5. Histopathological Changes in the Lungs of Hamsters Exposed to Ni-Compounds (i.t.)

Compounds	Group No.	Sex	No. of Hamsters Examined Histologically	No. of hamsters with stated findings: Deposition of Pigments 1+ 2+ 3+ 4+	Granulomatous Changes 1+ 2+ 3+	Bronchiolo-Alveolar Hyperplasia 1+ 2+ 3+	Squamous Metaplasia +1 +2	Primary Tumors
Ni Powder	1	M	26	9(3 6)	0	15(8 7)	1(1)	
	2	F	30	21(10 11)	0	20(7 11 2)	4(1 3)	1 (Adeno-squamous carcinoma
Ni_3S_2	3	M	30	3(3)	0	2(1 1)	1(1)	
	4	F	32	0	0	0	0	
Pentlandite	5	M	29	27(27)	15(7 8)	22(13 9)	0	1 (Bronchiolo-Alveolar Adenoma)
	6	F	31	31(31)	20(3 17)	18(10 8)	0	
Cr/Ni Stainless Steel	7	M	30	30(1 29)	2(2)	12(10 2)	0	
	8	F	32	32(32)	12(4 8)	10(9 1)	1(1)	
Cr/Ni Stainless Steel	9	M	31	31(13 9 22)	26(3 22 1)	15(14 1)	1(1)	
	10	F	31	31(15 14 17)	27(4 21 2)	10(8 2)	0	
Cr Stainless Steel	11	M	28	28(26 2)	27(11 15 1)	24(4 20)	0	
	12	F	28	28(21 7)	28(1 27)	14(10 4)	0	
NaCl-solution	13	M	30	0	0	5(4 1)	1(1)	
	14	F	30	1(1)	0	1(1)	0	

1+: very slight, 2+: slight, 3+: moderate, 4+: severe

TABLE 6. Carcinogenicity of Various Substances in Humans, Rats, and Hamsters (Selected results which show clear differences between rats and hamsters after similar exposure)

Test Material	Humans		Rat			Hamster		
	Carcin.	Author	Lung Tumors	Route	Author	Lung Tumors	Route	Author
Nickel Powder	S*	IARC 1987	+	i.tr.	Pott et al. 1987	-	i.tr.	this study
Nickel Subsulfide	S*	IARC 1987	+	inh.	Ottolenghi et al. 1974	-	i.tr.	this study
			+	i.tr.	Pott et al. 1987			
Cadmium	L	IARC 1987	+	inh.	Takenaka et al. 1983	-	inh.	Heinrich et al. 1988
			+	i.tr.	Pott et al. 1987			
α Quartz	L	IARC 1987	+	inh.	Holland et al. 1986	-	i.tr.	Holland et al. 1983
			+	inh.	Muhle et al. 1988c	-	i.tr.	Renne et al.1987
Diesel Engine Exhaust	L	IARC 1988	+	inh.	Brightwell et al. 1986	-	inh.	Brightwell et al. 1986
			+	inh.	Heinrich et al. 1986b	-	inh.	Heinrich et al. 1986b
			+	inh.	Mauderly et al. 1987			
PAH containing Exhaust	S	IARC 1984	+	inh.	Heinrich et al. 1986a	-	inh.	Heinrich 1988

S Sufficient Evidence for Carcinogenicity
L Limited Evidence for Carcinogenicity
\+ Induction of Lung Tumors
\- No Statistically Significant Increase of Tumor Rate
* Chemical Characterization by IARC: Nickel and Nickel compounds
i.tr. Intratracheal Instillation
inh. Inhalation

APPENDIX B

VERIFYING THE COMPOSITION OF CERTAIN COMMERCIAL NICKEL COMPOUNDS

FINAL REPORT

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VERIFYING THE COMPOSITION OF CERTAIN COMMERCIAL NICKEL COMPOUNDS

SUMMARY

Forty commercial samples chosen from three families of nickel compounds were purchased and chemically analyzed. The selection included 21 basic nickel carbonates, five nickel sulfides and 14 nickel oxides sold by 18 producers or distributors in eight countries. The analytical results were compared with the information provided on the container labels. A number of errors were found in the label information ranging from minor inconsistencies and incomplete information to actual misrepresentation of the product. For example, nickel(II) oxides containing only 1-2% Ni(III) are being offered for sale as "Nickel(III) Oxide, Ni_2O_3". Thus researchers should not accept at face value the chemical identity presented by producers or distributors in catalogues and on labels.

Since significant variations in biological properties have been found within each of these three families of nickel compounds, researchers should carefully establish which particular member of a family is being studied. Unfortunately, the literature on the biological effects of nickel compounds contains numerous studies where this was not done. Attributing the results of such studies to other or, worse, to all members of the same family of nickel compounds may introduce significant errors into risk assessments.

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INTRODUCTION

Risk assessment of nickel-related health hazards in an industrial environment requires a reliable knowledge of the bioavailability and toxicity of various nickel species in airborne dust. Different chemical forms of nickel have different bioavailabilities and may have different toxic properties (Sunderman, 1984). Unfortunately, the toxicological literature on nickel compounds is often unreliable for risk assessment as the species tested by the researcher might have differed from the species described in the literature. The fault may be attributed either to a lack of chemical understanding on the part of the researcher or to inadequate labeling practices by the producer or distributor of the nickel reagents that were studied.

To avoid making an incorrect assessment of risk, the risk assessor must be sure that the toxic properties reported in the literature were measured for the same nickel species as that present in the workplace being scrutinized. It is the objective of the present study to persuade bio-researchers of the importance of correctly characterizing the tested species by ascertaining and reporting its general stoichiometric composition and/or the stoichiometry of its nickel phases.

The need for detailed product descriptions

Evidence indicates that the extent of the toxic effects that may be produced by exposure to a metallic element vary depending on its chemical form (valency and type of compound) and physical form (particle size and surface area). Nonetheless, some researchers provide only minimal information on the substance investigated, e.g. identifying it only as "nickel oxide". Such researchers are unaware that some common

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nickel compounds are not unique substances. Instead, such substances belong to a family of compounds with similar gross composition but in which differences in stoichiometry -- sometimes subtle, sometimes not – may produce significant differences in their physicochemical properties and hence toxicological properties. Groups of compounds commonly known as "nickel carbonate", "nickel sulfide" and "nickel oxide" are the best examples of such families. To avoid apparent conflicts between reports of biological effects of a substance obtained from different sources and/or lots, it is necessary to include in each report information on pertinent physicochemical characteristics of each tested reagent.

"Nickel carbonate"

Large compositional variations are possible in the family known as "nickel carbonate". Most importantly, the family should be referred to as "basic nickel carbonate" or "nickel hydroxycarbonate" to reflect the presence of significant amounts of hydroxide. The ratio of $NiCO_3$ to $Ni(OH)_2$ in these compounds can vary widely but in commercial reagents it usually ranges from about 1:2 to 2:1.

"Nickel sulfide"

The name of the "nickel sulfide" accurately informs the reader that compounds belonging to this family are composed only of nickel and sulfur. Nevertheless, the JANAF Thermochemical Tables (1985) report Ni_3S_2 (cryst., liq.), Ni_3S_4 (cryst.), NiS (cryst.,liq., gas) and NiS_2 (cryst., liq.) all under the heading of "nickel sulfide". More detailed studies of the nickel-sulfur system (Lin et al., 1978) indicate that some of the above-mentioned sulfides exist in several crystalline modifications. Some of these are solid solutions that exist over a range of composition, which is generally a function of temperature. The detailed studies also indicate the existence of still other "nickel

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sulfide" phases identified as Ni_4S_3, Ni_6S_5 and Ni_7S_6. It is obvious that characterizing a tested substance as "nickel sulfide" conveys little useful information to the reader. Fortunately, Ni_3S_2 and NiS are the only two nickel sulfides that have been studied toxicologically. These are usually distinguished by referring to Ni_3S_2 as "nickel subsulfide" and to NiS as "nickel sulfide".

"Nickel oxide"

The properties of a particular sample of "nickel oxide" depend on the material from which it was made and the conditions under which it was formed, e.g. temperature, partial pressures of oxygen and water vapour, etc. Nickel oxides produced at high temperatures, i.e. ≥850° C, exhibit very small, reversible differences in stoichiometry that have significant effects on their chemical reactivity and electrical conductivity [2]. However, the limited information now available suggests that oxides formed at different high temperatures do not differ significantly in their biological behaviour from each other. By contrast, nickel oxides produced at low temperatures, i.e. <550° C, differ significantly from each other and from the high-temperature oxides.

Low-temperature nickel oxides can contain on the order of one percent Ni(III), are often contaminated with undecomposed starting materials (hydroxide or carbonate), interact rapidly with normal ambient atmospheres leading to significant amounts of adsorbed oxygen and water, and are generally difficult to replicate from batch to batch. The lower the temperature at which the oxides were produced, the more chemisorbed oxygen, which behaves chemically like Ni(III), they contain on the surface (Dell, 1954; Teichner, 1957; Gmelin, 1966, p.420). Chemically and biologically, these "black nickel oxides" are much more active than are the high temperature "green nickel oxides"

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(Sunderman, 1987). It is therefore important to distinguish not only between the low- and high-temperature oxides but to discriminate even between various low-temperature oxides.

The need for better product labeling

In contrast to the researchers who report only the family name of a compound they have studied, other researchers provide additional information, such as a chemical formula, a supplier's catalogue number and analytical data for a particular lot of the chemical. While such details appear reassuring, all too often such information is taken verbatim from the supplier's catalogue and labels, and is not verified analytically. There is ample evidence that unquestioning acceptance of such label or catalogue information has led to some gross errors in the toxicological literature of nickel.

The errors in label information are basically of two kinds: (1) complete misrepresentation of the contents of the bottle and (2) failure to differentiate between different members of the same family of nickel compounds. Examples of the first kind of error are:

- o basic nickel carbonate sold as "$NiCO_3.xH_2O$;
- o nickel(II) oxide sold as "Ni_2O_3".

Examples of the second kind of error are:

- o failing to specify the actual carbonate:hydroxide ratio in an otherwise properly labeled "basic nickel carbonate";
- o failing to mention the content of Ni(III), carbonate and hydroxide in an otherwise properly labeled "nickelous oxide, NiO".

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Concern that labeling errors might be common led NiPERA to sponsor a project which would compare the information provided on labels with the actual compositions of certain reagent-grade nickel compounds supplied commercially by manufacturers or major distributors worldwide. It was hoped that publishing the results of the study would lead to the accomplishment of several objectives:

- alert biological researchers to the need to characterize accurately the nickel compounds they investigate;

- alert biological researchers to the danger of accepting supplier's information at face value;

- identify sources of reliably labeled nickel reagents;

- persuade manufacturers and distributors of pure chemicals to pay more attention to product identification;

- lead to the establishment of criteria for a category of "certified" reagent-grade nickel chemicals for biological research;

- alert risk assessors to the need to ensure that the toxicological properties reported in the literature were measured for the same nickel species as that present in the workplace being evaluated.

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MATERIALS AND METHODS

Not all nickel compounds are likely to be mislabeled. Those most likely to be mislabeled are compounds produced by processes in which amorphous multiphase compounds are precipitated or in which compounds are thermally decomposed, as happens in carbonates, oxides, and certain sulfides. Oxidic compounds in which all nickel is purported by name or formula to have valency higher than two are also suspect because drying such materials, mostly produced by precipitation, results in decomposition and partial reversion to the divalent state (Gmelin, 1966, p.481). Other forms of nickel are much less susceptible to mislabeling and, in most instances, a quantified listing of impurities is a sufficient measure of characterization. For example, metallic nickel produced by different means is unlikely to be anything other than metallic nickel. Crystallized hydrated salts are likely to be properly labeled except for modest errors in the water of hydration. However, this kind of error is not expected to cause serious problems in biological work.

The present investigation covered the following groups of compounds:

- all nickel carbonates which do not indicate by name or formula the basic nature of the product;
- selected reagents identified as basic nickel carbonates;
- selected reagents identified as nickel sulfides;
- all nickel oxides identified by name or formula as having all nickel in a valence state greater than two;
- selected reagents belonging to the category of black nickel oxides.

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The reagents were selected from supplier catalogues circulated in Canada, France, Japan, U.K., and U.S.A. A total of 36 catalogues were reviewed and 27 compounds were ordered from 18 suppliers. Thirteen additional nickel reagents, purchased and/or analyzed by Inco Limited in connection with other projects, were also included in this report. In a few instances different lots of the same compound were available and provided a closer insight into the extent of compositional variations between lots.

Standard analytical methods were used to analyze each reagent. Unless stated otherwise, results reported refer to materials "as received". The determinations included nickel (electroplating), cobalt (AA), sodium (AA), total sulfur (combustion-IR), sulfate sulfur (gravimetry), total carbon (combustion-IR), carbonate carbon (gasometry), oxygen (combustion-IR), loss on ignition at 1050° C (gravimetry), and trivalent nickel (titrimetry). Trivalent nickel is present in nickel oxides both in the lattice and on the surface, the latter equivalent to surface chemisorbed oxygen. Those two were analytically distinguished by varying acidity in the oxidimetric titration: the very reactive surface Ni(III) was determined under mild acidic (1M H_2SO_4) conditions, whereas strong acidity (6M HCl) was required for the total Ni(III). Lattice Ni(III) was taken to be the difference between the total and the surface Ni(III). The analytical results are summarized in Tables 1 through 3. Producers of the analyzed nickel reagents are listed in Table 4.

DISCUSSION OF RESULTS

"Nickel Carbonates"

Without exception, all commercial nickel carbonates are basic salts (Table 1) and can be regarded as variable mixtures of nickel carbonate and nickel hydroxide. Sample #2, which the producer supplies in moist form, was air-dried before analysis.

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The observed weight loss amounted to 34%. Among the 21 analyzed specimens, the ratios of nickel carbonate to nickel hydroxide ranged from 1:0.6 to 1:2.1. While a slim majority of producers correctly identified their nickel carbonates as the basic salts, the often-used descriptive formula of $NiCO_3.2Ni(OH)_2.4H_2O$ was seldom supported by actual chemical composition. The majority of commercial basic nickel carbonates appear very close to the formula of $2NiCO_3.3Ni(OH)_2.xH_2O$ with "x" ranging between 5 and 8. Among the 21 samples analyzed, however, only the Aldrich reagent #9 is so identified. The observed between-lots variations seem linked to metal impurities, such as cobalt, rather than to the difference in basicity of the carbonate.

"Nickel Sulfides"

All nickel sulfides are more or less susceptible to air oxidation. Some producers recognize this and try to minimize the extent of oxidation by supplying the reagent under a protective atmosphere of argon (Table 2). There is, however, no consistency among producers on which sulfide merits protection: Aesar blankets NiS; Alfa blankets only NiS_2. (Nickel subsulfide, Ni_3S_2, is not commercially available). We found that once a bottle with nickel sulfide had been opened, it was difficult to maintain the chemical "status quo" even by supplying a fresh blanket of argon before the bottle was closed. Only when sample portions for the determinations of nickel and sulfur were taken at the same time as portions for oxygen did the analytical results total close to 100% (e.g. sample #1a, lot 071486). When samplings were done on different days, the totals always showed a tendency to exceed 100%, with oxygen assays being the most suspect. Oxygen contents in two of the sulfides, #1 (NiS) and #3 (NiS_2), kept gradually increasing in spite of refilling the bottles with argon each time they were opened. In sample #3 the 2.8% oxygen content increased to 3.4% within a period of two months. Similarly, increases from 1.8% to 2.8% and to 3.6% O were noted in sample #1 (lot 052185) after three and seven months of shelf life. For this particular sample, the first oxygen assay was done

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approximately one month after the nickel and sulfur assays. The observed instability of nickel sulfides towards air is indicative of problems a researcher may face when bio-effects of sulfides are to be studied.

Sulfide #4 is a shocking example of the discrepancy between the label identification and the actual composition of the supplied material. The extraordinarily large sodium impurity left no doubt that the "nickel sulfide" was made by wet precipitation. Qualitative tests showed the presence of significant amounts of thiosulfate but no water-soluble nickel. From the elemental assays, the apparent composition of sample #4 was calculated to be 51.2% NiS, 0.4% CoS, 14.2% Na_2SO_4, 3.4% Na_2CO_3, 11.9% $Na_2S_2O_3$, and 15.3% H_2O for a total of 96.4%.

"Nickel Oxides"

Results in Table 3 are presented in three groups. The first lists reagents labeled as "Nickel(III) or Nickelic Oxides"; the second contains "Nickel Oxides (black)"; and the third covers oxides labeled as "Nickel Peroxides". The label identification of the first oxide group implies the presence of all nickel in the trivalent form. Nonetheless, the actual Ni(III) content found in the oxides varied between 0.67 and 4.44% vs. the theoretical value of 71.0% in Ni_2O_3. Comparison reveals a close chemical similarity between the first and second group, and indicates that reagents identified as "Nickel(III) or Nickelic Oxides (Ni_2O_3)" are mostly black nickel(II) oxides, also called "acid soluble" oxides. Clearly, marketing black nickel oxide as Ni_2O_3 is misleading and bound to cause erroneous conclusions if the oxide were used by a researcher to study biological effects of trivalent nickel. The Baker black nickel oxide (sample #6) was ordered from the Sargent-Welch Scientific Company 1989-1990 catalogue #136 where it is listed as "Nickel Oxide, $Ni_2O_3.nH_2O$, black powder", no. BK2792-500GM. In this instance, the distributor's catalogue wrongly identified the product.

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Black nickel oxides are often produced by thermal decomposition of basic nickel carbonates and so their carbon content and LOI (loss on ignition at 1050° C) serve as measures of how complete the original decomposition has been. LOI's in the first two groups in Table 3 are dominated by volatilized water present in the oxides as nickel hydroxide. The striking difference in composition between the two lots of #4 Nickel(III) Oxide probably is not typical but it nonetheless emphasizes what could happen to an unsuspecting researcher in need of replenishing his/her laboratory supply. Within the first group of oxides which are all labeled as "Nickel(III) Oxides", oxide #5 is different from the rest. Not only is the Ni(III) content significantly higher but so are levels of sodium, carbon (as carbonate) and LOI. All suggest that the oxide was produced by precipitation rather than direct calcination. As a result, its biological properties most probably would differ from those of the rest of the investigated nickel(III) oxides in spite of the same label information on all the oxides.

The third group in Table 3 is comprized of hydrated nickel oxides, all labeled as "peroxides", consisting of various mixtures of nickelic and nickelous hydroxides. All were most probably produced by precipitation under strong oxidizing conditions. Drying of the primary product, mostly nickelic hydroxide, would have resulted in partial decomposition to nickelous hydroxide or, possibly, to nickelous oxide (Gmelin, 1966, p.481). The composition of the final product and the content of Ni(III) therefore is likely to vary according to the conditions of the drying process. Large differences in impurity levels of foreign salts, such as sodium carbonate and sulfate, can also be expected in different products as well as in different lots of the same product. "Nickel Peroxides" are currently the highest grade source of Ni(III) on the market but are also the source most likely to be contaminated by high levels of nickel(II) hydroxide and alkali metal salts. Formal formulae calculated for each of the three "peroxides" are as follows: sample #11 $NiO_{1.06}$ (Alfa), sample #12 $NiO_{1.09}$ (Merck), and sample #13 $NiO_{1.33}$ (Aldrich).

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CONCLUSIONS

Traditionally, users of reagent grade chemicals focus primarily on overall purity, usually with respect to the primary metal component. In the universe of nickel compounds, the impurity of greatest concern usually is cobalt, less frequently copper or iron. Lately, however, reagent-grade nickel chemicals are being used in toxicological studies with the objective of evaluating health risks posed by presumably similar nickel compounds found in certain airborne dusts. Unfortunately, some of these studies are a waste of time and effort because either the tested reagent was not correctly identified in the toxicological literature or because the airborne nickel in the workplace was not the same species as was reported in the literature.

The present survey of commercial reagent grade samples of basic nickel carbonates, nickel sulfides and nickel oxides has shown a number of discrepancies and inconsistencies between the reagent descriptions on container labels and actual compositions. The most serious examples exist in the family of nickel oxides where one product, often identified as "Ni_2O_3", is called "nickelic oxide" or "nickel(III) oxide" despite its content of only 1-2% of Ni(III) compared with the theoretical value of 71%. Implying by name or formula that all nickel is in the trivalent state is obviously misleading. The same substance is also marketed as "nickel oxide, black" or simply as "nickel oxide". Completely omitted from this label is the presence of a small amount of Ni(III), carbonate and hydroxide in the otherwise nickel(II) oxide, information which may be vital to the researcher. Of the 11 nickel oxides analyzed, only two products have been found to meet the criteria for correct identification: the #7 Alfa "Nickel Oxide, black, NiO (contains Ni_2O_3)", and the #8 BDH "Nickel Oxide (a variable mixture of NiO and Ni_2O_3)".

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Bio-researchers who plan to evaluate potential health hazards of nickel compounds should ensure that their test reagents are well characterized with respect to all present chemical forms of nickel as well as in terms of general impurities. The results of the present investigation makes it clear that they cannot rely on the supplier to do this for them. Risk assessors and regulators should rely on published data only if it is clear that the nickel compound tested by the researcher was the same as the nickel species of concern in the workroom environment. Toxicological studies lacking adequate physicochemical information on the tested nickel compound(s) should be dismissed as unreliable for risk assessment purposes.

It is further hoped that the data presented herein will alert and encourage producers of fine chemicals to pay more attention to the accuracy of the factual information provided on the labels and in the catalogues of their products. If the accurate description of the product were not possible by name and/or correct formula alone, further compositional information should be included to allow full characterization by calculation. For example, to find the basicity of nickel carbonate, the actual contents of Ni, CO_2, and major metal impurities have to be known together with the loss on ignition (LOI) at high temperatures, e.g. 1050° C. To characterize nickel oxides for a bio-researcher, the actual contents of Ni, major metal impurities, C, S, Ni(III) and LOI at 1050° must be known. The effort of having chemicals more accurately characterized is not expected to lead to increased production costs since it is consistent with the right-to-know regulations now in force or being considered in many countries. Cooperation by the chemical producers would assist the bio-researcher as well as the health risk assessor, and might even result in the establishment of new lines of certified nickel reagents.

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Letters were sent to each of the 18 manufacturers or distributors whose chemicals were tested. The discrepancies, if any, between the information on their labels and the results of the detailed chemical analyses were reported to them. If discrepancies were noted, they were asked for suggestions as to how they could be eliminated in the future. After five months, only Aldrich, Alfa, BDH, GFS, Kanto, Merck and Wako responded. Their responses generally indicated concern and included: dropping an item from their catalogue; changing the name to agree with the composition; packaging sulfides under argon. However, some suppliers also expressed reluctance to change names of reagents for fear of confusing long-standing customers. It is clear that most of these nickel compounds are sold for specific chemical purposes, not as "specimens" of particular chemicals for toxicological evaluation. Since this is likely to remain the case, the onus for properly characterizing the tested substance in the literature must remain with the bio-researcher.

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Table 1 - **BASIC NICKEL CARBONATES**

	Label	Cat. #	Producer	Lot #	Ni	Co	Na	CO_2	LOI (1050°C)	Formula Calculated ($NiCO_3$-$Ni(OH)_2$-H_2O)
1	Nickel(II) Hydroxycarbonate	1478	UCB	61 200643	45.8	0.042	0.014	21.6	41.6	1 - 0.6 - 1.7
2	Nickel(II) Hydroxi-carbonat (moist) 23-27% Ni	13614	Riedel-deHaën	6253	[38.0	0.019	0.008	16.1	50.6]*	1 - 0.8 - 4.5
3	Nickel(ous) Carbonate	NO4998	Pfaltz & Bauer	not listed	45.3	0.39	0.42	17.7	39.7	1 - 1.0 - 2.1
4	Nickel Carbonate, $NiCO_3.xH_2O$	89019	Alfa	082376	46.4	0.006	0.007	17.3	40.6**	1 - 1.0 - 2.3
4a	Nickel Carbonate, $NiCO_3.xH_2O$	89019	Alfa	A06F	47.2	0.056	0.077	14.4	39.4**	1 - 1.5 - 2.7
5	Nickel(II) Carbonate, $\sim NiCO_3.2Ni(OH)_2.4H_2O$	144-01035	Wako	CTR 3196	44.5	0.001	0.27	15.0	42.3	1 - 1.3 - 3.3
6	Nickel Carbonate, $NiCO_3$	1173	GFS	J99	48.5	0.049	0.025	15.2	37.9	1 - 1.4 - 2.3
7	Nickel Carbonate-Basic, $NiCO_3.2Ni(OH)_2.4H_2O$, Puratronic	400221***	Johnson-Matthey	S.86774C	44.7	0.0007	0.0004	13.4	43.1	1 - 1.5 - 3.9
7a	Nickel Carbonate (basic), $NiCO_3.2Ni(OH)_2.4H_2O$, Puratronic	400221***	Johnson-Matthey	S87302A2	43.6	0.0003	0.0002	12.2	44.5	1 - 1.7 - 4.8
8	Nickelous Carbonate	AC-6486	Anachemia	481101	48.2	0.013	0.037	14.7	38.6	1 - 1.5 - 2.5
9	Nickel(II) Carbonate Hydroxide, $2NiCO_3.3Ni(OH)_2.4H_2O$	33,977-6	Aldrich	04828HV	48.2	0.021	0.085	14.5	38.5	1 - 1.5 - 2.6
0	Nickel(II) Carbonate, basic, $NiCO_3.2Ni(OH)_2.4H_2O$	72245	Fluka	275099	46.5	0.041	0.37	14.0	39.5	1 - 1.6 - 3.0
1	Nickelous Carbonate, min. 45% Ni	1-2764	Baker	918092	47.0	0.035	<0.01	13.5	40.1**	1 - 1.6 - 3.2
2	Nickel Carbonate - basic	618326	Johnson-Matthey	30738	46.1	0.022	0.039	13.1	40.0	1 - 1.6 - 3.4
3	Nickel(II) Carbonate, $NiCO_3.xH_2O$	12350A	Aesar	20366	46.2	0.026	0.008	13.5	41.1	1 - 1.6 - 3.4
4	Nickel Carbonate, basic, $\sim NiCO_3.2Ni(OH)_2.4H_2O$	28114	Kanto	208B1350	42.4	0.0001	0.011	12.1	46.1	1 - 1.6 - 5.2
5	Nickel Carbonate Basic, $NiCO_3.2Ni(OH)_2.4H_2O$	MA6748	May & Baker	52/40/36	49.1	0.023	0.031	13.6	37.2	1 - 1.7 - 2.5
6	Nickel Carbonate, low Co,Fe, $\sim NiCO_3.2Ni(OH)_2.4H_2O$	29315	BDH	8570550K	48.6	0.0008	0.025	13.0	38.2	1 - 1.8 - 3.0
7	Nickel(II) Hydroxide-Carbonate, $\sim NiCO_3.2Ni(OH)_2.4H_2O$	6716	Merck	910-B114416	50.2	0.0003	0.013	12.7	36.1	1 - 2.0 - 2.5
8	Nickel(II) Hydroxycarbonate	N405	Labosi	42 9153	47.0	0.36	0.42	12.4	38.1	1 - 2.0 - 3.2
8a	Nickel(II) Hydroxycarbonate	N405	Labosi	54 9138	46.7	0.66	0.42	11.8	37.8	1 - 2.1 - 3.5

* Results in air-dried reagent
** LOI at 800 °C
*** distributed by Alfa

Table 2 - **NICKEL SULFIDES**

	Label		Cat. #	Producer	Lot #	Ni	Co	Na	C	S_{tot}	$S_{sulfate}$	O
	Nickel(II) Sulfide, 99.999%,	NiS [under Ar]	12831	Aesar	052185	64.5	--	--	--	35.7	--	18 (28)
a	Nickel(II) Sulfide,	NiS [under Ar]	12831B	Aesar	071486	65.5	--	--	--	33.2	--	1.4
	Nickel Sulfide,	NiS	89345	Alfa	C03GC	64.2	0.0004	--	--	36.2	0.06	0.2
	Nickel Sulfide,	NiS_2 [under Ar]	89342	Alfa	C03G	47.3	0.0005	--	--	51.7	0.21	28 (34)
	Nickel Sulfide (ous)		216315	K & K	27779	33.1	0.25	10.0	0.40	26.2	3.2	24.6

Table 3 - **NICKEL OXIDES**

	Label		Cat. #	Producer	Lot #	Ni	Co	Na	C	S	Ni^{III} tot	Ni^{III} surf	LOI (1050°C)
	Nickel(III) Oxide,	$Ni_2O_3.H_2O$	87997	Alfa	E27GC	77.7	0.088	--	--	--	0.67	0.04	0.98
	Nickel(III) Oxide, 77% Ni,	Ni_2O_3	12583	Aesar	021486	76.2	0.12	--	--	--	1.21	0.83	2.55
	Nickelic Oxide		NO4875	Pfaltz & Bauer	not listed	75.6	0.0005	--	0.19	0.004	1.22	0.87	3.83
	Nickel(III) Oxide	Ni_2O_3	147-01145	Wako	PDK 3204	71.9	0.011	--	0.34	0.040	2.05	1.32	6.81
a	Nickel(III) Oxide	Ni_2O_3	147-01145	Wako	WKQ 2743	64.4	0.013	--	0.93	0.06	1.65	1.36	15.6
	Nickel(III) Oxide,	Ni_2O_3	13629	Riedel-deHaën	IR10978	68.4	0.0003	0.23	1.10	0.006	4.44	3.98	12.6
	Nickel Oxide, Black		2792-01	Baker	A28139	77.7	0.00	--	0.02	<0.002	0.84	0.03	1.06
	Nickel Oxide, Black, NiO (contains Ni_2O_3)		87302	Alfa	092883	77.4	0.0006	--	--	0.03	0.81	0.62	1.84
	Nickel Oxide [mixture of nickel(II)/(III) oxide]		29326	BDH	03698904	77.4	0.0002	--	0.01	<0.002	2.31	0.06	1.35
	Nickel Oxide		1909	UCB	89 128173	77.4	0.001	--	0.07	0.02	1.17	0.80	1.92
	Nickel Oxide Black		72257	Fluka	275407	76.8	0.001	--	0.11	0.008	1.16	0.80	2.34
	Nickel Peroxide,	NiO_2	17989	Alfa	120385	63.4	0.026	2.55	1.08	0.49	8.15	--	10.9
	Nickel Peroxide (Hydrate),	$NiO_{1.4}$	806724	Merck	9259323	59.5	0.0006	0.86	0.37	0.17	10.8	--	22.0
	Nickel Peroxide Hydrate		33,272-0	Aldrich	03721LV	35.1	0.14	11.1	1.80	3.30	23.5	--	31.0

Comparative Deposition, Clearance and Carcinogenicity of Various Nickel Compounds Exposed by Inhalation in Rats

Final Report

A Report to the
Nickel Producers Environmental Research Association

by
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1. INTRODUCTION

Nickel sulfide roasting fumes and dust are recognized as having carcinogenic or cocarcinogenic potential with an assigned TLVs (ACGIH 1988). The IARC (Saracci 1981) also considers that nickel should be regarded as an occupational carcinogen. As the identity of the nickel compounds that may induce cancers of the nasal cavities and lungs in nickel refinery workers is uncertain, principal attention has been focused on possible differences in carcinogenic activities of specific nickel compounds to which workers have been exposed, and upon the identification of physical, chemical, or biological factors that could be used to predict the carcinogenicity of nickel species. Considering these possible differences and the main exposure routes of the workers in an occupational environment, an inhalation study is obviously important to determine the specific nickel compounds that induce cancers of the nasal cavities and lungs.

The penetration and deposition of particles into the nasal cavities and lungs and the clearance of those particles from the lungs are of primary importance in the development of a tumor due to chronic exposure.

Tanaka et al. (1985, 1986, 1988a,b) investigated the biological half-time of green nickel oxide(NiO(G)) and nickel monosulfide (amorphous) aerosol deposited in rat lungs and nickel distribution in a rat body by measuring changes in the exposure time, the clearance period, exposure concentration and aerosol diameter. This report describes the differences of nickel distribution in rat organs (lungs, liver, kidneys and spleen) due to various kinds of nickel compound aerosols inhalation, and shows the histopathological findings after 6 months exposure and 12 months clearance.

2. METHODS AND MATERIALS

2-1 Test Substance

In this experiment, nickel compounds used (INCO LIMITED, Canada) were green nickel oxide(NiO(G)), black nickel oxide(NiO(B)) and nickel subsulfide(Ni_3S_2). NiO(G) and NiO(B) were not handled by us but Ni_3S_2 was disintegrated in a methanol solution by a wet mill (Atrider MA-1SD, Mitsui Chemical Machinery Co. Japan).

The scanning electron micrographs of NiO(G), NiO(B) and Ni_3S_2 in an exposure chamber are shown in Photos 1, 2 and 3, respectively. These respirable aerosols were transported to the exposure chambers by a fluidized bed-type dust generator (Tanaka and Akiyama 1984).

2-2 Experimental Apparatus

The outline of the dust exposure system is shown in Figure 1. The dust generator consists of a screw feeder and a fluidized bed with an overflow pipe. The continuous dust feed is maintained by the screw feeder. But if dust only is fed into the fluidized bed by any dust feeder, it is very difficult to keep a constant feed rate over a long period of time. The reason for this is that the properties of fine particles are adhesive and agglomerative.

In our generator, this defect was overcome by mixing the dust with the fluidized particles. This is the key point of our dust generator, that is, the dust is mixed with the fluidizing particles before feeding, and these mixed particles are smoothly fed into the fluidized bed by the screw feeder.

To keep the dust generation rate constant the uniform mixing of the powder with fluidizing particles is very important. If the mixing is poor, there will be large variations in the dust generation rates.

Air from a compressor is introduced into a fluidized bed through a control valve, silica-gel air drier and flow meter. The air velocity is high enough to transport the dust particles but not the fluidizing particles. The fluidizing particles, that is, the glass beads, fall back into the bed and maintain the fluidization until discharged from the overflow pipe into the large particle receiver. The air flow rate was 25 L/min, as the incipient fluidization velocity was 14 L/min.

Dusts from the generator was introduced into the exposure chamber and then was mixed with filtered room air. The aerosol concentrations of the nickel compounds in the exposure chamber were monitored continuously by a light-scattering method and were measured gravimetrically at daily intervals by the isokinetic suction of air through a glass fiber filter. The size distribution of the aerosol in the exposure chambers was determined by using an Andersen cascade impactor.

Each exposure chamber volume is 0.48 m^3. Three chambers for exposure groups and one chamber for control groups were used in an air-conditioned room. Each chamber has 4 cages and 7 rats were placed in each cage. Photo 4 shows the exposure chamber. In photos 5 and 6, the in- and out-side of the chamber can be seen. Photos 7 and 8 show the dust generator and a light scattering method. Photos 9 and 10 show the air sampler for the measurement of the mass concentration of the nickel compounds and the Andersen sampler.

2-3 Exposure Conditions

Nickel compounds used for this study, the exposure duration, the exposure concentrations, the mass median aerodynamic diameter and the geometric standard deviation are shown in Table 1.

One typical example of the daily dust concentration of each nickel compound monitored by the light scattering method is shown in Figures 2, 3 and 4.

All animals exposed were male Wistar rats, about 4 weeks of age, approximate 80 g in body weight.

The rats were exposed to these nickel compound aerosols for 6 h/d, 5 d/wk fo months. Controls were exposed to clean air in adjacent, identical chambers, und similar flow (150 L/min), temperature (24±1°C) and humidity (50±5 % conditions.

Some rats were sacrificed 24 h after the termination of the final repeated exposu and the remaining rats were kept for 12 months clearance period before sacrific The control rats were also sacrificed at the same time.

2-4 Measurement of Solubility of Nickel Compounds

The solubility of nickel compounds used for this experiment was examined b dissolving 1 g of each nickel compound in 50 mL of both distilled water and sali solution. After shaking at 37 °C for 1 week, each sample was filtered through qualitative filter paper (Toyo filter paper No.5C) and membrane filter (pore size 0.2 μm). The filtrate was adjusted to 50 mL in a volumetric flask and the dissolve nickel concentration was measured by a flame atomic absorption spectrophotomet (HITACHI Atomic Absorption Spectrophotometer Model 180-30).

2-5 Analytical Procedure for Determination of Nickel

The inhaled and deposited nickel contents in rat organs exposed to nickel com pounds in the inhalation chamber were determined by a flameless atomic absorptio spectrophotometry (AAS; HITACHI Polarized Zeeman Effect Atomic Absorptio Spectrophotometer Model Z-8000). The rats were sacrificed and their viscera organs, lungs, liver, kidneys and spleen were removed, weighed , and then treate with a mixture of nitric acid and sulfuric acid until completely digested. The sampl solution for AAS analysis was prepared from the digested solution by dilution wit

0.1N nitric acid in volumetric flasks. Blood samples were also obtained and diluted 1:10 with 0.1N nitric acid without digestion for nickel analysis. In order to decide the suitable conditions for AAS, dry and ash processes of blood samples were chosen carefully to prevent bubbling and splashing.

The determination of nickel was carried out using 10 μL of the sample solutions mentioned above by AAS under the conditions shown in Table 2.

A standard solution for nickel analysis was prepared from a nickel chloride standard solution (1000 ppm as Ni) for atomic absorption spectrophotometry (Wako Pure Chemical Industries). Standard solutions and sample solutions were analyzed in duplicate or triplicate. The calibration curve was obtained by the least square method from the analytical data which were obtained after treatment with the same procedure for organ samples. There was a linear relationship between nickel concentration and the absorbance as shown in Figure 5. The detection limit of nickel was 1 ppb.

2-6 Estimation of Lung Deposition and Clearance Rate

The deposited nickel content in the lungs just after the exposure and after the 12 months clearance period was determined by the nickel concentration and lung weight. By using these data the lung deposition fraction and clearance rate were calculated. In order to calculate the expected minute respiratory volume of rats (V mL/min), Guyton's equation (Guyton 1947) in which the average body weights of the animals during the respective exposure periods was used. The total amounts of inhaled nickel compounds (A μg) were estimated by the following equation:

$$A = V \times C \times T \times 0.06$$

where C (mg/m^3) is the average concentration of nickel compounds in the exposure chamber and T (hrs) is the total exposure time. The apparent deposition fraction for

each rat was obtained by the deposited nickel compound just after the exposure a the calculated total amounts of inhaled nickel compounds.

The clearance rate of nickel compounds from the lungs during the 12 mont clearance period was estimated by the ratio of the cleared amounts to the lung burc just after termination of the 6 months exposure. The cleared amount was the diff ence between the observed nickel amounts in lungs at 6 months and that after months.

2-7 Histopathological Examination

Rats were sacrificed by decapitation. Sections of the lungs, head, liver, kidne pancreas, spleen, and mediastinal lymph nodes were fixed in 10% formalin for li microscopy. A three dimensional investigation by serial sections was used for t detection of nickel compound particles in the lung. For the investigation of nasal a paranasal sinuses, some frontal sections of the face had been made (Horie et 1985).

For electron microscopy, 1mm cubes of the same tissues were fixed in 2.5 phosphate-buffered glutaraldehyde overnight, postfixed in 1% phosphate-buffer osmium tetroxide, dehydrated in a graded ethanol series, and embedded in Ep 812. Ultrathin sections were cut with a diamond knife and stained with uran acetate and lead citrate. The thick-thin correlative technique was used to relate tl osmiophilic material (surfactant), visible in the thick section of light microscop with its corresponding ultrastructural continuum, the adjacent thin section of tl electron micrograph. A JEM 100C electron microscope was used to investigate tl ultrastructure, and a Hitachi H500 analytical electron microscope was used to dete of nickel localization.

3. RESULTS

3-1 Solubility of Nickel Compounds

The solubility of nickel compounds to distilled water and saline solution at 37 °C for 1 week is shown in Table 3. NiO(G) and Ni_3S_2 are more soluble in a saline solution than in distilled water. Ni_3S_2 is more soluble in a saline solution and distilled water than NiO(G) or NiO(B).

3-2 Growing Rate of Rats

Figures 6, 7 and 8 show the growing rate curves of body weight during the experiment in NiO(G), NiO(B) and Ni_3S_2, respectively. There was no significant difference in body weight between exposed rats and controls.

3-3 Organs Weights after the 12 Months Clearance and the 6 Months Exposure

Table 4 shows the organ weights of rats after the 12 months clearance of the 6 months repeated exposure. There were no significant differences in organs weights, except for lungs in the case of Ni_3S_2, between the exposed rats and the controls. The wet lung weights of the exposed rats were much heavier than those of the controls in the exposure to Ni_3S_2.

3-4 Nickel Concentration in Organs

Nickel concentrations in the lungs, liver, kidneys, spleen and blood of control and nickel exposed rats are shown in Figures 9-13, respectively. Using these data, nickel concentration in each organ just after the exposure to nickel compounds and after the 12 months clearance period are compared with that of control rats statistically.

a) Nickel Concentration in Lungs (Figure 9)

Nickel concentration just after the exposure was the highest in the rat lun exposed to NiO(G), NiO(B) and Ni_3S_2 when compared to the level in other orga The concentration in the lungs was 20.6±4.7 μg/g for NiO(G), 35.8±10.8 μg/g f NiO(B) and 4.6±1.1 μg/g for Ni_3S_2, respectively. The level for NiO(G) a NiO(B) was much higher than that for Ni_3S_2.

Nickel concentration in the lungs after the 12 months clearance period was sti high in NiO(G) and NiO(B) exposure groups ($p < 0.01$) when compared to t control, but it was lower in the Ni_3S_2 exposure group. The concentrations in th lungs were 3.6±3.1 μg/g for NiO(G), 9.1±5.3 μg/g for NiO(B) and 0.3±0.1 μg/ for Ni_3S_2, respectively. However, these observed values were significantly lowe ($p<0.01$) than that detected just after the inhalation exposure.

b) Nickel Concentration in Liver (Figure 10)

The nickel concentration in the liver just after the exposure to Ni_3S_2 was signifi cantly higher than that in the control groups ($p<0.01$). The concentration in the liv for Ni_3S_2 was 1.0±1.4 μg/g and the level was about 30 times higher than that fo NiO(G) and NiO(B). On the other hand, there were no differences in the nick concentration between the exposed rats and controls in the NiO(G) and NiO(B exposed groups.

After the 12 months clearance period, there were no significant differences o nickel concentration in the liver exposed to the three nickel compounds betwee exposed rats and control.

A significant decrease of nickel concentration in the liver exposed to Ni_3S_2 wa observed between just after exposure and after the 12 months clearance perio ($p<0.01$).

c) Nickel Concentration in Kidneys (Figure 11)

There were statistical differences in the nickel concentrations just after the exposure to NiO(B) and Ni_3S_2 between exposed rats and control ($p<0.01$), but no difference in the NiO(G) exposure group.

After the clearance period there were no significant differences in the nickel concentration in the rat kidneys exposed to NiO(G), NiO(B) and Ni_3S_2 between exposed rats and control.

d) Nickel Concentration in Spleen (Figure 12)

The nickel concentration in the spleen just after the exposure to NiO(G) was significantly higher than that in the control group ($p<0.01$). On the other hand, there were no differences in the nickel concentration between the exposed rats and controls in the NiO(B) and Ni_3S_2 exposure groups.

After the 12 months clearance period significant differences of nickel concentration in the spleen exposed to the three nickel compounds were not observed between exposed rats and control.

e) Nickel Concentration in Blood (Figure 13)

Nickel concentrations in blood just after the exposure and after the clearance period were almost the same level as those of the control rats.

3-5 Apparent Deposition Fraction in Lung

Figure 14 shows the apparent deposition fraction (%) in the lungs defined as the ratio of the lung deposited nickel amount to the respired nickel amount which was estimated from the exposed nickel concentration, total exposure time and respiratory volume. The inhaled amounts for NiO(G), NiO(B) and Ni_3S_2 were 8.5±0.4 mg, 8.2±0.4 mg and 3.8±0.2 mg, and the deposited amounts in the lungs were 44±11 μg, 78±25 μg and 18±4 μg, respectively. The results obtained were 0.5±0.1 % for NiO(G) , 1.0±0.3 % for NiO(B) and 0.5±0.1 % for Ni_3S_2 , respectively.

3-6 Clearance Rate

Nickel amounts in the lungs detected just after the exposure to nickel compoun and after the 12 months clearance period are shown in Figure 15. The lung burd of each nickel compound after the 12 months clearance period was 8±7 μg f NiO(G), 21±12 μg for NiO(B) and 0.3±0.1 μg for Ni_3S_2, respectively. Th deposited nickel compounds just after the exposure were cleared during the follo ing 12 months. The clearance rates from lungs for NiO(G), NiO(B) and Ni_3S were 82%, 73% and 98% , respectively.

3-7 Histopathological Findings

In this animal experiment, we used the following criteria for histopathologic diagnosis of the main tumors.

A. Pulmonary adenoma

A localized lesion consists of alveolar structures lined by atypical cells. The large-sized, hyperchromatic cells show replacing growth for alveolar lining cells, high nuclear cytoplasmic ratio and projections into an alveolar lumen.

B. Pulmonary adenocarcinoma

Differential diagnosis from pulmonary adenoma is based upon the following findings: 1) Structural atypism of the glandular tumor cells, as well as intra-alveolar growth. 2) Extrapleural projections of the tumor cells, penetrating through the pleura.

C. Acinar cell adenoma

Localized nodular growth of tumor cells discloses large-sized acinar structures.The tumor cells show enlarged nuclei with prominent nucleoli, high nuclear cytoplasmic ratio and oxyphilic zymogen granules.

D. Islet cell adenoma

Differential diagnosis from islet cell hyperplasia is based upon the following findings: 1) Comparatively large-sized mass with an irregular margin of the lesions. 2) Replacing growth of the islet-like tumor cells show residual island-like acini of the exocrine cells within the tumor.

E. Renal cell carcinoma

1) Atypical clear cells invading the adjacent renal parenchyma 2) The cancer cells are similar to human Grawitz tumor, i.e. monotonous nuclei and clear cytoplasm.

F. Hepatocellular carcinoma

1) Cord-like arrangement of the atypical tumor cells associated with capillary stroma. 2) The tumor cells, showing high nuclear cytoplasmic ratio, prominent nucleoli, numerous mitotic figures and eosinophilic cytoplasm similar to the liver cells.

G. Fibrosarcoma

Spindle cell sarcoma, showing fibroblastic differentiation, is designated as fibrosarcoma.

H. Leukemia/lymphoma

Destruction of lymph node architecture by lymphoid tumor cells and the tumor cell invasion into the other organs are noted.

The results of the histopathological investigation are listed in Table 5. There is no significant increase of the lesions, but cases of acinar cell adenoma are somewhat increased in exposure groups, when compared to the control.

The pulmonary tumors, which are thought to be related to these experimental procedures, are listed in Table 6. This Table also fails to demonstrate a significant difference between the exposure group and control group, in spite of an appearance

of pulmonary adenocarcinoma in Run No.4 (NiO(B) exposure). After carel investigation of paranasal sinuses, it was concluded that there was no neoplasm the upper respiratory tract of all the animals.

Electron microscopy clarifies prominent lysosomal granules in the bronch epithelium, projection of Clara cells and accumulation of tubular myelins in t peribronchial lymphatics, which are evident especially in the immediately sacrific groups after the exposure to nickel compounds.

4. DISCUSSION

In the present paper, the deposition, clearance and carcinogenicity of three nick compounds, NiO(G), NiO(B), Ni_3S_2, were studied by rats using inhalatic method.

The nickel concentrations in the rat lungs were highest when compared to t concentration in the liver, spleen and kidneys, and nickel concentration in the lun of the controls was lower than those of the exposed groups except for Run No (Figure 9). Significant decreases of nickel concentration in the lungs (Figure were also observed between just after the exposure group (Run No.1, 3, 5) an after the clearance group (Run No.2, 4, 6). In other organs, significant differenc of nickel concentration between nickel exposed rats (Run No.1, 3, 5) and contr were observed in the liver for Ni_3S_2 (Figure 10), in the kidneys for NiO(B) an Ni_3S_2 (Figure 11), and in the spleen for NiO(G) (Figure 12). After the clearanc period, there were no significant differences between nickel exposed rats (Run N 2, 4, 6) and control. Some amount of nickel compounds deposited in the lungs ma transfer to other organs and then metabolized during the exposure and clearanc period, but a detailed metabolizing mechanism for each compound could not b determined just by this study.

The apparent deposition fraction in the lungs was the same level for NiO(G) and Ni_3S_2. The level for NiO(B) was 2 times higher than that for NiO(G) and Ni_3S_2. The deposition of nickel compounds may be affected by the chemical and physical properties of aerosol and exposure conditions, such as aerodynamic diameter, exposure concentration and exposure period etc. Solubility is one of the important factor for deposition and metabolism of nickel compounds. The solubility of the nickel compounds used in this study was measured in distilled water and saline solution as shown in Table 3 with the following ranking: Ni_3S_2>>NiO(B)>NiO(G). Highly soluble aerosol deposited in the lungs is considered to enter easily into systematic circulation and transfer to an organ, resulting in a decrease of the content in the lungs. The solubilities of NiO(G) aerosol used in this experiment were lower than that of NiO(G) (Soekawa Chem. Ind., Japan; color, green), which was used in our previous experiment (Tanaka et al. 1985), however the apparent deposition fraction of NiO(G) in this experiment was lower than that in our previous results obtained by Soekawa NiO(G) aerosol (Kodama et al. 1985). The apparent deposition fraction of NiO(B) in the lungs was higher than that for NiO(G), in spite of the high solubility of NiO(B). The difference of apparent deposition fraction in lungs of the nickel compounds may not be elucidated only from the solubilities.

The clearance rate of nickel compounds from the lungs in 12 months was estimated by the ratio of the cleared amount to the lung amount just after the exposure.

The clearance rates for NiO(G), NiO(B) and Ni_3S_2 were 82 %, 73 % and 98 %, respectively. The level of Ni_3S_2 was higher than that of NiO(G) and NiO(B), and this may be attributable to the high solubility of Ni_3S_2. There was no clear evidence between the solubility and the clearance rate in NiO(G) and NiO(B). The persistence time of nickel compounds in the lungs is an important factor in the development of tumor or fibrosis, and should be examined in detail.

The histopathological findings demonstrated that insoluble NiO(G) and NiC particles activated the epithelial cells of Clara cells and type II pneumocy Besides, Ni_3S_2 particles failed to demonstrate any different lesions in the respira system. Finally, neither evidence of neoplastic growth nor severe inflammat reaction was observed in the NiO(G), NiO(B) and Ni_3S_2 groups. Moreover, ir the experimental groups, no detectable abnormalities were noted in the other orga

Our previous report (Horie et al. 1985) has clarified that insoluble NiO particles activated bronchioloalveolar epithelium and accumulated tubular myelin the peribronchial lymphatics. These facts are also confirmed in this experim However, the three types of nickel compounds, namely NiO(G), NiO(B) , Ni_3S_2, failed to demonstrate any carcinogenicity using this type of inhalat system. As for the slight increase in the acinar cell adenoma of the pancreas, the should be sufficiently ascertained in future, including a clearer explanation of mechanism.

5. CONCLUSION

The following results were obtained from the inhalation experiments of nicl compounds by rats.

1. The solubility of these chemicals to saline solution was 0.3 ppm for NiO(G), 3.5 ppm for NiO(B) and 310 ppm for Ni_3S_2, respectively.
2. The apparent deposition fractions(%) in the lungs were 0.5±0.1 for NiO(G), 1.0±0.3 for NiO(B) and 0.5±0.1 for Ni_3S_2, respectively.
3. During the 12 months, 82% of deposited NiO(G), 73% of NiO(B) and 98% of Ni_3S_2 were cleared from lungs, respectively.
4. There was no significant difference of neoplastic growth between the exposure group and control group, in spite of an appearance of pulmonary adenocarcinoi

in Run No.4 (NiO(B) exposure group). Moreover, in all the experimental groups, no detectable abnormalities was noted in the other organs, except for a slight increase in the acinar cell adenoma of pancreas.

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Table 1

Experimental Conditions

Nickel Compounds	NiO(G)			NiO(B)			Ni_3S_2		
Run No.*	1	2		3	4		5	6	
	E	E	C	E	E	C	E	E	C
number of rats	10	50	20	10	50	20	10	50	20
Exposure & Clearance Period**(month)	6	6-12		6	6-12		6	6-12	
Total Exposure Time***(hour)	762	762		708	708		696	696	
Exposure Concentration ($mg/m^3 \pm SD$)	1.1± 0.4	1.1± 0.4		1.3± 0.4	1.3± 0.4		0.5± 0.4	0.5± 0.4	
MMAD (GSD)	4.1 (2.2)	4.1 (2.2)		3.6 (2.3)	3.6 (2.3)		2.6 (1.9)	2.6 (1.9)	

* E or C shows the exposure group or control one, respectively.
** 6 mo. six months exposure; 6-12 mo denotes a clearance period of 12 months after six months exposure.
*** 6h/d, 5d/wk

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Table 2 Operating Conditions for AAS

APPARATUS

HITACHI POLARIZED ZEEMAN ATOMIC ABSORPTION SPECTROPHOTOMETER

INSTRUMENTAL CONDITIONS

LUMP CURRENT	:	10.0 mA
WAVELENGTH	:	232.0 nm
SLIT	:	0.2 nm
CUVETTE	:	TUBE (PYRO TYPE)
CARRIER GAS	:	200 ml/min
INTERRUPTED GAS	:	0 ml/min
SAMPLE VOLUME	:	10 µl

CALCULATION

MEASUREMENT MOOD	:	AAS (CONC)
ZEEMAN A. A. MOOD	:	ZAA
CALCULATION	:	P/H ONLY
CALCULATION TIME	:	7.5 SEC
STATISTICS	:	MEAN, SD, RSD
x-SCALE(TIME)	:	500 SEC
TIME CONSTANT	:	0.2 SEC
CALIB. CURVE(P/H)	:	ABS=F (CONC)LINEAR

TEMPERATURE PROGRAM

STAGE	TEMP.(° C) START	TEMP.(° C) END	TIME(SEC)	TEMP.(° C) START	TEMP.(° C) END	TIME(SEC)
DRY	80	120	60	80	120	30
				120	150	30
				150	200	30
ASH	700	700	40	500	600	45
				700	900	55
ATOM	3000	3000	7.5	3000	3000	7.5
CLEAN	3000	3000	5	3000	3000	5
	(FOR ORGAN)			(FOR BLOOD)		

Table 3 Solubility of Ni Compounds (ppm)

Nickel compounds	n	Distilled Water	Saline Solution
NiO(G)	8	0.1± 0.0	0.3± 0.0
NiO(B)	8	7.1 ± 0.1	3.5± 0.2
Ni_3S_2	10	151.0± 8.0	310.0±48.0

Table 4

Organ Wet Weight after 6 months Exposure and 12 months Clearance

(mg/g-body weight ± SD)

		N*	Lung	Liver	Kidney	Spleen
NiO(G)	C	20	2.8± 0.3	23.2± 1.9	5.2± 0.6	1.8± 0.2
(Run No.2)	E	47	2.6± 0.3	22.5± 2.1	5.2± 0.6	1.7± 0.4
NiO(B)	C	17	3.0± 0.7	23.5± 2.7	5.6± 0.6	2.0± 0.4
(Run No.4)	E	40	2.8± 0.3	22.7± 2.4	5.4± 0.5	1.8± 0.4
Ni_3S_2	C	16	2.5± 0.3	22.9± 3.4	5.0± 0.5	1.7± 0.3
(Run No.6)	E	47	2.9± 0.4*	21.9± 2.9	4.9± 0.6	1.7± 0.3

* N is number of rats sacrificed; C.control; E.experimental animal.
Significance level:* P<0.01. as compared with the controls(C) by t-test.

Table 5

Histopathology of Rats Inhalated by Various Types of Nickel Compound

Type of compound	NiO green			NiO black			Ni_3S_2		
Run number *	1	2		3	4		5	6	
	E	E	C	E	E	C	E	E	C
Total number of rats	10	50	20	10	50	20	10	50	20
(Number of sacrificed rats at the end of each experiment)	(10)	(47)	(20)	(10)	(40)	(17)	(10)	(47)	(16)
Number of rats with each lesion									
Lung Tumor									
Adenoma	0	0	1	0	4	2	0	0	0
Adenocarcinoma	0	1	0	0	0	0	0	0	0
Emphysema	0	6	2	0	1#	0	0	0	0
Hemorrhage	0	4	1	0	0	2	0	0	0
Pneumonia	0	0	0	0	0	0	0	1	0
Tumor of other organs									
Pancreas: Acinar cell adenoma	0	2	1	0	3	0	0	9	1
Islet cell adenoma	0	0	0	0	3	0	0	0	0
Soft part: Fibrosarcoma	0	1	0	0	1#	0	0	0	0
Kidney: Renal cell adenocarcinoma	0	1	0	0	0	0	0	0	0
Papilloma of the pelvis	0	0	0	0	2	0	0	2	0
Liver: Hepatocellular carcinoma	0	0	0	0	1#	0	0	0	0
Leukemia/lymphoma	0	0	0	0	1#	0	0	0	0
Pituitary adenoma	0	0	0	0	1#	0	0	0	0
Salivary gland: Mixed tumor	0	0	0	0	0	0	0	1	0
Lacrimal gland: Adenoma	0	0	0	0	0	0	0	0	1

* Run number: ref. Table 1

Table 6

Incidence of Pulmonary Adenoma and Adenocarcinoma among Rats Inhaling NiO(G), NiO(B) and Ni_3S_2

	Exposure group	Control group
Total number of rats	150	60
Number of rats with adenoma	4	3
Number of rats with adenocarcinoma	1	0
Adenoma + Adenocarcinoma (%)	5 (3.3%)	3 (5.0%)

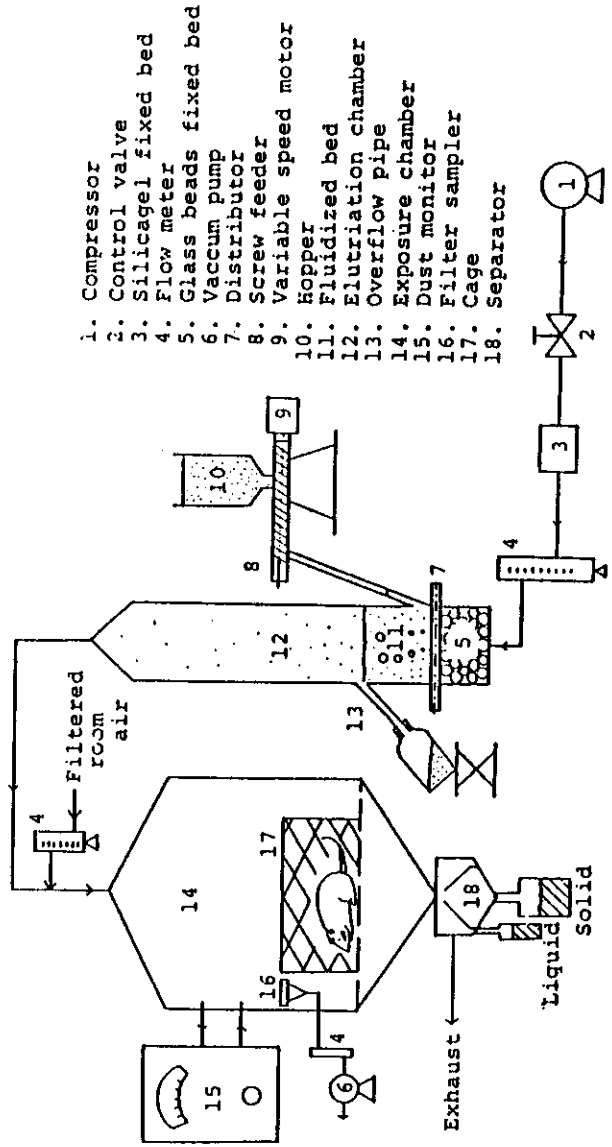

Fig.1 Schematic diagram of dust exposure system.

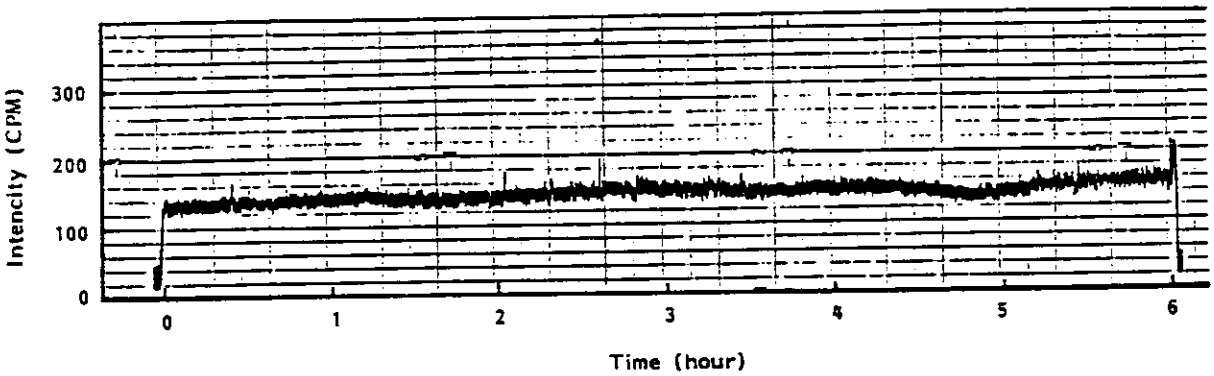

Fig. 2 NiO(G) dust concentration by light scattering method.

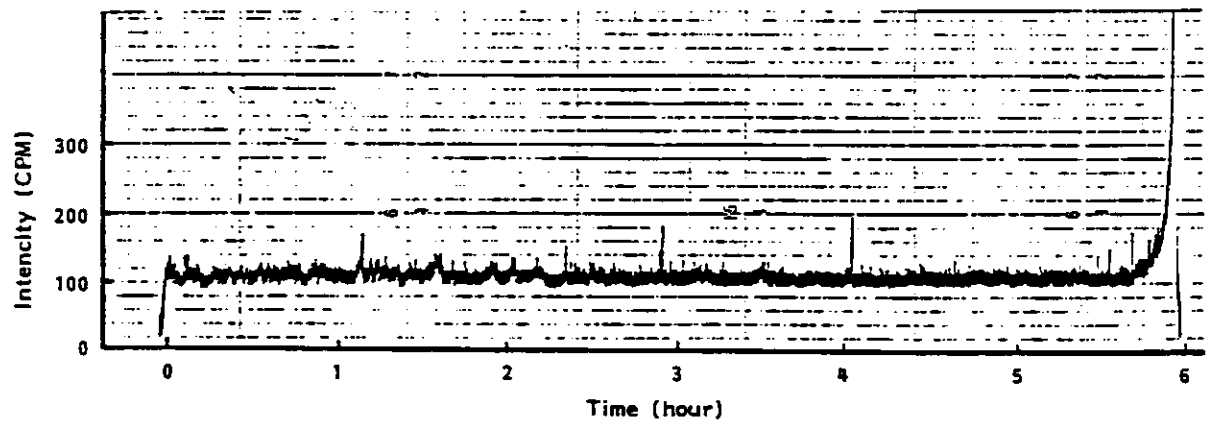

Fig. 3 NiO(B) dust concentration by light scattering method.

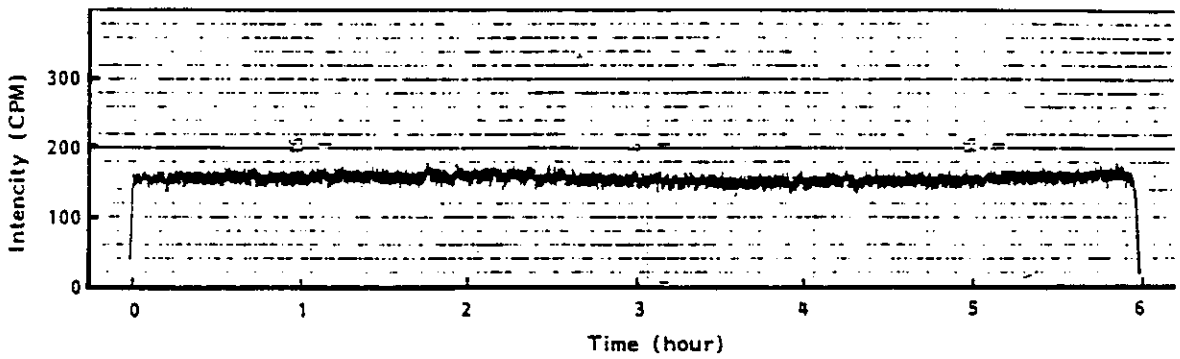

Fig. 4 Ni_3S_2 dust concentration by light scattering method.

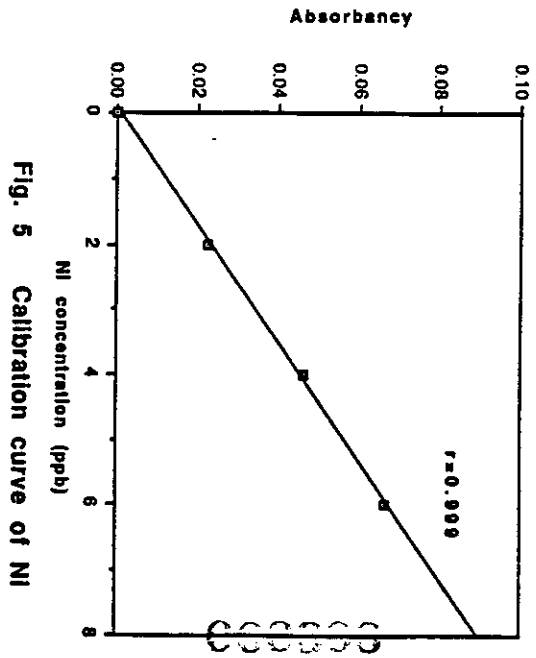

Fig. 5 Calibration curve of Ni

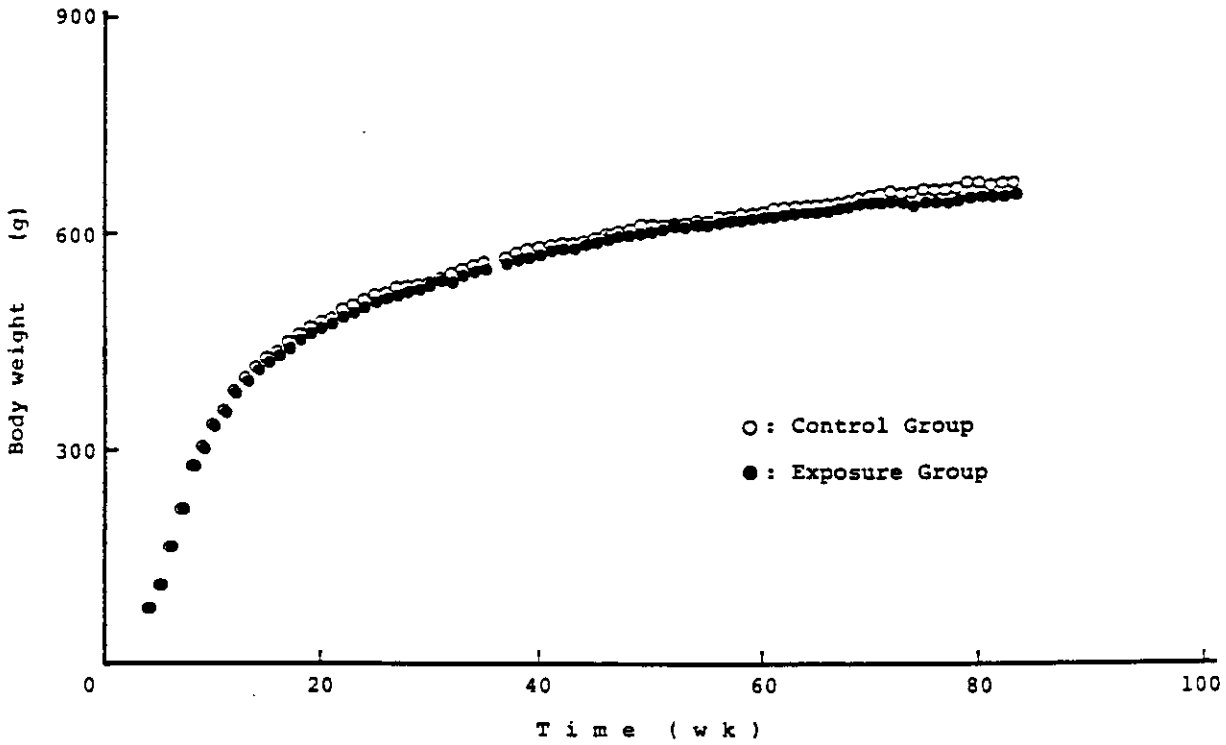

Fig. 6 Comparison in growing rate between exposed rats and controls (NiO(G)).

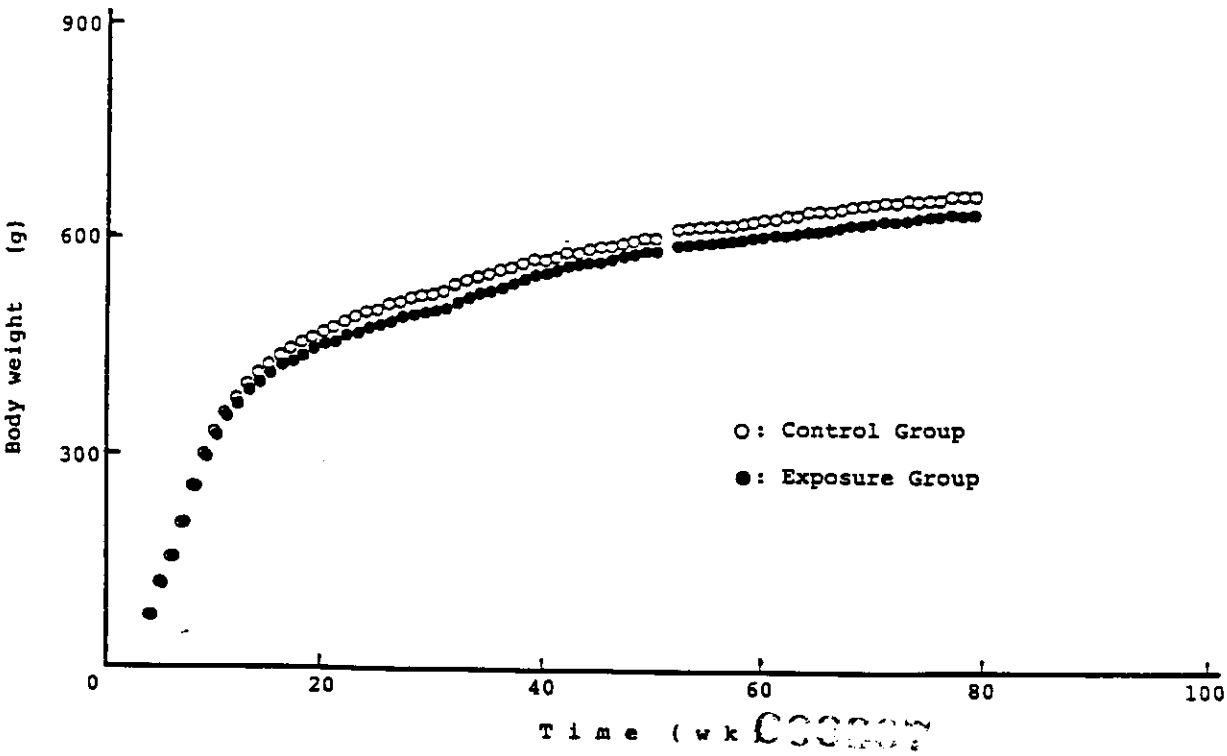

Fig. 7 Comparison in growing rate between exposed rats and controls (NiO(B)).

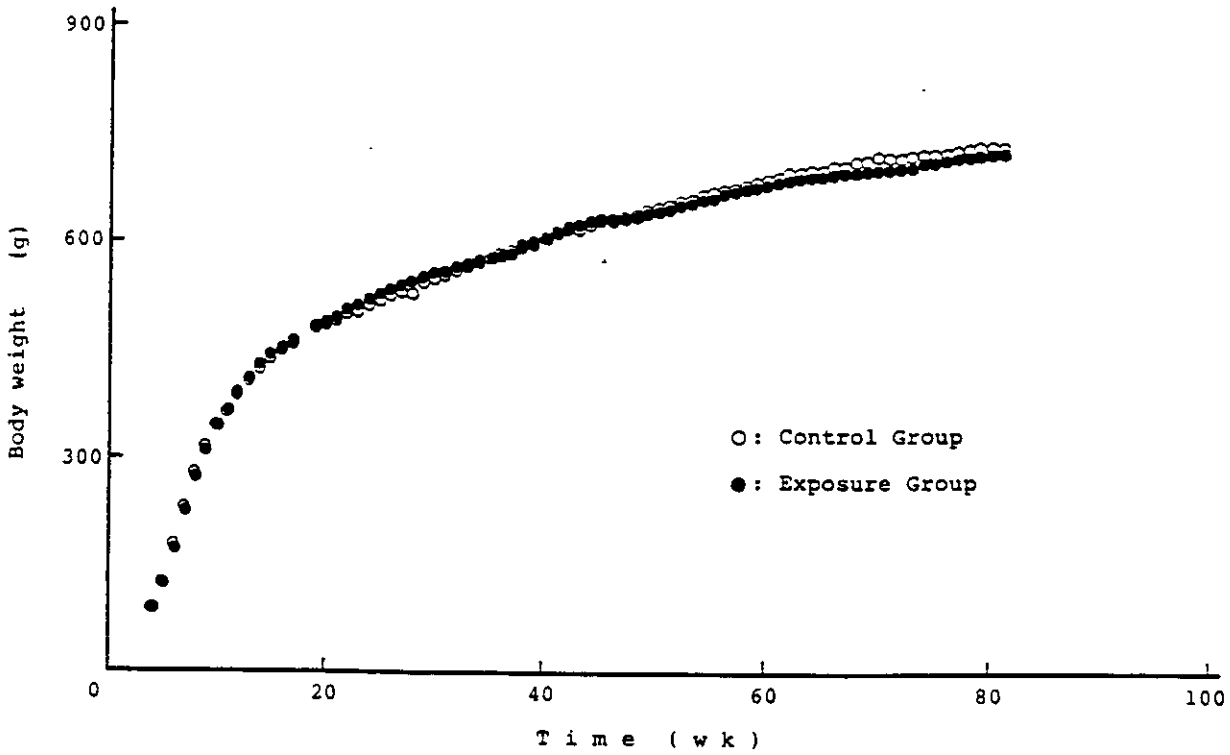

Fig. 8 Comparison in growing rate between exposed rats and controls (Ni_3S_2).

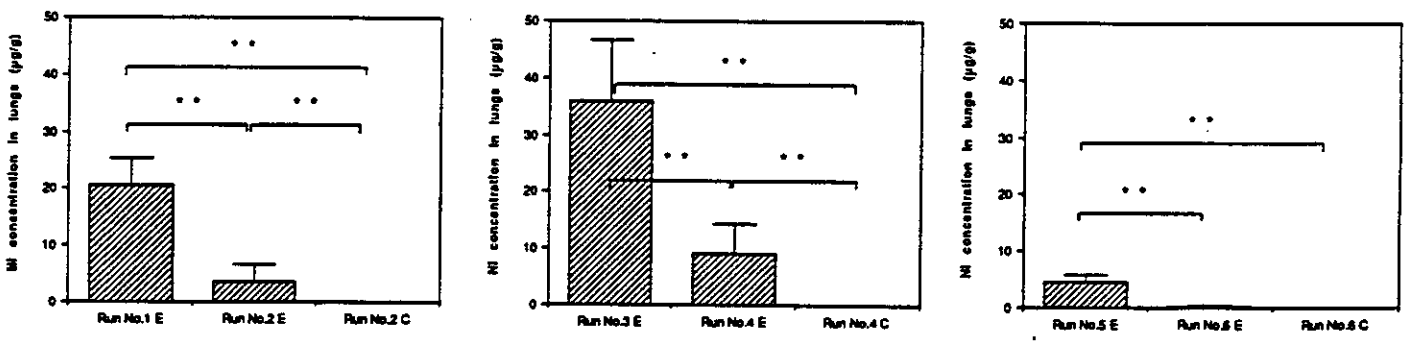

Fig. 9 Ni concentration in rat lungs
(** p<0.01, Conditions and designations of each run are presented in Table 1)

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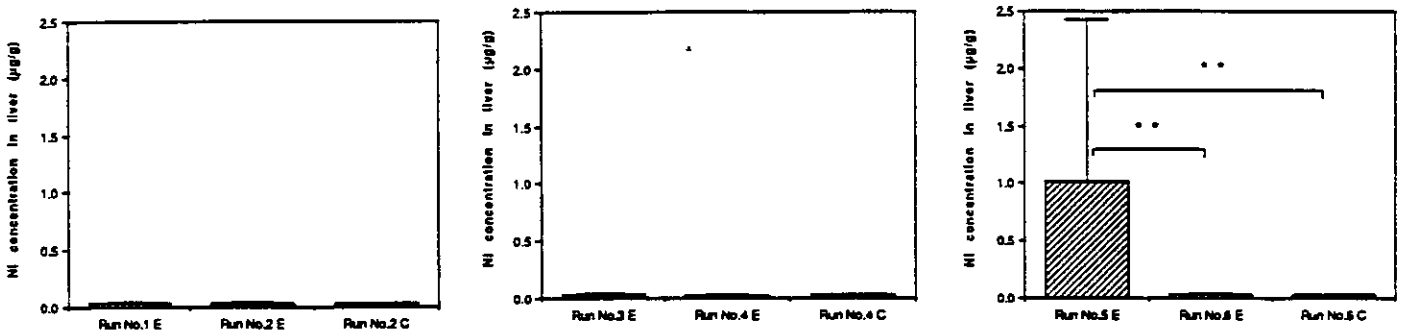

Fig.10 Ni concentration in rat liver
(** p<0.01, Conditions and designations of each run are presented in Table 1)

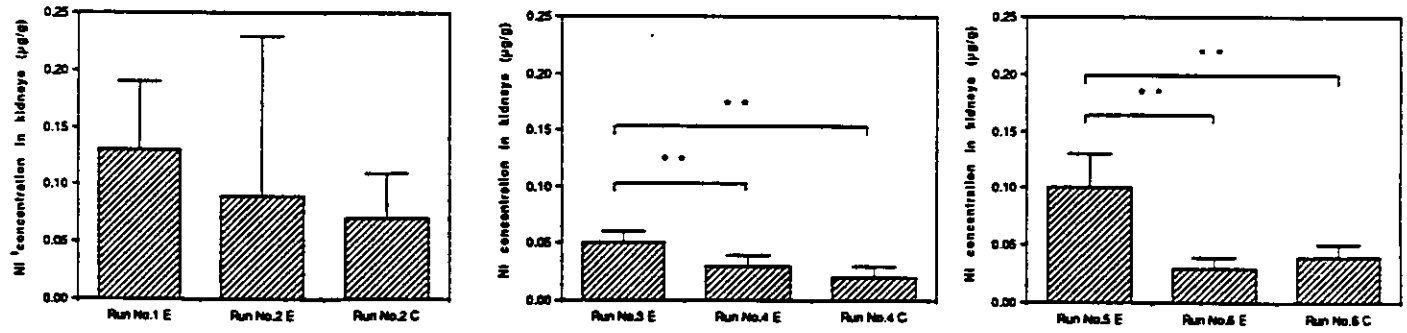

Fig.11 Ni concentration in rat kidneys
(** p<0.01, Conditions and designations of each run are presented in Table 1)

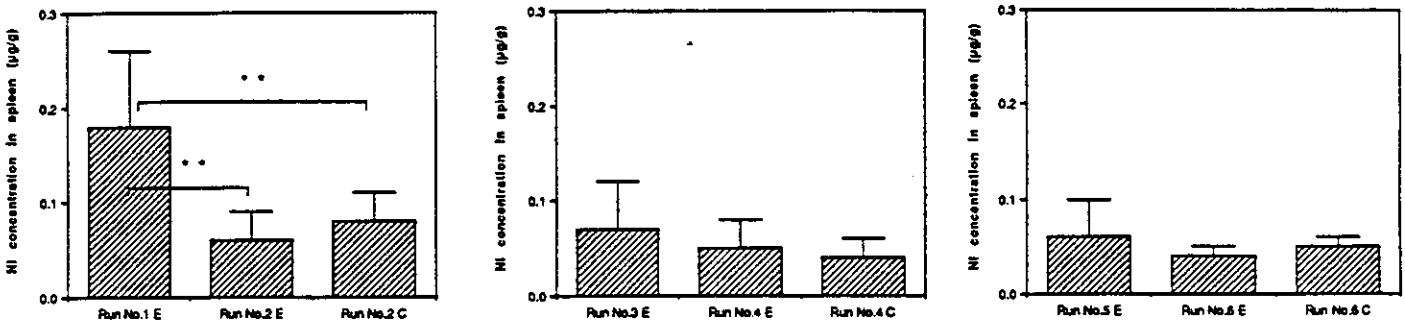

Fig.12 Ni concentration in rat spleen
(** $p<0.01$, Conditions and designations of each run are presented in Table 1)

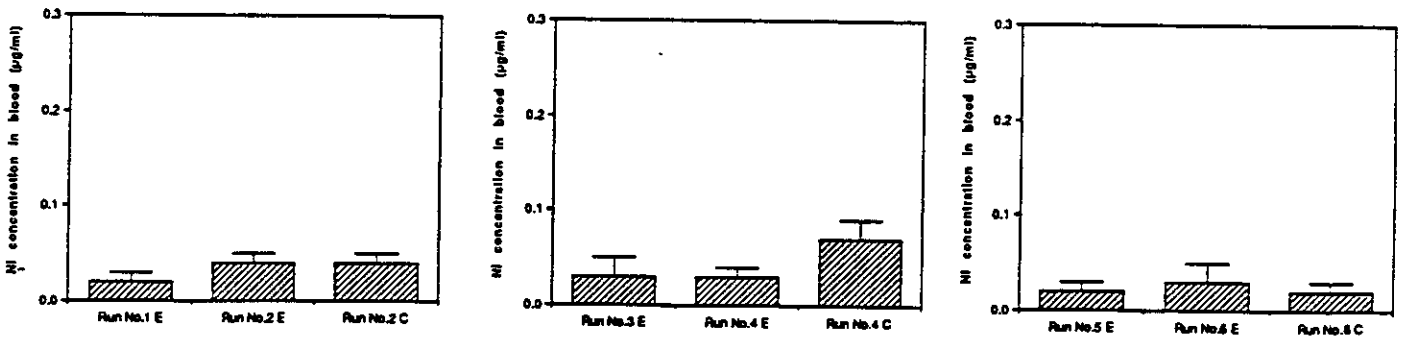

Fig.13 Ni concentration in blood
(Conditions and designations of each run are presented in Table 1)

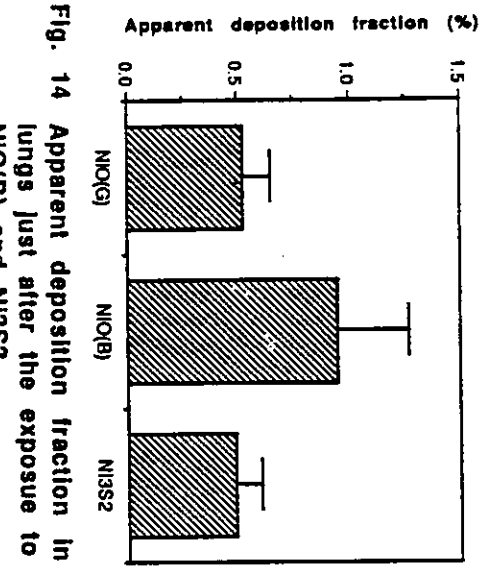

Fig. 14 Apparent deposition fraction in rat lungs just after the exposue to NiO(G), NiO(B) and Ni3S2.

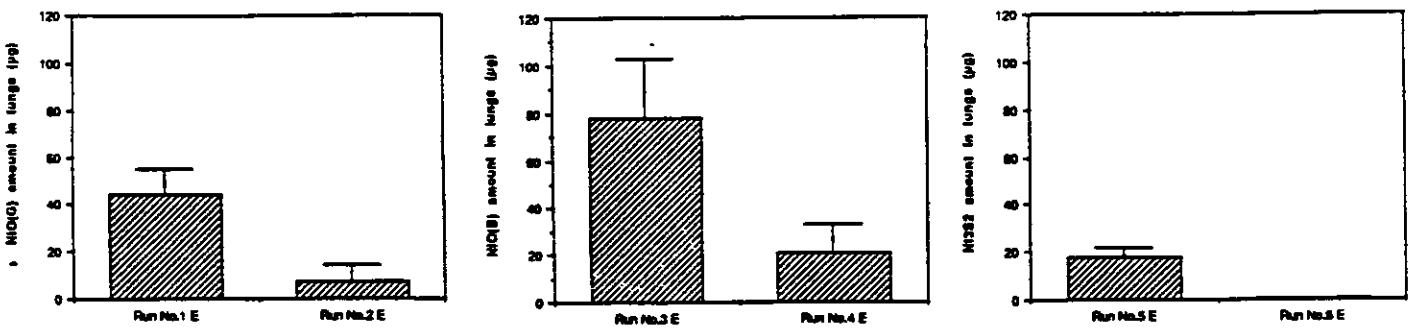

Fig.15 Ni amount in rat lungs just after 6 months exposure and after 12 months clearance following 6 months exposure

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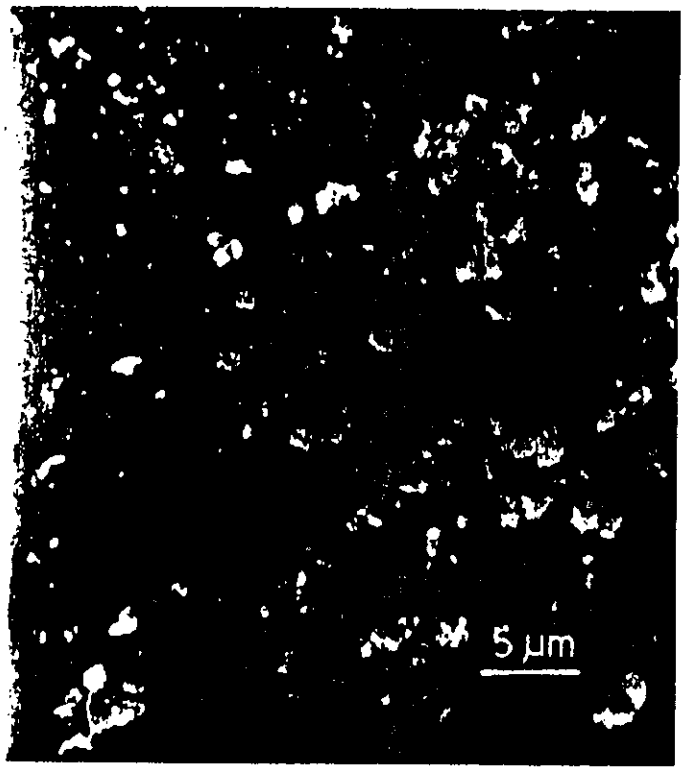

Photo 1 NiO(G) particles in chamber.

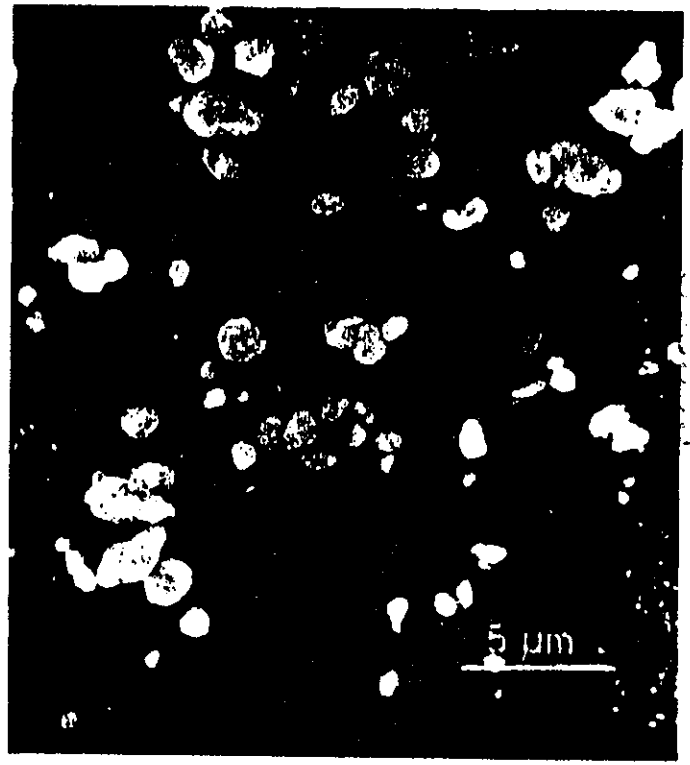

Photo 2 NiO(B) particles in chamber.

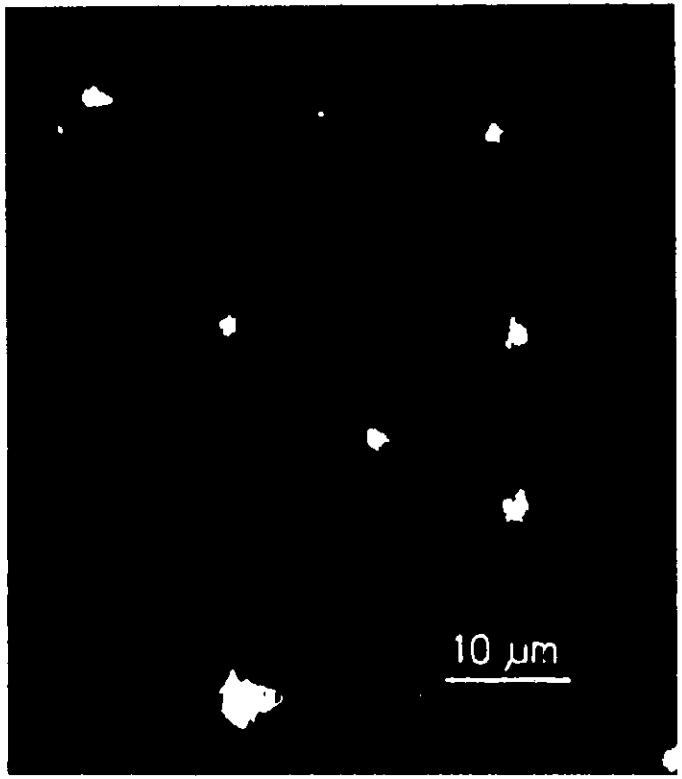

Photo 3 Ni_3S_2 particles in chamber.

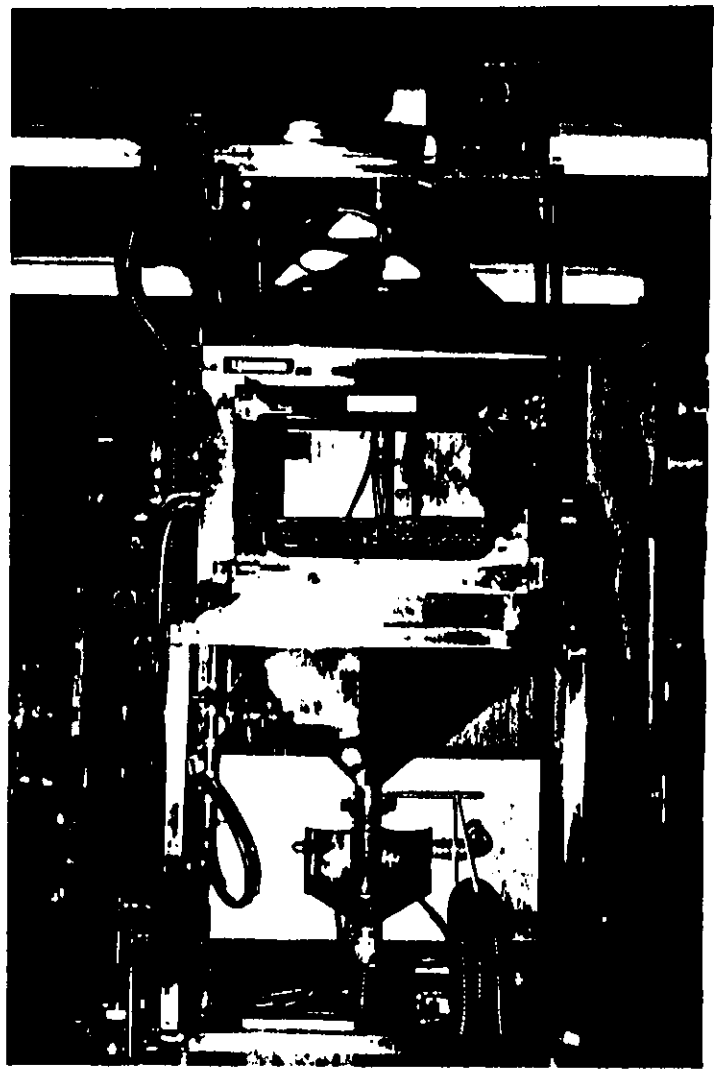

Photo 4 Exposure chamber.

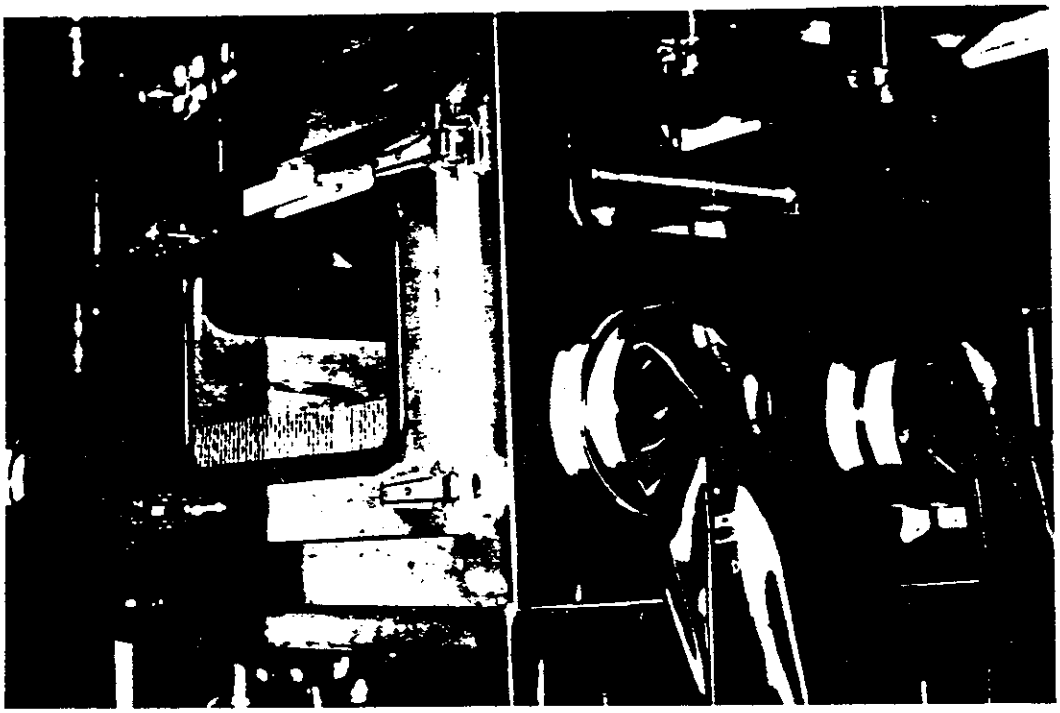

Photo 5 Exposure chamber.

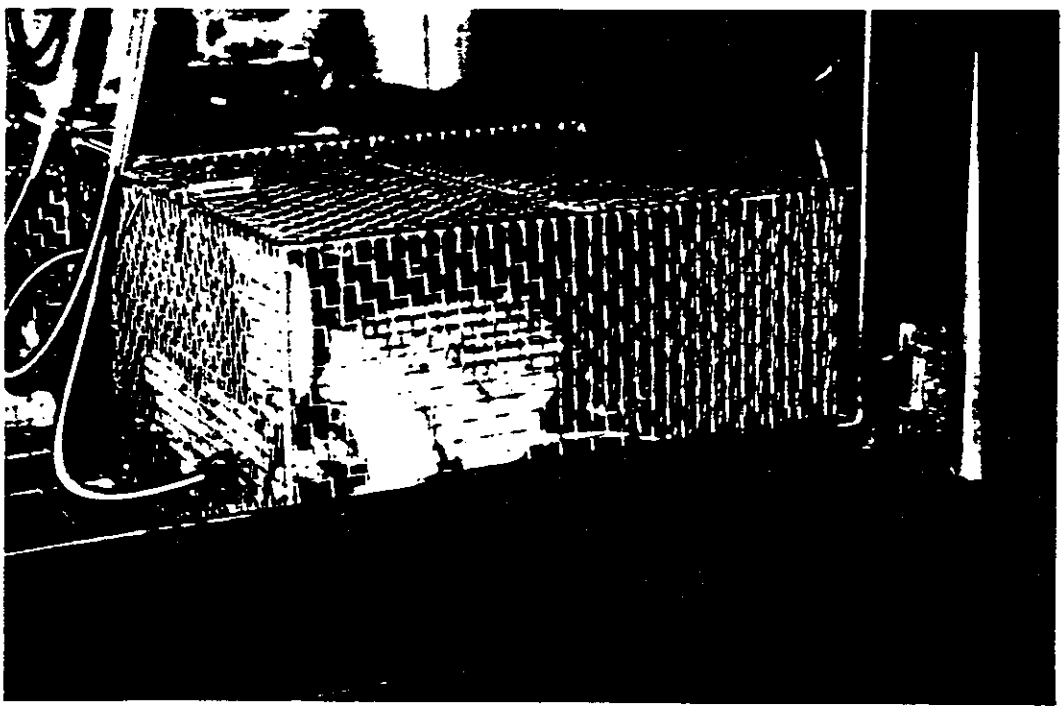

Photo 6 Exposure chamber (inside).

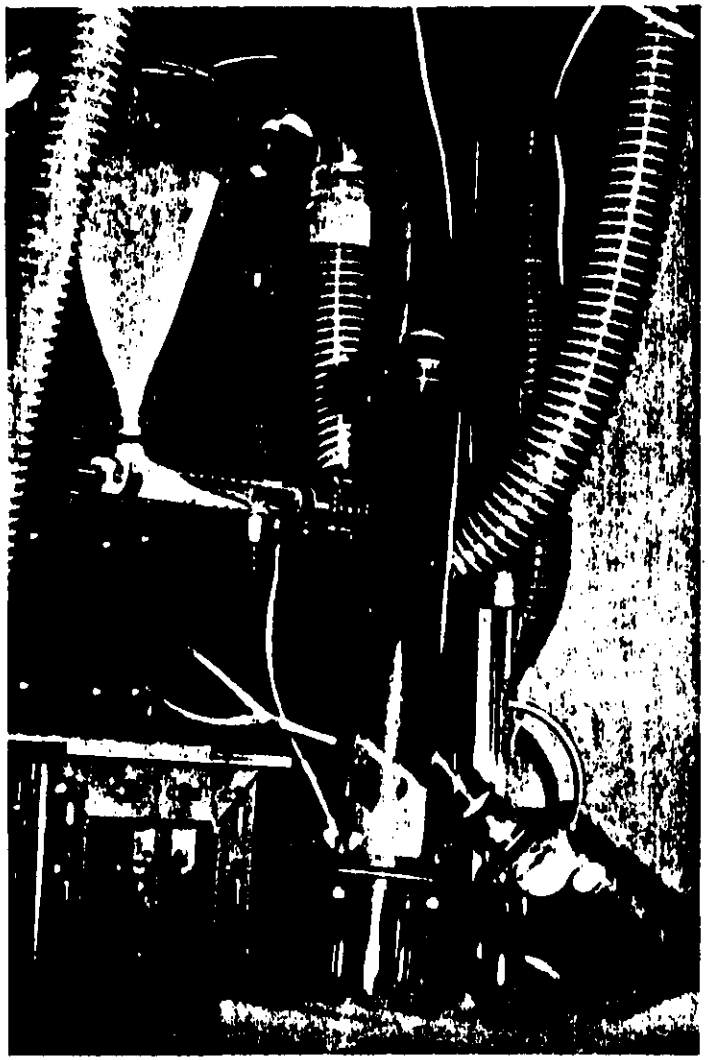

Photo 7 Dust generator.

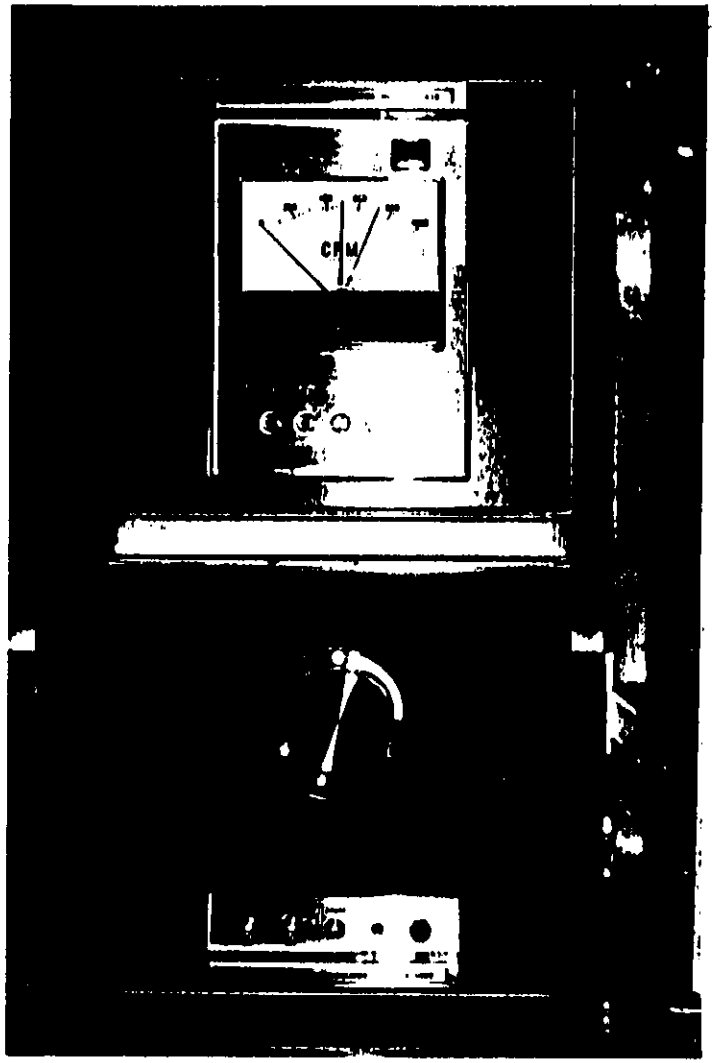

Photo 8 Direct dust indicator.
(Shibata Co., Japan)

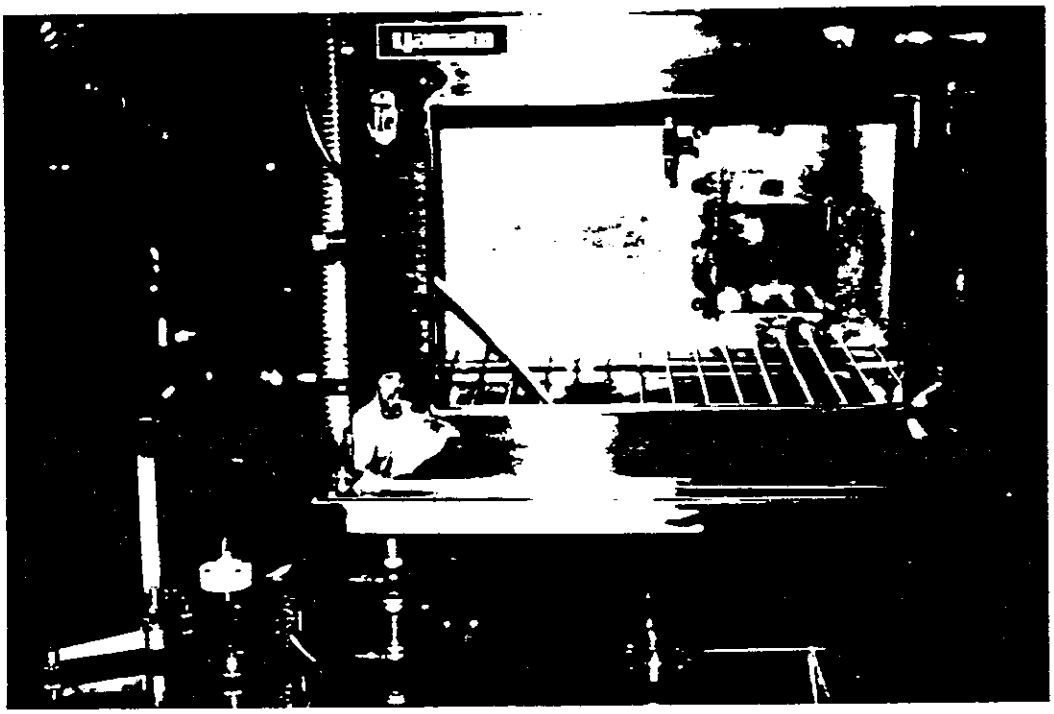

Photo 9 Dust sampling system by filter method.

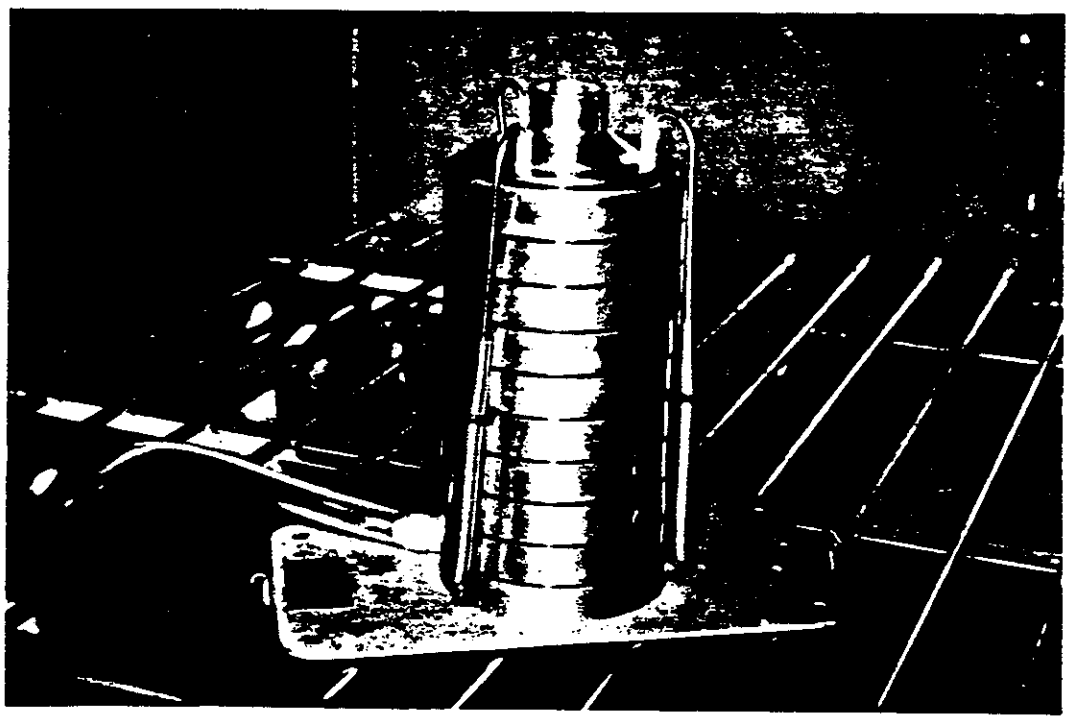

Photo 10 Andersen sampler.

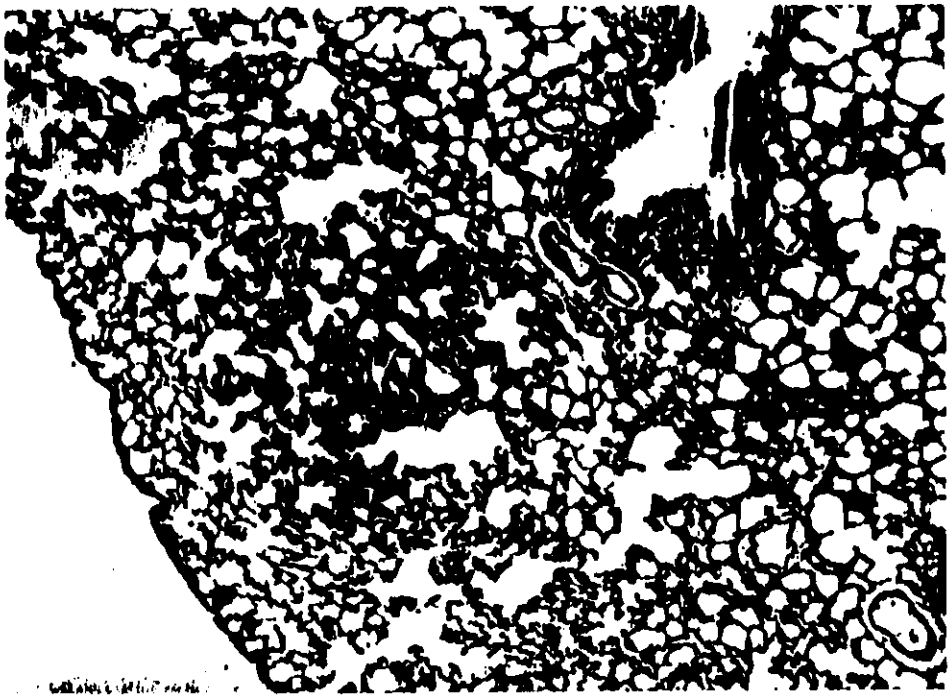

Photo. 11 Pulmonary adenoma, showing a localized hyperchromatic lesion. NiO(B)21 X80.

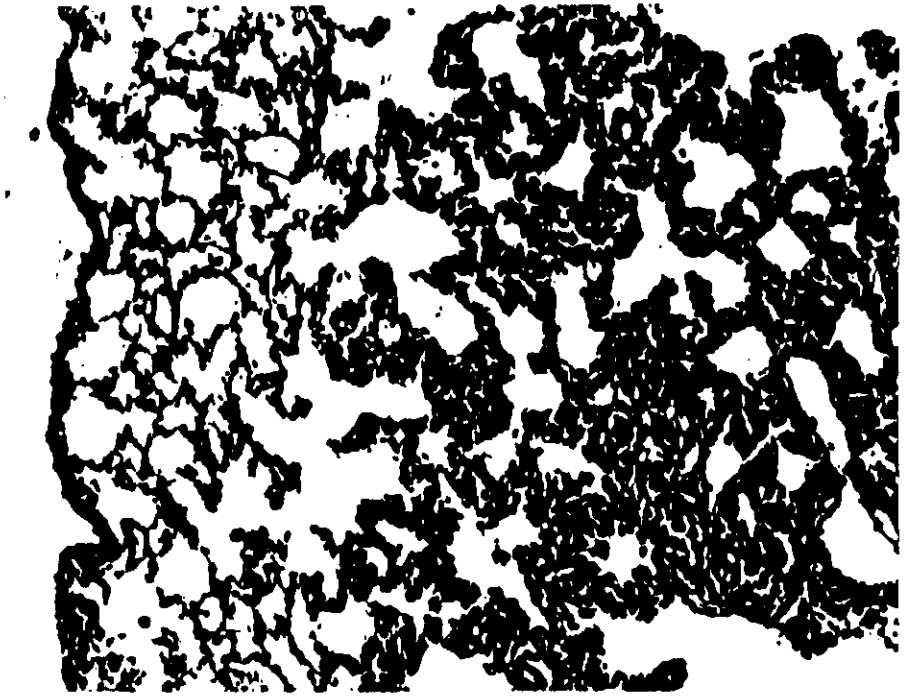

Photo. 12 An enlarged view of Photo 11 shows alveolar structures lined by hyperchromatic tumor cells. NiO(B)21 X200.

Photo. 13 Pulmonary adenocarcinoma, showing invasive growth into the adjacent alveoli. NiO(G)18 X80.

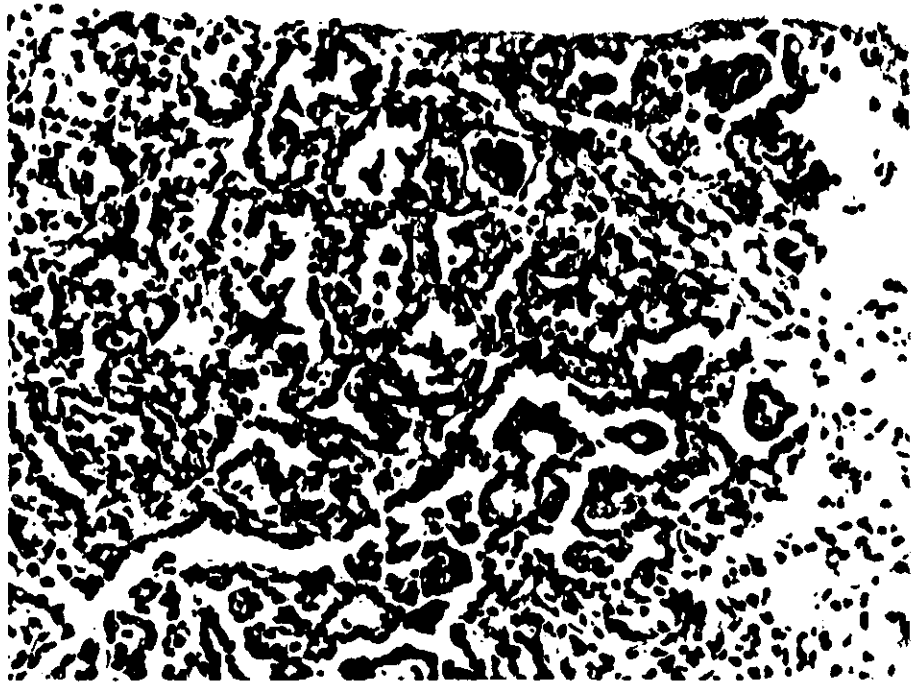

Photo. 14 An enlarged view of Photo 13 shows structural atypism including intra-alveolar extension. NiO(G)18 X300.

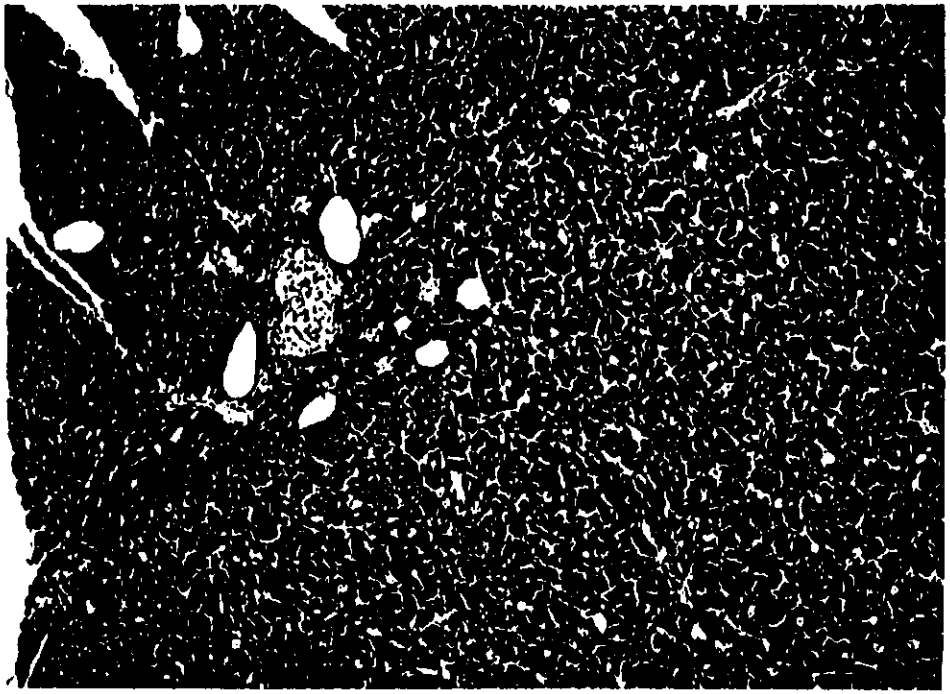

Photo. 15 Acinar cell adenoma of the pancreas. Ni_3S_241 X80.

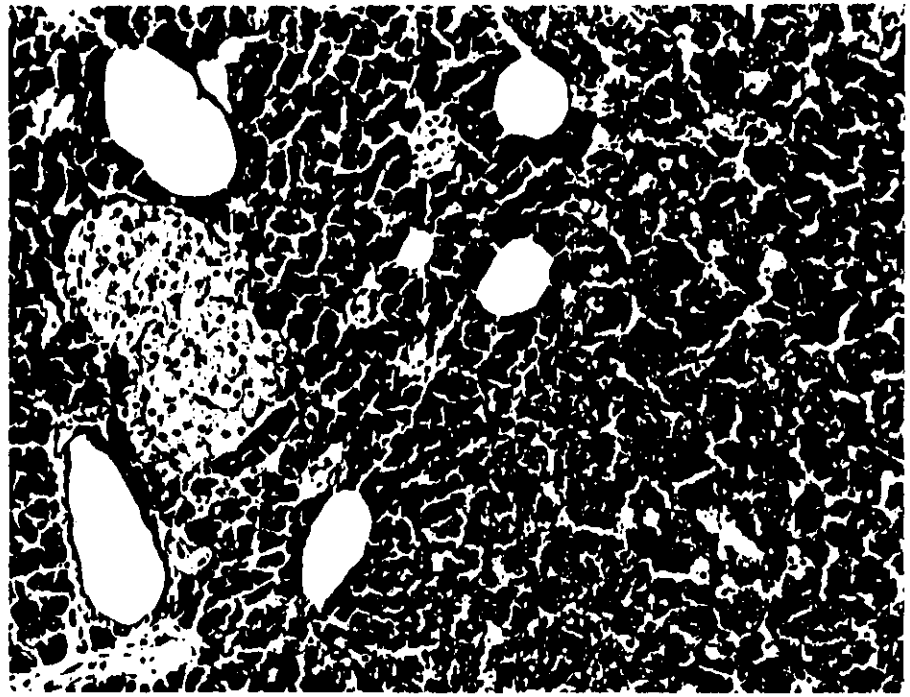

Photo. 16 An enlarged view of Photo 15 shows tumor cells with zymogen granules, high nuclear cytoplasmic ratio and large nuclei with prominent nucleoli. Ni_3S_241 X200.

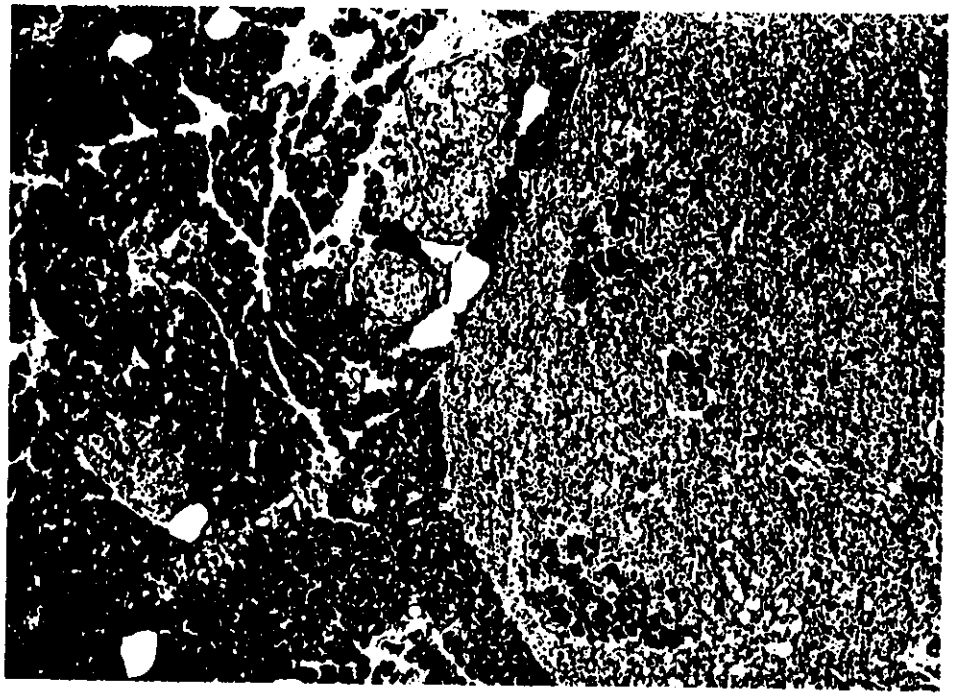

Photo. 17 Islet cell adenoma of the pancreas. NiO(B)24 X80.

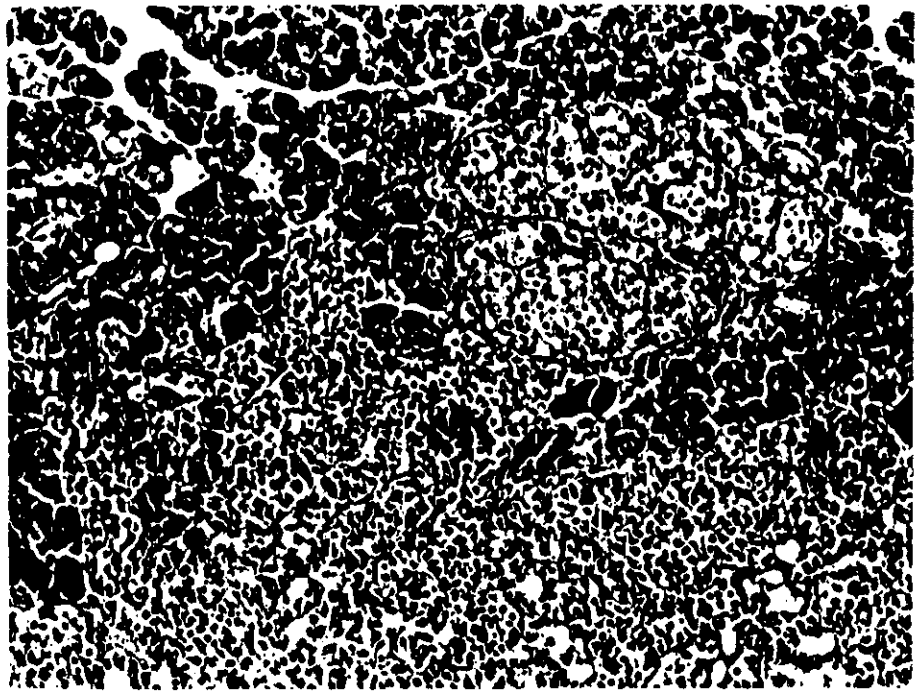

Photo. 18 An enlarged view of Photo 17 shows replacing growth in the adjacent exocrine pancreas and monotonous tumor cell nuclei with comparatively light cytoplasm. NiO(B)24 X200.

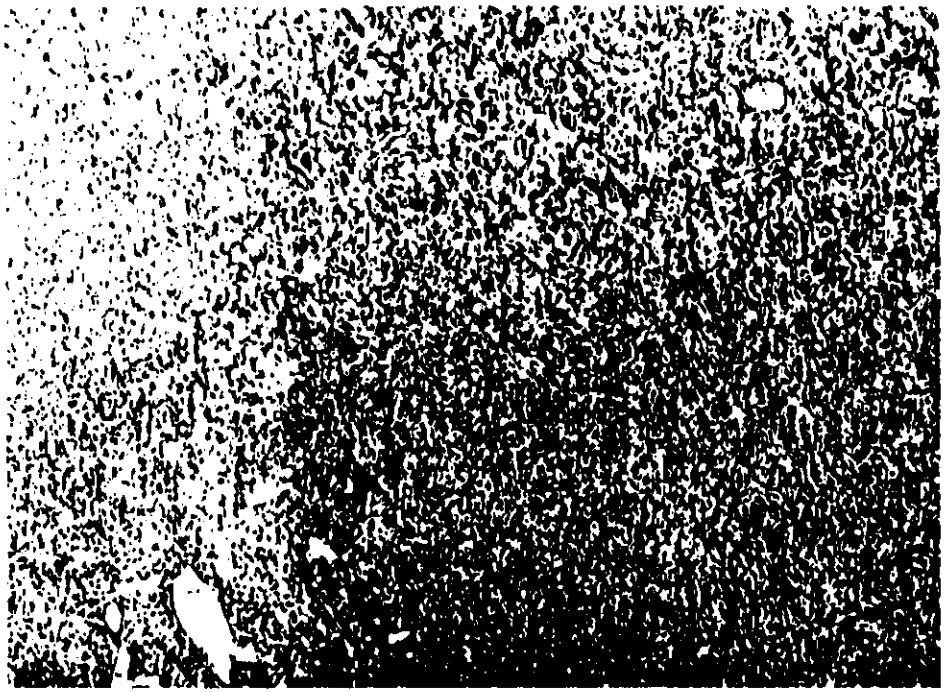

Photo. 19 Fibrosarcoma, showing spindled tumor cells with fibroblastic features. $Ni_3S_2$11 X80.

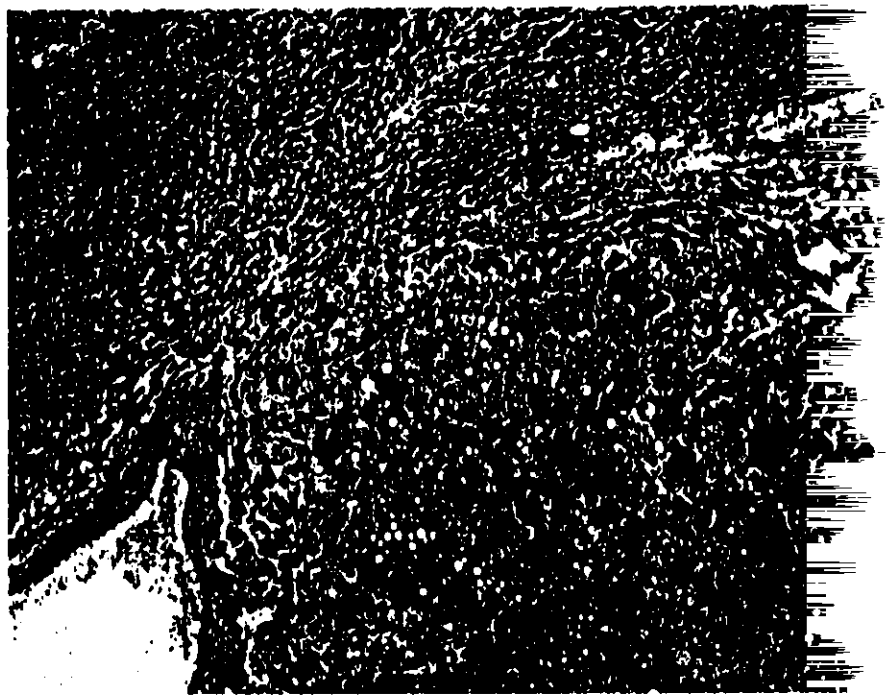

Photo. 20 Hepatocellular carcinoma, showing nodular growth of atypical cells in right lower part of the plate NiO(B)20 X80.

APPENDIX D

PULMONARY EFFECTS OF METALLIC DUSTS

-Nickel and Iron-

University of Toronto Library
SCIENCE & MEDICINE DEPARTMENT

by

Moon Ko Kim, B.Sc., M.P.H.

A thesis

Submitted in Conformity with the Requirements

for the degree of

Master of Science

in the

Department of Physiological Hygiene

School of Hygiene

University of Toronto

1969

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I. INTRODUCTION

Cancer of the lung in man, particularly pulmonary carcinoma, showed the most remarkable increase in incidence in the past fifty years and has become one of the most serious problems in public health. Its origin has been linked with a number of environmental factors, notably inhalation of cigarette smoke and pollution of the air by chemicals and radioactivity. The concept that environmental factors cause or attribute to pulmonary cancers is supported by epidemiological and experimental studies published during the last decades.

In nickel refining most of data show an association between furnace operations and increased risk of lung cancer. Hueper and Conway (1) noted that the smelting and refining of nickel presented a recognized risk in producing respiratory cancer in workers engaged in these operations. They noted further that there is a suspected risk in nickel ore mining. Similiarly, Doll (2), in a review of occupational cancer, classified exposure to calcined dust containing nickel as an established, and to iron dust and fumes as a suspected risk. There was, however, no support for suggestion that lung cancer is the result of direct chemical carcinogenic action. In Ontario there is no evidence of any increase respiratory cancer among nickel miners and in huge Sudbury smelter complexes (3).

Most experimental carcinogenic studies on nickel or iron have been carried out by parenteral injection of various nickel or iron compounds into animal body; little work appears to have been done on the deposition of metallic dust within body tissue following inhalation. In the studies

on occupational carcinogenesis, it is important for scientific and medicolegal reasons to investigate the possibility of producing experimentally cancer of the same histologic type and location in animals by duplicating as closely as practicable exposure conditions prevailing for man.

The inhalation method of this experiment has been attempted to seek a likely explanation of mechanism of human exposure to inhaled carcinogens.

II. REVIEW OF LITERATURE

1. Nickel and Its Compounds

A. Epidemiological Data

Nickel is one of the most industrially important metals. Seventy percent of the free world's consumption of nickel is mined in the Sudbury area of Ontario. The metal has many uses in the numerous high temperature corrosion resistant alloys, in electroplating, in the production of catalysts and a relatively new use in the production of nickel-cadmium batteries. Exposure to nickel fumes and nickel dust of metallic nickel and its compounds or to nickel carbonyl vapors is frequent for industrial workers of many types and many operations.

It has been reported that nickel and/or its compounds are carcinogenic and toxic. The first indication concerning the occurence of an excessive number of cancers of the nasal passages and of the lungs among workers in a refinery in Wales was contained in the Annual Report of Chief Inspector of Factories for the year of 1932, which was published in 1933 (4).

Subsequent reports dealing with these cancers were made by Cooper (5); Amor (6); Carrozi (7); Bridge (8); and Merewether (9). In the Annual Report of the Chief Inspector of Factories for the year of

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1948, it was noted that, for the period of 1923-1948, there were 47 cases of cancer of the nose and 82 cases of lung cancers among nickel workers.

The situation at the Welsh refinery was reviewed again by Doll (10), Morgan (11) and Williams (12). Doll noted that for the years 1948-1956 "the risk of nickel workers dying from lung cancer was approximately five time 'normal'" and the same period their risk of dying from nasal cancer was 150 times normal.

Morgan reported that there were 131 cases of lung cancer and 61 of nasal cancer among nickel refiners for the period of 1923 to 1957. Workers showing an increased incidence of respiratory cancer were those involved in dusty operations rather than those exposed to nickel as a gaseous compound.

Williams examined histologically and chemically the lungs of 5 men who had worked at the Welsh refinery. Four of the 5 had pulmonary carcinoma (3 squamous cell, and 1 alveolar cell). Cancer was not observed in the fifth worker. There was evidence of long-standing inflammation in 4 of the lungs. All showed varying degrees of nonspecific diffuse interstitial fibrosis. Williams suggested that exposure to nickel together with chronic inflammation of the lung should be considered as the responsible carcinogenic factor.

In 1962, Passey (13) tabulated 144 deaths from cancer of lung in nickel workers of the Welsh Refinery and computed the average age at death in these workers to be 57.6 years. The average length of employment in nickel refineries was 27 years; the average time between the first exposure and death from lung cancer was 30.5 years.

In Norway, Løken (14) reported three cases of lung cancer among members of this occupational group who had been employed in electrolytic refining of nickel.

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Goldblatt and Wagstaff (15) mentioned the absence of respiratory cancers among employees of a German nickel refinery at Ludwigshafen but it may be that this refinery had not been in operation for a sufficient period to cover the average latent time of nickel cancer.

Rockstroh (16) reported an increase in respiratory cancers in German workers exposed to dust and fumes from ores containing nickel, bismuth, cobalt and large amount of arsenic in a nickel refinery. He suggested that dusts and fumes might be responsible for bronchitis and that bronchial carcinoma developed later as a result of the influence of inhaled arsenic, nickel and cobalt.

Sutherland (17) carried out a study of mortality in workers employed in an Ontario nickel refinery. Furnace workers showed the greatest risk of lung cancer and sinus cancer. The author noted that the risk of death from lung cancer in furnace workers (3 years or more exposure) is about 3.6 times that of normal. There was, however, no real evidence of any increase in electrolytic workers, workers in non-dusty areas, and office workers.

Mastromatteo (3) noted that there is no evidence of any increase in respiratory cancer among Ontario nickel miners, and no significant increase in huge Sudbury smelter complexes that have been processing the nickel ore to nickel matte since the turn of the century.

In 1965, Tatarskaya (18) reported 2 cases of cancer of upper respiratory tract in workers engaged in the electrolytic purification of nickel in the USSR.

The observations on the sequential occurence of lung cancers and nasal cancers among nickel workers thus adhere to an epidemiological pattern common to occupational and chemical cancers in general.

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B. Experimental Data

Production of cancers at various sites in experimental animals has been conducted by many investigators.

The concept of a nickel etiology of respiratory cancers was tested in animals by Campbell (19), who exposed mice to the inhalation of powdered nickel matte and observed that these animals had a lung tumor incidence significantly higher than that of the unexposed control mice.

Finely divided metallic nickel was shown to be carcinogenic to rats (20, 21). When pure nickel powder was implanted into the femoral marrow and pleural cavities, and subcutaneous tissues of 175 rats, cancer developed at the site of injection in 28 per cent of them.

Recent experiments of Hueper (22) seem to demonstrate more conclusively the carcinogenic properties of metallic nickel. Rats and guinea pigs exposed to powdered nickel developed malignant pulmonary neoplasms.

Hueper and Payne (23) administered finely powdered nickel intrapleurally to rats and produced cancer in one-third of the animals treated. Intrapulmonary deposited nickel powder produced intrapulmonary sarcoma in only one of 34 animals exposed.

The relationship between the inhalation of nickel and pulmonary cancer has been studied by Sunderman and his associates (24, 25, 26). These studies established that pulmonary cancer may be induced in rats exposed to a single heavy concentration of nickel carbonyl (200 mg./m^3) as well as in rats exposed to repeated inhalations of sublethal concentrations (30 mg./m^3, or 60 mg./m^3) for a period of a year. After one year of exposure the rats showed extensive pulmonary changes including a remarkable degree of squamous metaplasia of bronchial epithelium.

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Sunderman and Donnelly (27) indicated that inhaled nickel carbonyl is carcinogenic to the lungs of rats. The lesions included the common types of pulmonary cancer, squamous cell carcinoma, adenocarcinoma, and anaplastic carcinoma. All of the pulmonary lesions were found between 24 and 27 months after the initial exposure to nickel carbonyl.

Similiary neoplastic responses were obtained in rats subcutaneously implanted with nickel sulfide. Gilman and Ruckerbauer (28) reported sarcoma formation in rats and mice implanted intramuscularly with dust from the flue of a nickel refinery. Gilman and Basrur (29) reported that intramuscular implantation of discs of nickel sulfide resulted in a 70 to 80 % incidence of rhabdomyosarcoma in rats within 4 to 6 months. Gilman (30) also reported that nickel sulfide, nickel oxide, cobalt sulfide and cobalt oxide were carcinogenic on single intramuscular injection in rats. The sulfide of each metal induced a significantly higher tumor incidence than did its oxides.

Belobragina and Saknyn (31) exposed rats by intratracheal instillation and inhalation of furnace dusts from a nickel smelting plant in USSR. The sinter dust, which contained about 65% nickel sulfide and nickel oxide produced connective tissue nodules: electric furnace dust containing about 95% nickel oxide produced a diffuse pulmonary sclerosis. No tumors were produced.

Heath and his associates (32, 33, 34) reported that cobalt, nickel or cadmium, when injected as the powdered metal into the thigh muscle of rats, produced a high incidence of rhabdomyosarcomata, whereas a number of other metals, including iron, copper, zinc, manganese, beryllium and tungsten are not carcinogenic under these conditions. They also indicated

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that primary rhabdomyosarcomata develop in the presence of excessive local concentration of the dissolved metals induced in rats by the intramuscular implantation of powdered metallic cobalt, nickel or cadmium.

2. Iron and Its Compounds

A. Epidemiological Data

Iron is by far the most extensively used metallic element, and occupational and non-occupational exposure of man to metallic iron and its compounds is relatively common. The extensive production and use of various types of iron and of diverse iron products offers frequent opportunities for the inhalation of dust and fumes of iron and its various alloys and compounds by iron ore miners, arc welders, grinders, polishers, silver finishers, and metal workers.

The existence of a causal interelation between pulmonary siderosis and primary cancers of lung has been suggested by several epidemiological observations.

According to Kennaway and Kennaway (35), metal grinders had an excessive incidence of pulmonary malignancy, as much as 2.25-fold that of the general population. Turner and Grace (36) found that foundry workers, smiths and metal grinders had a mortality from lung cancer higher than that for any other occupational group in Sheffield.

The recent epidemiological investigations of the frequency of lung cancer among members of occupations with pulmonary siderosis (boiler scalers, hematite miners, foundry workers) reported from England suggested that the presence of siderosis confers on the lungs an increased liability to development of cancer as shown in the following studies.

Siderosis of Lung and Pulmonary Cancers

Author	Occupation	Autopsies	Lung Cancer	
		number	number	percent
McLaughlin and Harding (38)	Foundry workers	149	16	10.8
Faulds and Steward (37)	Hematite miners	180	17	9.4
Harding and Massie (40)	Boiler scalers	12	3	20.0
Faulds and Steward (37)	Controls	2220	45	2.0

Similiar observations were reported for iron ore miners in Lorraine. Braun and his associates (41) noted an incidence of bronchial cancer among iron ore miners in Lorraine which was much higher than that in control groups of workers (during a 6-year period, 64 bronchial cancers in 10,000 iron ore workers).

According to statistical data of Minnesota State Health Department (42) the number of deaths from lung cancer among iron ore miners residing in St. Louis and Ithaca County is consistently higher over a five-year period than among other residents of Minnesota as shown in the following table.

Death due to Cancer of the Lung among Iron Ore Miners and Residents of Minnesota

Year	Number of deaths		Death rate per 100,000	
	Minnesota residents	St. Louis Ithaca county miners	Minnesota residents	St. Louis Ithaca county miners
1950	328	5	11.0	37.6
1951	289	4	9.7	30.0
1952	329	12	11.0	90.1
1953	367	8	12.3	60.1
1954	345	6	11.6	60.1

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The studies of Breslow, Hoaglin, Rasmussen, and Abrams (43) on the 518 histologically-proved cases of lung cancer in California suggested the existence of an increased liability to lung cancer for members of the following occupational groups; welders, sheet steel workers, steam-fitters, boilermakers, crane operators, and nonferrous metal smelter workers, that is, individuals who are exposed to metal dusts and fumes.

Dunner and his associates (44, 45, 46) reported high frequency rate of lung cancer among boiler scalers, for example, 5 lung cancers among 17 cases of pneumoconiotic scalers. It may be possible that boiler scalers sustain a carcinogenic exposure to chromate-containing scale, if chromates were used as anti-rusting agents, or that these workers sustain a pulmonary deposition of iron oxides.

The three cases of lung cancer discovered by Vorwald and Karr (47) among 15,587 workers roentogenologically examined were iron miners. Their ages were 59, 64 and 68 years and period of occupational exposure to hematite dust was 27, 35, and 43 years, respectively.

Levin and his co-workers (48) recorded a positive statistical correlation between an occupational exposure to iron oxide and heat and cancer of lung.

In summary, there is a considerable body of evidence to suggest that there is a specific industrial hazard from exposure to iron dust or fumes. None of it, however, is conclusive and at the present time the case must be regarded as not proven.

B. Experimental Data

Experimental studies on animals exposed to iron oxide and hematite, respectively, gave contradictory results as to the production of lung

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tumor. While Vorwald and Karr (49) using guinea pigs and rats, failed to obtain lung cancers with hematite dust, Campbell (50) reported that there was an increase of lung tumors in mice inhaling iron oxide dust (32.7% in experimental mice against 9.6% in control).

Hueper (51) reported the negative experimental observation of cancerous response around intramuscular and intrapleural depots of finely powdered iron.

Saffiotti and his associates (52, 53, 54, 55) recently reported repeated intratracheal instillations of benzo(a)pyrene with hematite dust induce up to 100% incidence of respiratory tract tumors, mostly bronchogenic carcinoma. The morphology of these tumors appears very close to that of human lung cancer; squamous cell carcinoma are the most frequent type followed by anaplastic carcinomas and by a few adenocarcinomas. In a group exposed to hematite alone, however, two of 48 showed peripheral bronchiolar adenomatoid lesions.

The production of sarcoma in the subcutaneous tissue of mice, rats, hamsters, and rabbits injected repeatedly with large amount of iron-carbohydrates (dextran, polymaltose, destrin) has been reported (56, 57, 58).

Twenty-four subcutaneous injections of 0.5 ml. of iron dextran given at weekly intervals to rats, was followed by sarcomata irrespective of whether the injected material was given always into the same site, or whether it was distributed between 2, 4, or 6 sites (59).

Two iron complexes, Muscularon and Imferon, were tested for carcinogenecity in mice by intramuscular and subcutaneous injections. Ten injections of 3 different doses were used to determine the most tolerable nontoxic dose without any carcinogenic effect. Out of 101 mice treated with Imferon, one hybrid mouse developed a transplantable

fibrosarcoma. The administration of Muscularon by two different routes caused six tumors in 153 mice. The use of iron complexes as a therapeutic drug in iron deficiency anemias requires further consideration, since the iron is localized at the injection site (60).

Subcutaneous implants of aluminium foil induced sarcomas in 8 of 18 rats, but no sarcomas developed in 25 rats similiarly implanted with rough-surfaced iron chips and observed for 25 months (61). The possible reasons for the different responses of the iron and aluminium implants are discussed: it is concluded that a smooth-surfaced implant expedites the induction of sarcomas. Of 25 additional rats receiving 3 subcutaneous injections of a suspension of powdered iron scales, 1 developed sarcoma at the injection site. Mice receiving a single injection of powdered iron scales as newborns did not differ materially from control mice after 21 months observation. It is concluded that iron is only weakly carcinogenic to the rodent.

Williams (62) investigated the relationship between pulmonary fibrosis, metapalasia of the alveolar lining cells and carcinoma of the lung. He found a significant relationship between fibrosis and metaplasia, but none between metaplasia and carcinoma.

Sagaidak (63) observed the development of chronic bronchitis and bronchogenic carcinoma in rats intrathecally injected with solution of radioactive ferrous citrate and suspension of ferrous oxide in physiologic saline.

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III. MATERIALS AND METHODS

1) Animals

The experimental animals were male albino rats of Wistar strain, weighing either from 110 to 150 grams or 350 to 450 grams, depending upon age. A total of 287 rats was employed in this study. All rats were fed a standard commercial diet from Master Laboratory Cubes, Toronto, Canada. The rats were weighed and injected with streptomycin sulphate, 25 mg. per 150 grams of body weight, as a prophylactic, bimonthly.

Twenty rats from random sampling were killed and the lungs were examined before the experimental part of this study was commenced. All of them had normal lungs.

The number of rats used in each dust-group is summarized in Table I.

Table I: Experimental Animals and Dusts

Groups	Dusts	No. of Rats			
		Start	Died	Killed	Continuous Experiment
Group I	Ni	77	12	29	36
Group II	Ni+Dust C+Fe_2O_3+FeS	76	13	23	40
Group III	Fe+Fe_2O_3+FeS	67	11	29	27
Group IV	Control	67	5	33	29

2) Dusts

The dusts used in this experiment can be described as follows:

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Group I: Metallic nickel dust

This powdered nickel dust was obtained from the International Nickel Company of Canada, Limited.

Group II: This dust was prepared by milling a mixture of equivalent weight of each following dusts:

Metallic Nickel Dust
Dust C*
Hematite (Fe_2O_3)
Pyrrhotite (FeS)

* Dust C is a synthetic dust prepared by mixing the following chemical compositions:

$NiSO_4.6H_2O$	24.1%
Ni_3S_2	68.7%
NiO	7.2%
	100.0%

Group III: This dust was prepared by mixing an equal weight of each of the following dusts:

Metallic Iron Dust
Hematite
Pyrrhotite

3) Exposure Conditions

The dust dispersal machines and exposure chambers previously described by Fisher and Christie (64) were employed in this study.

In brief, dispersal of dust was accomplished by dilution of 1 gram of the dust with 1000 grams of nickel shot. The dust was separated therefrom and transferred to the exposure chambers at constant rate without change in particle size by air flowing at the rate of 108 cubic feet per hour. This rate of air supply was greatly in excess of minimum requirement for maintenance of the animals.

Dust exposure was conducted for 6 hours a day, 5 days a week.

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When animals were being exposed to the dusty atmosphere the front of each chamber was closed with a wooden door equipped with a window and a sampling orifice. The dust-tight doors were replaced by wire screens during periods of not exposure. Control animals were housed in ordinary cages.

4) Dust Counts and Determination of Particle Size

Dust counts of air in the exposure chambers were made with a Bausch and Lomb Dust Counter modified for operation with 5-cc or 10-cc air samples having high dust concentration. The measurements have been conducted from time to time. The samples were taken from a small opening in the front of cages, midway between top and bottom.

Determination of size-distribution of particles has been made by microscopic method in comparison with the sizes of the circles above or below the oblong eyepiece graticule calibrated with microscopic micrometer.

Dust counts of the air in the rat cages are presented in Table 2:

Table 2: Dust Counts

Group	Dust	No. of Samples	Million Particles per cu. ft.	Standard Deviation
Group I	Ni	186	5.16	1.40
Group II	Ni+Dust C+Fe_2O_3+FeS	145	8.52	2.55
Group III	Fe+Fe_2O_3+FeS	198	15.90	3.91

The particle size of dust in the experimental atmospheres of cages of the various groups is shown in Table 3.

Table 3: Particle Size Distribution of Dust

Group	Dust	Cumulative %			
		< 0.25μ	< 0.5μ	< 1.0μ	< 2.0μ
Group I	Ni	36.9	65.5	88.9	97.8
Group II	Ni+Dust C+Fe_2O_3+FeS	43.0	72.4	91.5	98.7
Group III	Fe+Fe_2O_3+FeS	50.1	79.8	95.2	99.9

5) Determination of Nickel and Iron

Spectrophotometric methods for the determination of nickel and iron in air and lung tissue were employed (65, 66, 67).

In brief, nickel was separated from interfering elements by chloroform extraction of nickel dimethyl-glyoxime, and converted to the diethyldithiocarbamate complex, yellowish green in colour, and extracted with isoamyl alcohol. The nickel is determined in this solution by spectrophotometric measurement of the concentration of the yellowish green complex at 385 mμ.

Determination of iron in air and biological materials employed the reaction of ferrousion with 4,7-diphenyl-1,10-phenanthroline, bathophenanthroline. This forms a coloured complex, with an intensity proportional to the amount of iron present and which may be extracted by chloroform. This coloured complex is measured by spectrophotometric method at 538 mμ.

Nickel and iron concentration is exposure cages is shown in Table 4.

Table 4: Nickel and Iron Concentration in Cages

Group	No. of Samples	Nickel (mcg./cu. ft.) Average	S.D.	Iron (mcg./cu. ft.) Average	S.D.
Group I	41	87.3	8.06	-	-
Group II	16	59.5	5.60	53.2	5.70
Group III	21	-	-	85.0	6.50

6) Pathological Examinations

Pathological examinations were conducted on rats which died and others which were killed by a blow on the head. The lungs were examined in the gross for abnormality. From all experimental rats, samples of lung tissue were embedded in paraffin and paraffin sections 5 microns thick have been made with microtome and stained with haematoxylin-eosin for microscopic examination.

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IV. RESULTS

Death Distribution. The death distribution of rats in the various experimental groups is presented in Table 5. At the end of 21 months of experiment, the total number of deaths in the nickel-containing dust group (Group I) was 12. In the nickel-iron-containing dust group (Group II) 13 rats died and 11 rats died in the iron-containing dust group (Group III). By comparison, the total number of deaths among control rats was 5.

Table 5. Death Distribution of Rats

Group	No. of rats start	No. of death rats				Total
		0-6 months	7-12 months	13-18 months	19-21 months	
Group I (Ni)	77	3	0	4	5	12
Group II (Ni+Dust C+Fe_2O_3+FeS)	76	3	4(1)*	3	3(2)	13
Group III (Fe+Fe_2O_3+FeS)	67	0	1	4(1)	6(2)	11
Control	67	0	0	3	2	5

* Parenthesis shows the number of sub-group rats which were exposed to dust for 7 months followed by fresh air in each period of exposure.

Body Weight. In Table 6 and Figure 1 the mean weight of rats exposed to various dust groups is compared with the mean weight of the control rats. This comparison was made on the young rats as experiment commenced. It will be seen that the mean weight of the exposed rats was less than that of control rats throughout the entire period of study. At the end of

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22 months of experiment the mean weight of surviving rats in the nickel-containing dust group (Group I) was 611 grams; the average weight was 621 grams in the nickel-iron-containing dust group (Group II) and the average weight was 635 grams of the iron-containing dust group (Group III). By comparison, the mean weight of surviving control rats at the end of 22 months of experiment was 691 grams. From 16 months of experiment, the reduction rate of body weight of rats in dust exposure groups showed greater than that of the control rats.

Table 6: Body Weight (in grams) of Rats Exposed to Various Atmospheres

Group	Months from initial exposure											
	0	2	4	6	8	10	12	14	16	18	20	22
Group I (Ni)	125	358	445	496	540	574	612	626	637	635	630	611
Group II (Ni+Dust C+Fe_2O_3+FeS)	125	370	448	496	548	592	638	661	669	651	630	621
Group III (Fe+Fe_2O_3+FeS)	125	345	445	520	560	592	621	648	677	670	648	635
Control (Fresh Air)	125	380	481	543	598	635	660	681	695	699	695	691

Lung Weight. The changes of wet lung weight of rats exposed to experimental atmospheres are shown in Table 7. The average of wet lungs weight of rats exposed to nickel-containing dust (Group I) was 1.7 times that of the average weight of wet lungs of control rats throughout the entire period of experiment. The average wet weight of the lungs of rats exposed to the nickel-iron-containing dust (Group II) was 2.0 times that of the control group. In the iron-containing dust group (Group III) the corresponding figure was 1.4 times that of the control group. In rats first

exposed to dust for 7 months and then to fresh air for 11 or 14 months, there was no increase of wet lungs weight over that of rats exposed to dust for 7 months.

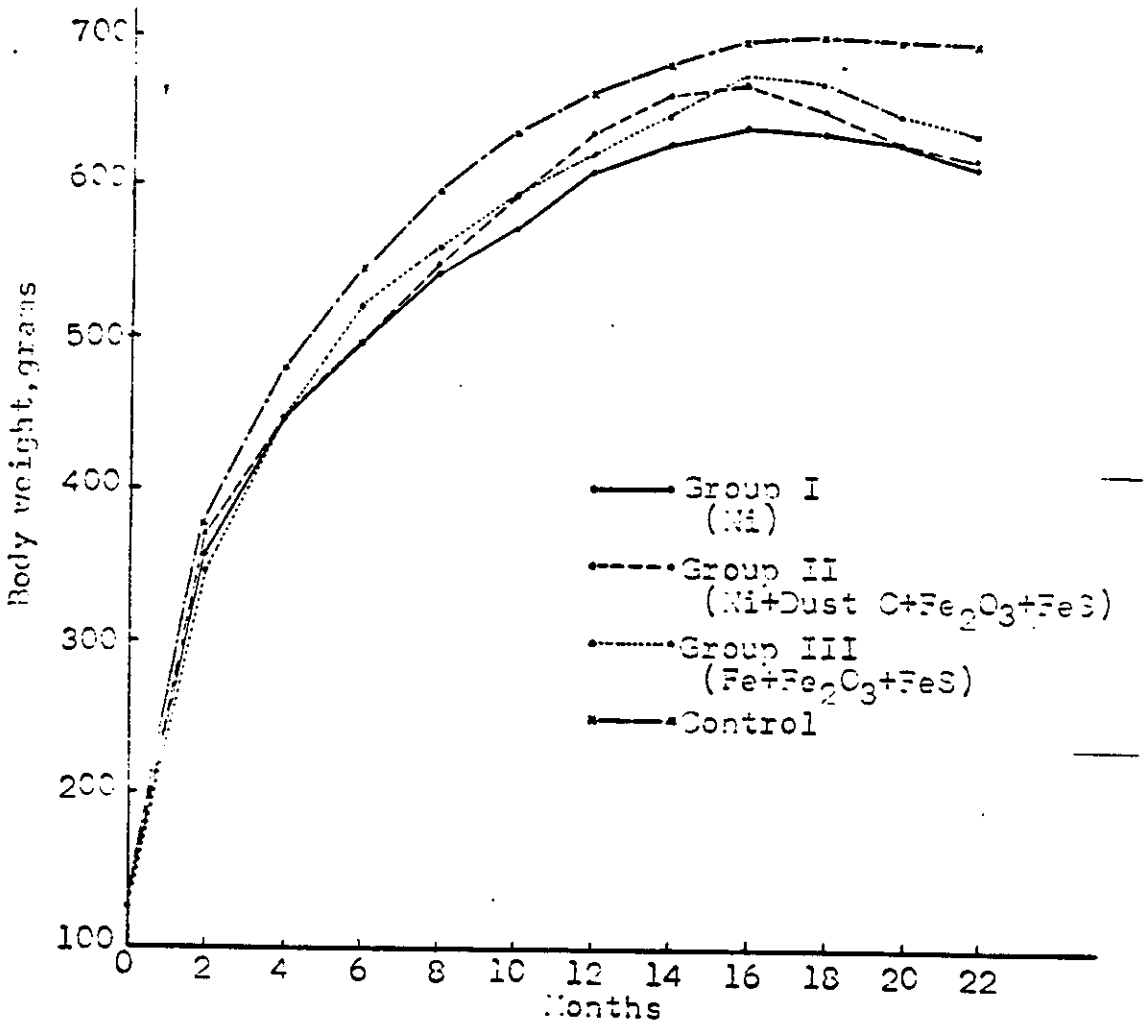

Figure 1: Body Weight of Rats Exposed to Various Atmospheres.

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Table 7: Wet Lung Weight of Rats Exposed to Various Atmospheres

Group		Exposure					
		*A		*B		*C	
		No. of Rats	Lung Wt. (grams)	No. of Rats	Lung Wt. (grams)	No. of Rats	Lung Wt. (grams)
Group I (Ni)	Continued	10	5.12	12	6.60	11	7.85
	Sub-group	-	-	2	5.75	6	5.02
Group II ($Ni+Dust\ C+Fe_2O_3+FeS$)	Continued	10	5.77	9	8.53	9	8.90
	Sub-group	-	-	4	5.75	4	6.27
Group III ($Fe+Fe_2O_3+FeS$)	Continued	10	4.78	10	5.23	11	5.35
	Sub-group	-	-	2	4.60	7	5.11
Control		10	3.27	10	3.65	18	4.47

*A (Exposure A): Exposure to dust for 7 months followed by 3 months fresh air

*B (Exposure B): Exposure to dust for 7 months, fresh air for 5 months and dust for 6 months

*C (Exposure C): Exposure to dust for 7 months, fresh air for 5 months, dust for 6 months and fresh air for 3 months

Nickel Content of Rat Lungs. Nickel content of rat lungs exposed to dust atmosphere is given in Table 8. Nickel concentration of the lungs has increased in accordance with nickel concentration of the air in exposure chambers and the duration of exposure. In the rats exposed to the nickel-containing dust for 7 months followed by 3 months of fresh air (Exposure A), nickel content of the lungs was 19 times that of control rats. In the exposure to nickel-containing dust for 7 months, fresh air for 5 months and nickel-containing dust for 6 months (Exposure B

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the average nickel content of the lungs was 45 times that of the control group. In instances when the schedule of Exposure B was followed by 3 month exposure to fresh air (Exposure C) the average nickel content of rat lungs was 40 times that of control group. In the nickel-iron-containing dust exposure group, the average nickel concentration of rat lungs was 17 times in Exposure A, 32 times in Exposure B and 29 times in Exposure C that of control group, respectively.

In the exposure to nickel-containing dust or nickel-iron-containing dust for 7 months followed by fresh air for 11 months or 14 months, the average nickel concentration of rat lungs was decreased from that of rats exposed to dust for 7 months and then killed.

Table 8: Nickel Content of Rat Lungs Exposed to Various Atmospheres

Group		Exposure					
		A		B		C	
		No.of Rats	Lung Nickel mcg(Ni)	No.of Rats	Lung Nickel mcg(Ni)	No.of Rats	Lung Nickel mcg(Ni)
Group I (Ni)	Continued	10	280.2	10	575.7	11	531.1
	Sub-group	-	-	-	-	6	237.0
Group II (Ni+Dust C+Fe_2O_3+FeS)	Continued	10	246.0	9	406.0	9	389.4
	Sub-group	-	-	4	202.5	4	181.2
Group III (Fe+Fe_2O_3+FeS)	Continued	10	39.2	8	53.9	11	53.2
	Sub-group	-	-	2	30.8	7	24.2
Control		10	14.8	10	12.7	18	13.3

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Iron Content of Rat Lungs. Iron content of rat lungs in various experimental groups is presented in Table 9. The average iron concentration of rat lungs exposed to iron-containing dust for 7 months followed by 3 months of fresh air (Exposure A) was 6.0 times the average iron concentration of lungs of control rats. In the exposure to iron-containing dust for 7 months, fresh air for 5 months and iron-containing dust for 6 months (Exposure B), the average iron concentration of the rat lungs was 6.3 times that of control rats. In instances when the schedule of Exposure B was followed by 3 months exposure to fresh air (Exposure C), the average iron concentration of rat lungs was 5.2 times that of control group.

In nickel-iron-containing dust exposure group, the average iron concentration was 4.4 times in Exposure A, 4.6 times in Exposure B, and 3.3 times in Exposure C against the average iron content of the rat lungs of control group, respectively.

The high iron content of rat lungs was reduced following extended exposure to fresh air, a similar observation was made in respect of rats exposed to nickel-containing dust.

Table 9. Iron Contents of Rat Lungs Exposed to Various Atmospheres

Group		Exposure					
		A		B		C	
		No.of Rats	Lung Iron mcg(Fe)	No.of Rats	Lung Iron mcg(Fe)	No.of Rats	Lung Iron mcg(Fe)
Group I (Ni)	Continued	10	891.4	10	1210.1	11	1322.0
	Sub-group	-	-	-	-	6	819.8
Group II (Ni+Dust C+Fe_2O_3+FeS)	Continued	10	2730.0	9	3668.3	9	2752.3
	Sub-group	-	-	4	2145.0	4	2003.8
Group III (Fe+Fe_2O_3+FeS)	Continued	10	3692.4	8	4802.5	11	4420.0
	Sub-group	-	-	2	3580.0	7	3155.7
Control		10	615.2	10	794.0	18	846.0

Pathological Examinations

1) Nickel-Containing Dust Exposure Rats (Group I)

Exposure	No. of Rats	Time on Experiment
A	10	Dust 7 months exposure followed by 3 months fresh air.
B	14	Exposure A + Two months fresh air and 6 months dust exposure
C	10 *(6)	Exposure B + Three months fresh air

* The parenthesis shows the number of sub-group rats which had been exposed to dust for 7 months followed by 14 months fresh air.

Exposure A

Gross Description: The lungs are of normal size and configuration, and vary in weight from 3.5 g. to 6.5 g., with a mean weight of 5.1 g. The pleural surface was smooth and there were no adhesions, and the only consistent gross finding was the presence of small subpleural yellowish-white plaques which varied from 1-2 mm. in diameter. The bronchi and pulmonary vessels appeared normal.

Microscopic Description: There was a marked histiocytic infiltration within most of the lungs, the alveoli tending to be packed with histiocytes which were large and foamy, and contained dust particles. In occasional rats the histiocytic response showed a tendency to localize in peri-bronchial and subpleural locations, but in the majority of the rats the response was diffuse. The bronchi were lined by ciliated, columnar epithelium and the pulmonary vasculature was normal.

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Exposure B

Gross Description: The lungs were slightly enlarged, the average weight being 6.6 g., varying from 5.0 g. to 8.0 g. The pleural surface was again smooth and there were numerous yellowish dust plaques sub-pleurally, which were tending to become confluent, and most of the plaques measured 0.5-1 cm. in diameter. The bronchi and pulmonary vessels were normal.

Microscopic Description: The alveoli are, for the most part, packed with foamy histiocytes which, in some instances, are vacuolated and appear to contain lipoid material, and occasional small peribronchial lipoid granulomas, made up of giant cells and histiocytes with lipoid crystals being seen. These granulomas are small and often in direct relationship to a small blood vessel or bronchus. In one rat of this group (AEC2) there is tumor of carcinoid pattern in the lung. In three rats in this group there are severe bronchiectasis and pneumonia present with early squamous metaplasia of bronchial lining. In the remainder of the group the bronchi are lined by normal ciliated epithelium.

Exposure C

Gross Description: The lungs averaged 7.9 g. in weight, and were covered by smooth pleura with no adhesions. The pleural surface was studded with plaques which were becoming confluent and were faintly yellowish. On cross section of the lung there were also present yellowish plaques which measured up to 3 mm. in diameter on the cut surface. The bronchi, for the most part, appeared normal.

In two rats of this group there were tumours present - AFCF had a small tumour mass at the hilus of the left lung which measured 1 cm. in diameter, and was white and firm. Another rat - AAA3 had a tumour mass 1 cm. in diameter in both the right and left upper lobes of the lung, and there

was a large oval tumour mass in the mesentery of the colon which was white and firm and measured 5 cm. in diameter.

Microscopic Description: In the 9 rats in this group in which no tumour was present, there were very numerous subpleural and peribronchial and perivascular lipoid granulomas present which occasionally reached 0.5 cm. in diameter. In addition there was a varying degree of diffuse histiocytic response through the remainder of the lung, the histiocytes being large with eosinophilic vacuolated cytoplasm. In these rats the bronchi were lined by ciliated columnar epithelium. Occasional rats showed a moderate degree of hyperplasia. There was no tumour formation.

In rat AFCF the tumour mass was irregularly spherical. It was made up of columns and cords of cells with eosinophilic cytoplasm and round or oval hyperchromatic nuclei. The columns and cords were arranged in a carcinoid pattern. The lesion was solitary and there was no evidence of lymphatic permeation..

In rat AAA3 the mesenteric tumour was in a lymph node and there were large areas of necrosis present. The remainder of the node was made up of sheets of atypical cells with large hyperchromatic nuclei and occasional mitotic figures. The appearance is that of a lymphosarcoma and the discrete lesions in the right and left upper lobes were similar.

Exposure C: Sub-group

This sub-group consisted of 6 rats which had been exposed to dust for 7 months, and to fresh air for 14 months.

Gross Description: In this group the lungs averaged 5.0 g. in weight and there were no tumours present. The pleural surface of the lungs was dotted with small yellowish sub-pleural plaques, but the parenchyma appeared normal.

Microscopic Description: There were small peribronchial and subpleural aggregates of histiocytes containing dust which had occasionally formed small lipoid granulomas. The bronchi were lined by intact mucosa of the ciliated type.

2) Nickel-Iron Containing Dust Exposure Rats (Group II)

Exposure	No. of Rats	Time on Experiments
A	10	Same as the nickel-containing dust exposure group (Group I)
B	13	
C	9 (4)	

Exposure A

Gross Description: This group is made up of 10 rats. The average lung weight was 5.7 g. The lungs were covered by smooth pleura in which there were yellowish plaques which varied from 1 mm. to 4-5 mm. in diameter, and varied from being discrete to becoming confluent. The parenchyma occasionally contained discrete plaques of yellowish consolidation which were up to 1 mm. in diameter. The bronchi and trachea were normal. Occasional rats had some small mediastinal and perihilar lymph nodes, the largest measuring 0.8 cm. in diameter.

Microscopic Description: In almost all of the rats there was a diffuse histiocytic response, the histiocytes being large with eosinophilic vacuolated cytoplasm, and many of them contained dust particles. In several rats the aggregates of histiocytes were more discrete with areas of intervening normal lung, but no granulomas formed. The lymph nodes showed evidence of chronic lymphadenitis and one lymph node contained particles of dust within histiocytes in the sinuses of the lymph nodes.

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Exposure B

Gross Description: This group was made up of 13 rats with an average lung weight of 8.5 g. The pleural surface of the lungs were studded with yellowish plaques which were becoming confluent, and on the cut surface of the lungs there were occasionally small discrete areas of yellowish consolidation which measured up to 1-2 mm. in diameter. The bronchi appeared normal.

Microscopic Description: There was a widespread histiocytic infiltration of the alveolar spaces with a slight tendency for this to be accentuated in the subpleural, peribronchial and perivascular spaces. No granulomas had formed. There were no tumours present in any of these rats.

Exposure C

Gross Description: This group was made up of 9 rats, the average lung weight being 8.9 g. The pleural surface was studded with plaques which were yellowish-white and tended to become confluent and there were areas of yellowish consolidation scattered throughout the parenchyma. The bronchi appeared normal and there were no gross tumours present in this group.

Microscopic Description: In all of this group there were present aggregates of dust in peribronchial, perivascular and subpleural areas with some histiocytes diffusely throughout the lung field containing dust. In many of the rats there were small granulomas of the lipoid type present and these again were in the peribronchial, perivascular and subpleural areas. There was no tumour seen.

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Exposure C: Sub-group

Gross Description: This sub-group was made up of 4 rats. The average lung weight was 6.3 g. The pleural surface revealed numerous tiny yellowish subpleural plaques with no visible dust in the parenchyma. The bronchi appeared normal.

Microscopic Description: The dust tended to be gathered into subpleural, peribronchial and perivascular areas and was present within histiocytes in the alveoli, and there were a few small lipoid granulomas in the usual peribronchial, perivascular and subpleural sites. There were no tumours present in this group.

3) Iron-Containing Dust Exposure Rats (Group III)

Exposure	No. of Rats	Time on Experiment
A	10	Same as the nickel-containing dust exposure group (Group I).
B	10	
C	11 (7)	

Exposure A

Gross Description: There were 10 rats in this group with an average lung weight of 4.8 g. The pleural surface of the lungs was smooth and there were numerous yellowish-white plaques which varied from very tiny pinpoint size to 0.5 cm. in diameter, and they were tending to become confluent. In occasional rats there were areas of yellowish consolidation within the parenchyma, but for the most part the aggregates appeared to be subpleural in the gross.

Microscopic Description: There was a very marked histiocytic response which tended to be subpleural and peribronchial, and there were large aggregates of dust within the histiocytes which, for the most

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part, were more apparent in the peribronchial areas. No granulomas were seen.

Exposure B

Gross Description: This group was made up of 12 rats with an average lung weight of 5.2 g. The pleural surface was relatively smooth and only occasional tiny 2-3 mm. plaques were visible in the immediate subpleura. The cut surface of the lungs was congested and there was no evidence of consolidation. The bronchi were normal.

Microscopic Description: There was present a diffuse histiocytic response which, however, for the most part tended to be more marked in the peribronchial, perivascular and subpleural spaces. In one rat of this group (CEBD) there is bronchiactasis and squamous metaplasia. There was no evidence of granuloma formation. The bronchi appeared normal and no tumours were seen.

Exposure C

Gross Description: This group was made up of 11 rats, the average lung weight being 5.4 g. The pleural surface was, for the most part, smooth, and there were scattered small, subpleural visible dust plaques. One rat CAC3 whose lungs weighed 8.3 g. had multiple small tumour masses measuring up to 0.75 cm. in diamter present in both lungs. Another rat CEBF had a large necrotic tumour mass present in the liver which measured 2 cm. in diameter and was sharply circumscribed from the surrounding liver. The lungs showed no evidence of tumour in the gross.

Microscopic Description: In the 9 rats in which no tumour could be seen in the gross there was no visible tumour microscopically. The dust was gathered into focal aggregates and in only one rat were small lipoid granulomas seen. In rat CAC3, the lesions were circumscribed

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and were made up of papillary masses of cells with eosinophilic cytoplasm and fairly regular round or oval hyperchromatic muclei. The appearance, again, was that of a carcinoid type of tumour and there were multiple areas in both lungs with some small central areas of necrosis. No relationship could be established to a main bronchus. CEBF revealed a large tumour mass in the liver with a somewhat similar architecture to that seen in the carcinoid like tumours in the lungs. There was, however, no tumour present in the lungs in this rat. In the liver tumour there were large areas of necrosis present, and occasional cells showed mitotic figures and there were occasional giant tumour cells present with very bizarre muclei.

Exposure C: Sub-group: This sub-group was made up of 7 rats, with an average lung weight of 5.1 g. For the most part the lungs in this group were dotted with small plaques of yellowish subpleural thickening. The parenchyma appeared normal. In rat S-CCBE there was a tumour mass 1.5 cm. in diameter in the right lower lobe. The lesion was circumscribed and, again, no gross relationship to a bronchus could be made out.

Microscopic Description: In the 6 rats in which no tumour mass was present there were focal aggregates of dust which tended to be peribronchial, subpleural and perivascular. No granulomas were seen. Rat S-CCBE had a well differentiated papillary adenocarcinoma present in the right lower lobe.

4) Control Group

The control group consisted of 38 rats which were exposed to fresh air continuously for from 10 to 21 months. The average weight of the lungs was 3.8 g. and the lungs appeared normal with two exceptions. Rat DAB2 exposed to air for 21 months had some small subpleural plaques

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and within the microscopic examination there were some small focal lesions with dust and some small subpleural granulomas. There were some areas of bronchiectasis present in this rat. Rat BICF had what appeared to be normal lungs on gross examination. On microscopic examination there was present a small focal tumour mass which was irregularly spherical and lobulated and the tumour was made up of columns and cords of cells with eosinophilic cytoplasm and round or oval, fairly regular, nuclei. The appearance was that of a carcinoid like tumour.

Plate 1: Very marked peribronchial granulomas in the lung of rat BACD exposed to nickel-iron-containing dust (Group II) for 7 months, fresh air for 5 months, nickel-iron-containing dust for 6 months and fresh air for 3 months. X80.

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Plate 2 : Lung from rat AFCD exposed to nickel-containing dust (Group I) for 7 months, fresh air for 5 months and nickel-containing dust for 6 months. Bronchiectasis and squamous metaplasia. X32 & X200.

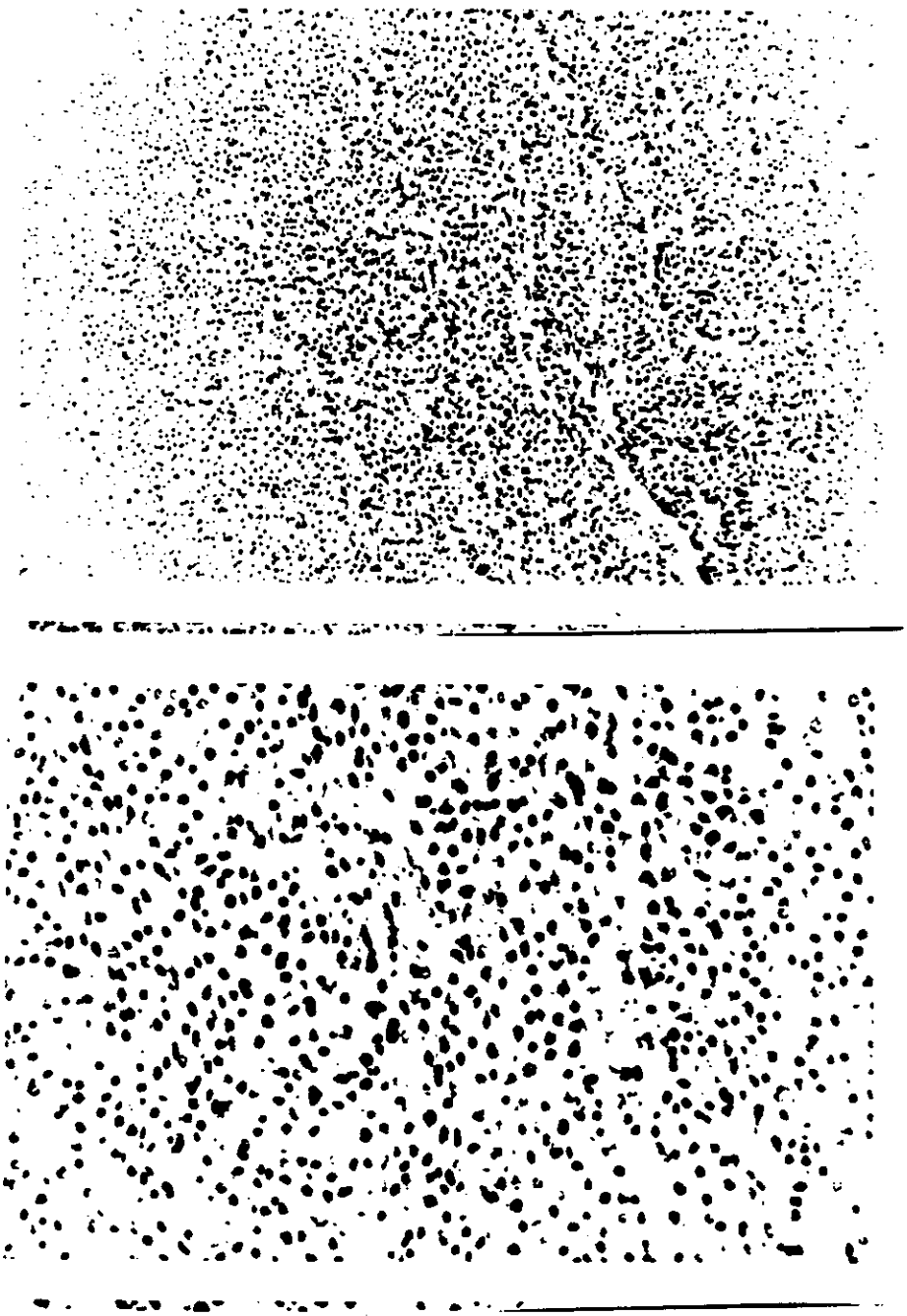

Plate 3 : Lung from rat AEC2 exposed to nickel-containing dust (Group I) for 7 months, fresh air for 5 months and nickel-containing dust for 6 months. Tumor in lung carcinoid pattern. X80 X200.

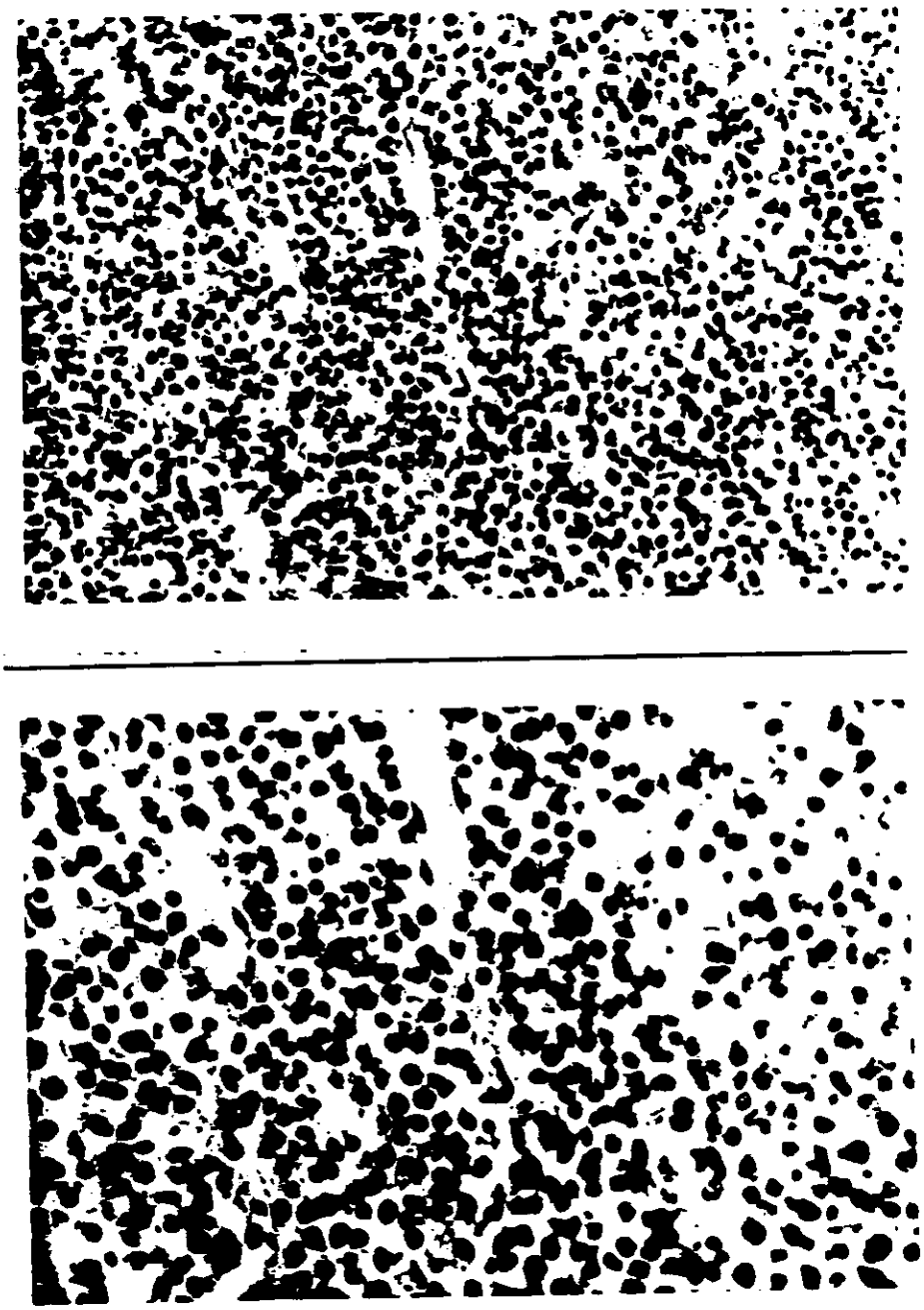

Plate 4 : Lung from rat AAA3 exposed to nickel-containing dust (Group I) for 7 months, fresh air for 5 months, nickel-containing dust for 6 months and fresh air for 3 months. Lymphosarcoma in the lung. X200 & X320.

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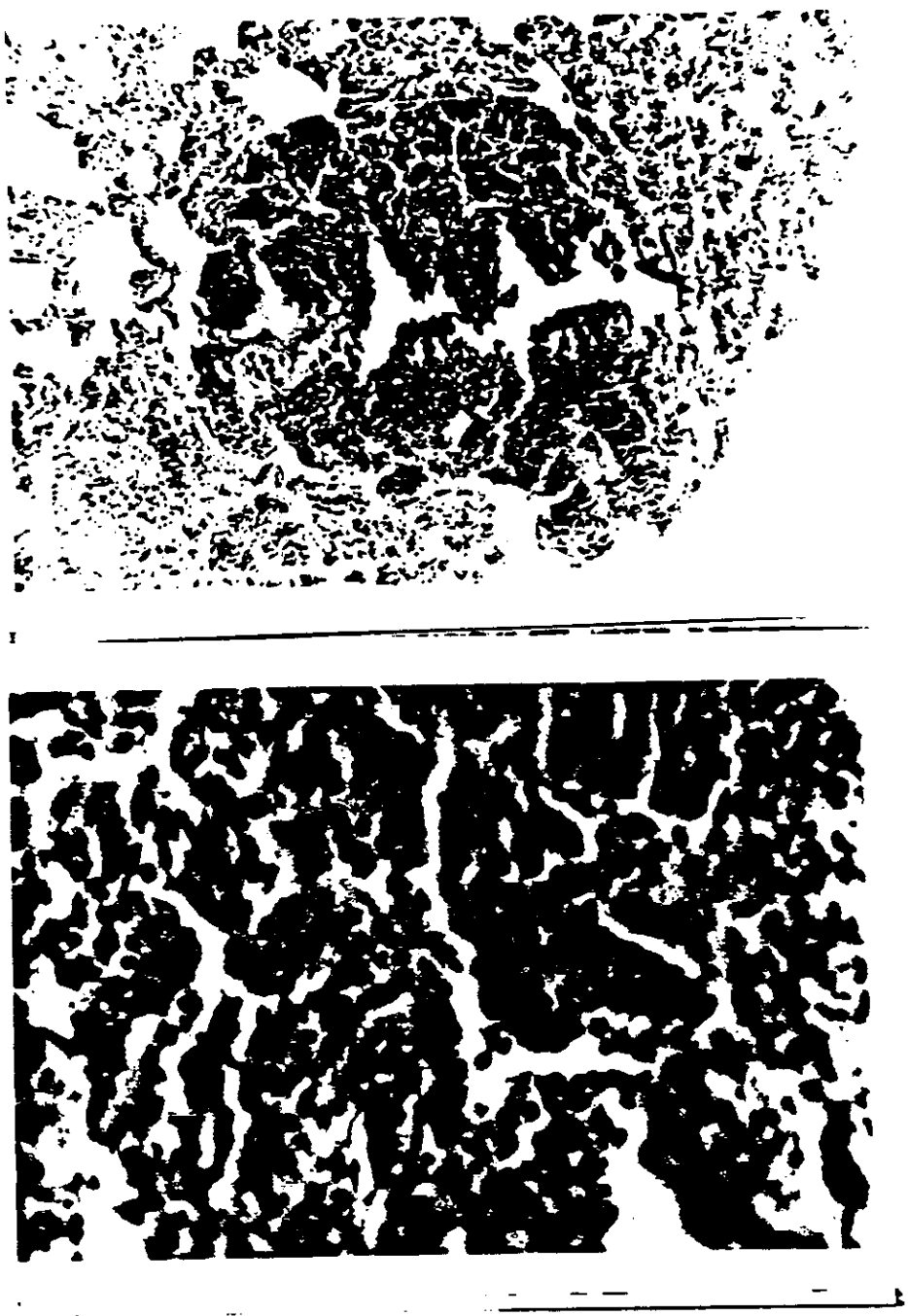

Plate 5 : Lung from rat CEBF exposed to iron-containing dust (Group III) for 7 months, fresh air for 5 months, iron-containing dust for 6 months and fresh air for 3 months. Tumor in lung carcinoid pattern. X80 & X320.

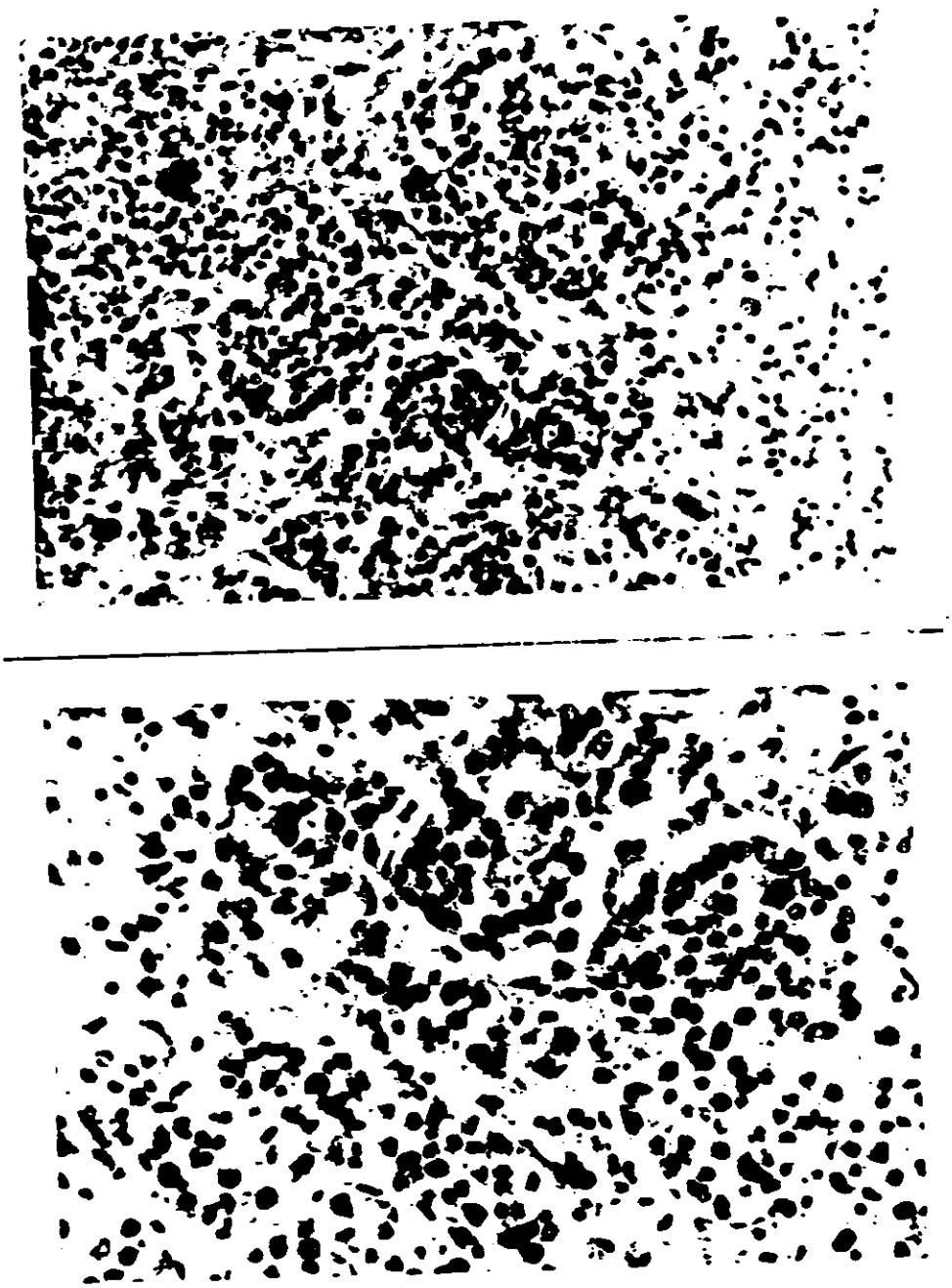

Plate 6 : Lung from rat CAC3 exposed to iron-containing dust (Group III) for 7 months, fresh air for 5 months, iron-containing dust for 6 months and fresh air for 3 months. Tumor in lung carcinoid pattern. X200 & X320.

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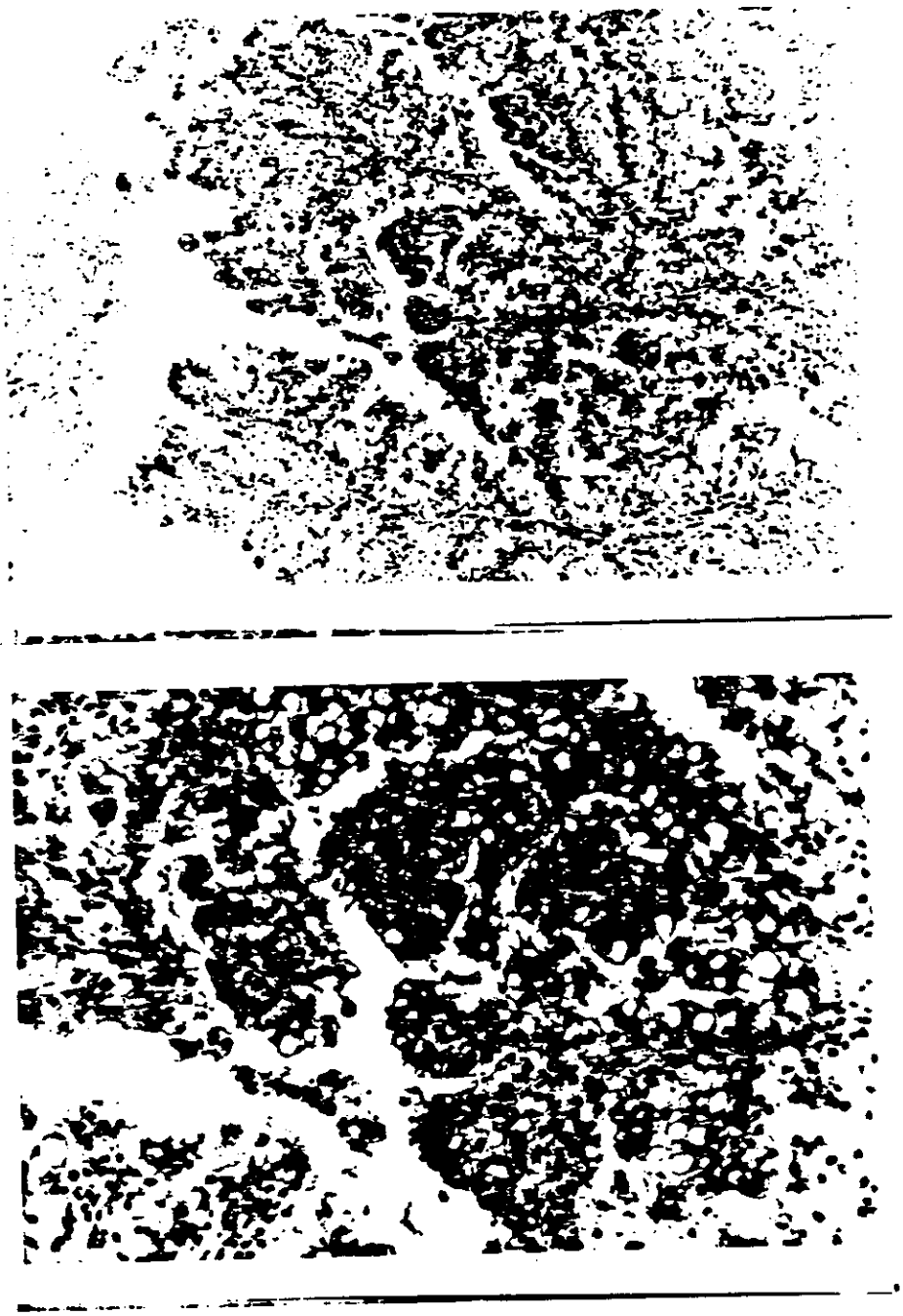

Plate 7 : Lung from rat S-CCBE exposed to iron-containing dust (Group III) for 7 months and fresh air for 14 months. Papillary adenocarcinoma. X80 & X 200.

Plate 8 : Lung from control group BICF exposed to fresh air for 21 months. Lymphatic permeation and carcinoid like tumor of lung. X 320.

V. DISCUSSION

The results which have been presented show the effects in rats of exposure for a period of 21 months to metallic dusts containing nickel and/or iron. The prime purpose was to determine whether or not pulmonary cancer would follow such exposure. Under the conditions of the experiment, there is no support for the suggestion that, in rats, lung cancer is the result of direct carcinogenic action of the inhaled dust.

There are references in the literature (20, 21) showing that finely divided metallic nickel is carcinogenic to rats when injected into the femoral marrow cavity, the pleural cavity, the nasal sinus, intramuscularly, or subcutaneously. These experiments of carcinogenesis are open to much question ever since Schinz and Uelinger (68) first showed in 1941 that injection of arsenic, chromium, and cobalt into the femur of rabbits produced metatasizing sarcomas and an adenocarcinoma. Heath (69, 70) reported that metallic cobalt injected intramuscularly produced sarcoma in rats. O'Gara (61) reported that subcutaneous implants of aluminium foil induced sarcoma in 8 of 18 rats.

Negative experimental observations recorded by Hueper and Payne (51) also support the experimental results of the present work. In their study rats and hamsters inhaled finely divided nickel powder and sulphur dioxide together. No tumours were produced by this combination. Previous experiments in this department by Christie and Fisher (71) showed no good evidence of the induction of pulmonary tumour following prolonged inhalation of metallic dusts by rats. They used nickel refinery dust, a synthetic metallic dust which was the same as used in this experiment, iron sulfide, cobalt sulfide, and nickel sulfide. Eleven of 348 exposed

rats developed lung tumours as did 3 of 85 controls. Sixteen of the exposed rats showed squamous metaplasia of the bronchial epithelium; this was also observed in 1 rat in control group. In general, the chronic inhalation of nickel refinery dust, the synthetic dust, iron sulfide, and nickel sulfide was associated with the occurence of lung tumour and squamous metaplasia in rats, but the significance of this is difficult to assess because of similar changes in control group rats.

The results of the present experiment in which rats inhaled nickel-containing dust, nickel-iron-containing sut, and iron-containing dust was not surprising because simultaneously conducted experiments on rats exposed to inhalation of fumes generated by the application of heat from carcinogenic coal tar and petroleum asphalt containing irritative constituents, such as acridines, had not resulted in lung cancer even though the atmospheric contaminants are recognized as carcinogen to man (72). The reasons for this failure to cause cancer are obscure.

The failure to obtain bronchogenic carcinomas in experimental animals by the inhalation of various carcinogenic agents (beryllium and radioactive chemicals excepted) suggests that in the experimental animal additional factors acting upon the bronchial mucosa together with the carcinogen might be essential for eliciting a carcinogenic response. The success reported in this respect by Sundermann et al (24) when using nickel carbonyl seems to support this view, since nickel carbonyl disintegrates readily into finely dispersed metallic nickel and carbon monoxide and is extremely toxid to the lung tissue.

The occurence of lung cancer in individuals having siderosis through occupational exposure inhalation of iron oxide suggested that

iron in some form at the particular site might be somewhat carcinogenic (1,73). This suspicion was enhanced by observations of Faulds and Stewart (37), and of McLaughlin and Harding (38) of an excessive frequency of lung cancer among English hematite miners and iron foundry workers suffering from occupational siderosis of the lungs. No good evidence of induction of pulmonary tumour in rats after chronic inhalation of iron-containing dust has been established in the present experiment. Only three of 38 rats exposed to iron-containing dust were observed to have lung cancer; two were carcinoid type of tumour and one was papillary adeno carcinoma, while one case of carcinoid like tumour was found in the 38 rats of control group.

The specific carcinogenic action of the inhaled nickel and/or iron dust is unknown and it is the subject of continuing research.

It is, however, noteworthy that the occurence of subpleural, peri-bronchial and perivascular granulomas of the lungs exposed to the nickel-containing dust and nickel-iron-containing dust had been increased in accordance with the period of dust exposure. Twelve of 40 rats exposed to nickel-containing dust and 11 of 36 rats exposed to nickel-iron-containing dust were observed to have granulomas of the lungs. By comparison, there was only one case in each of the control (38 rats) and iron-containing dust (38 rats) groups.

Nickel and iron content of the rat lungs exposed to dust has increased with increasing concentration of nickel and iron in the air in the exposure chambers and with duration of exposure. In rats first exposed to dust and then to fresh air, the nickel and iron content of the lungs seemed to be reduced in accordance with the period of fresh air exposure. The average wet weight of lungs of rats exposed to dust was approximately 50% greater than that of the control rats. Since, however, this study is going on, more facts may be determined later.

VI. SUMMARY

Pulmonary effects following exposure of rats for periods as long as 21 months to the nickel-containing dust, nickel-iron-containing dust, and iron-containing dust has been studied. The following conclusions can be drawn at this time:

1) The death rate of rats exposed to various dust groups was approximately 2.5 times that of control group on the period of 21 months of the experiment.

2) The average weight of rats chronically exposed to dusts was found to be approximately 10% less than that of the control rats throughout the entire period of study.

3) The average wet weight of lungs of rats exposed to dusts was approximately 56% greater than that of the control rats.

4) Nickel or iron content of lungs of rats exposed to various atmospheres has been determined. Nickel or iron content of the rat lungs exposed to various dusts has increased in accordance with the nickel or iron concentration of the air in exposure cages and the duration of exposure. A decreasing tendency of nickel or iron content of the rat lungs has been observed in the extended exposure to fresh air after dust exposure.

5) Three cases of lung tumours in nickel-containing dust exposure group have been found among 40 rats examined. Two were lung tumour of carcinoid pattern and the other was lymphosarcoma. In the iron-containing dust exposure

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group 3 of 38 rats were observed to have lung cancer. The type of lung carcinoma of these was two carcinoid and a papillary adeno-carcinoma. No tumour of lung has been found in nickel-iron-containing dust exposure group. One case of carcinoid like tumour was found in the 38 rats of the control group.

6) The occurence of the subpleural, peribronchial and perivascular granulomas of the rats lungs exposed to the nickel-containing dust and nickel-iron-tontaining dust has been increased in accordance with the period of dust exposure. Similar conditions were found in only one case of each group of control rats and iron-containing dust group.

APPENDIX A

Determination of Nickel and Iron in Air and Biological Materials

1. Treatment of Samples

Cellulose filters used for sampling of dusts are wet ashed with 25 ml of mixed acid solution in a 125-ml Erlenmeyer. Impinger samples are transferred to a 125-ml Erlenmeyer flask, taken to dryness and treated like the filters. The method was also adapted to biological samples by first drying the sample over a low flame. After the initial reaction subsides, samples are digested on the hot plate until fumes of sulphur trioxide evolve. If the mixture darkens or chars at this point, concentrated nitric acid is added until sulphuric acid is refluxing freely with no further charring or darkening. The Erlenmeyer flasks are cooled, the contents transferred to 100-ml measuring flasks and diluted with distilled water to 100 ml.

2. Determination of Nickel

Reagents

1. Dimethylglyoxime solution. Dissolve 0.25 g. C.P. dimethylglyoxime in 50 ml of 95 per cent ethanol and dilute to 250 ml with distilled water.

2. Sodium diethyldithiocarbamate solution. Dissolve 1 g. of C.P. sodium diethyldithiocarbamate in 100 ml of distilled water. Filter and dilute to 500 ml.

3. Reagent A. Dissolve 200 g. of diammonium citrate in 600 ml of water; adjust to pH 9.0 to 9.5 with ammonium hydroxide, and transfer to a 1-liter separatory funnel. Add 10 ml of dimethylglyoxime

solution and make 3 extractions with 30-ml portions of chloroform. Filter the aqueous solution and dilute to 1 liter.

4. Reagent B. Dissolve 200 g. of diammonium citrate in 600 ml of water, adjust to pH 9.0 to 9.5 with ammonium hydroxide, and transfer to a 1-liter separatory funnel. Add 10 ml of sodium diethyldithiocarbamate solution and extract with 20-ml portions of carbon tetrachloride until the carbon tetrachloride layer is colorless. Vigorous agitation is required. Add 5 ml more of sodium diethyldithiocarbamate and again extract with carbon tetrachloride. If the solvent layer is colorless the extraction is complete; if it remains yellow, add more sodium diethyldithiocarbamate solution and continue the extraction. When the extraction is complete, filter the solution and dilute to 1 liter.

5. Hydrochloric acid, approximately 0.5 N. Dilute 40 ml of hydrochloric acid (sp. gr. 1.18) to 1 liter with distilled water.

6. Nickel standard. Dissolve 0.5 g. of pure nickel in 20 ml of nitric acid (1:1) and dilute to 1 liter. Prepare a working standard solution by diluting 10 ml of this solution to 1 liter with 0.5 N hydrochloric acid. One ml of the working standard solution contains 5 ug. of nickel.

7. Ammonium hydroxide, 1:50. Dilute 20 ml of concentrated ammonium hydroxide to 1 liter with distilled water.

8. Ammonium hydroxide, 1:1. Dilute 500 ml of concentrated ammonium hydroxide to 1 liter with distilled water.

9. Mixed acid solution. Mix 1 part of sulfuric acid (sp. gr. 1.84) with 1 part of perchloric acid (70 to 72 per cent) and add 3 parts of nitric acid (sp. gr. 1.43).

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Isolation of Nickel. To the prepared sample or aliquot add 10 ml of Reagent A and dilute with distilled water to a volume of approximately 50 ml. Using a pH meter, adjust the pH of the solution to 8.5 with ammonium hydroxide. Transfer the solution to a 125-ml separatory funnel and when cool, add 5 ml of dimethylglyoxime solution. Shake for about 30 seconds and add 10 ml of chloroform. After a few minutes standing, stopper securely and shake vigorously for 1 minute. After separation, draw off all but a few drops of the solvent layer into another 125-ml separatory funnel containing 25 ml of dilute ammonium hydroxide (1:50). Repeat the extraction with an additional 5 ml of chloroform. If the chloroform layer from this extraction is colorless, draw off the solvent layer as completely as possible into the second funnel. If the solvent layer is still colored, continue the extractions as before with additional 5-ml portions of chloroform, drawing off completely only the final colorless layer. Shake the combined solvent extracts and dilute ammonium hydroxide vigorously for 1 minute, allow the phases to separate cleanly, and draw off the aqueous layer through a pipette attached to a vacuum line. Wash down the sides of the funnel with distilled water, and again remove the aqueous layer as before.

Add to the solution 25 ml of 0.5 N hydrochloric acid. Shake vigorously for 1 minute and allow the phases to separate. Draw off and discard the solvent layer. Add a few ml of carbon tetrachloride, and shake briefly to extract any dissolved chloroform. Draw off the solvent as completely as possible, being careful to dislodge and remove the drops that float on the surface.

Color Development. To the acid solution add 5 ml of Reagent B and a small piece of red litmus paper. Add dilute ammonium hydroxide (1:1)

until the solution is alkaline to litmus, followed by 10 ml of isoamyl alcohol and 5 ml of diethyldithiocarbamate solution. Stopper the funnel and shake vigorously for at least 2 minutes. After standing for 15 minutes, transfer the solvent layer to a 1-cm cuvet and determine the optical density at a wavelength of 385 mμ. A reagent blank is prepared in the same manner. If the solutions become turbid due to the separation of dissolved water, they may be placed momentarily in hot water.

Calculations. The optical density readings of the samples are referred to the standard curve to determine the concentration. If the optical density indicates more than 50 ug. of nickel, the analysis should be repeated taking a smaller aliquot.

Preparation of standard curve. A standard curve is prepared from appropriate dilutions of the working nickel standard with 0.5 N hydrochloric acid. A representative standard curve is illustrated in Figure 2.

3. Determination of Iron

Reagents

1. Bathophenanthroline 0.001 M solution in ethanol. Dissolve 33.2 milligrams of bathophanthroline (4.7-diphenyl - 1.10-phenanthroline) in ethanol and make up to a volume of 100 ml with 95% ethanol. This solution is stored in the refrigerator when not in use.

2. Hydroxylamine Hydrochloride, 10%. Prepare 200 ml of a 10% solution in distilled water. Traces of iron are removed from this solution by extraction with chloroform in the presence of 10 ml of added bathophenanthroline reagent.

3. Sodium Acetate Buffer: Prepare 200 ml of a solution 2M in acetic acid and 2M in sodium acetate. As before, traces of iron

are removed by extracting with chloroform in the presence of 10 ml of added bathophenanthroline reagent.

4. Nitric Acid: When required, "Baker's Analysed Reagent" will probably prove satisfactory. Concentrated nitric acid may be redistilled from an all glass still if the acid should make a high iron contribution to the blank.

5. Perchloric Acid: When required, use double distilled perchloric acid 70% available from the G. Frederick Smith Chemical Company.

6. Ammonium Hydroxide: When required, "Baker's Analyzed Reagent" will probably prove satisfactory. If the reagent available should have a high blank value, a satisfactory reagent may be prepared by absorbing cylinder ammonia gas in distilled water.

7. Standard Iron Solution: Using pure precipitated iron powder (Antara Chemicals) or electrolytic iron wire, standard iron solutions are prepared as follows: 0.40 grams of iron powder (or wire) is dissolved in dilute (1:1) hydrochloric acid and diluted to one liter with water (Solution A). 50 ml of A is transferred to a second one-liter volumetric flask together with 10 ml of concentrated hydrochloric acid and made up to a volume of one-liter (Solution B). 25 ml of B is added to a one-liter volumetric flask together with 10 ml concentrated hydrochloric acid and made up to one-liter with water (Solution C). Solution C contains 0.5 micrograms of iron (Fe) per ml.

8. Chloroform: "Baker's Analysed Reagent" containing 0.5% ethanol as stabilizer is satisfactory. The use of isoamyl alcohol or nitrobenzene is not as satisfactory as chloroform. For extractions, a mixture of chloroform and absolute ethanol is prepared in the

volume ratio of 9 to 1. This is to be understood as the chloroform referred to in the procedure.

Analysis: All glassware must be clean. It may be necessary to rinse glassware with hydrochloric acid (1:1) before use to remove traces of iron. To prepare a standard curve a range of iron standards is pipetted into 125 ml separatory funnels, such as 0.5, 2.5, 5.0, 7.5, 10, 12.5 micrograms of iron as Fe. The volume is made up to 25 ml, and 25 ml of distilled water are added to a seventh funnel for blank determination. With shaking, 2.0 ml of hydroxylamine hydrochloride solution is added to each funnel. Then 5.0 ml of bathophenanthroline solution is added and the contents are again shaken. The pH is adjusted to pH 4-6 with congo red paper by adding ammonium hydroxide dropwise. Five ml of buffer solution is added with shaking. Now 8.0 ml of chloroform is added, and the funnel is shaken thoroughly. After adding 5.0 ml of distilled water, the contents are again shaken gently and allowed to settle for at least 15 minutes. The chloroform layer is allowed to flow slowly down one side of a test tube 16 cm. long, 1.5 cm. in diameter. The transfer from the tube to a 10 ml volumetric flask is made by pouring down the other side of the tube. The volume is made up to 10 ml by adding absolute alcohol. Using chloroform as the reference, the standard iron samples are read at 538 millimicrons on a Beckman DU Spectrophotometer, in a 1-cm light path cell.

Calculations. The optical density readings of samples are referred to the iron standard curve (Figure 3) to determine the concentration.

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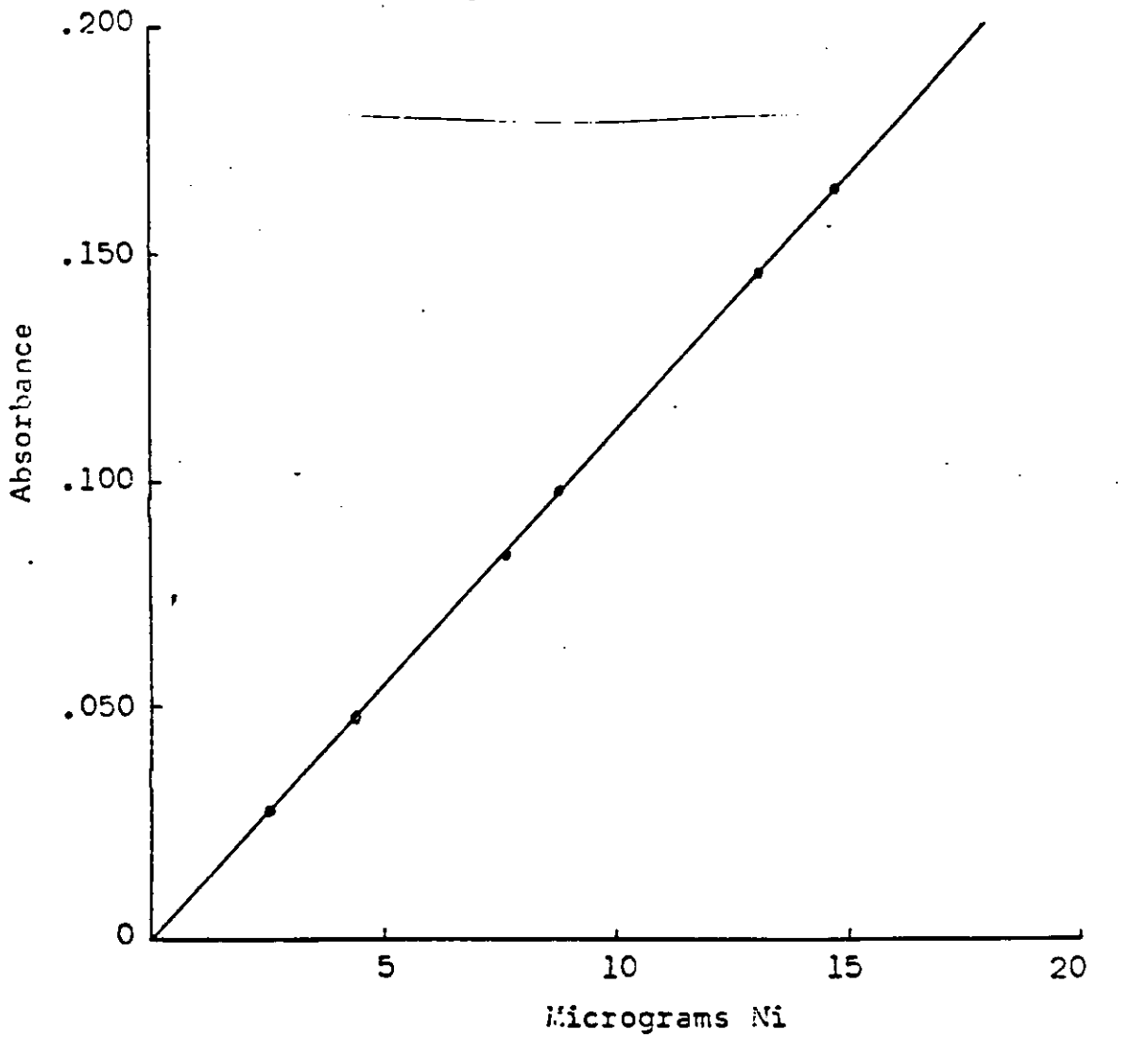

Figure 2: Nickel Standard Curve.

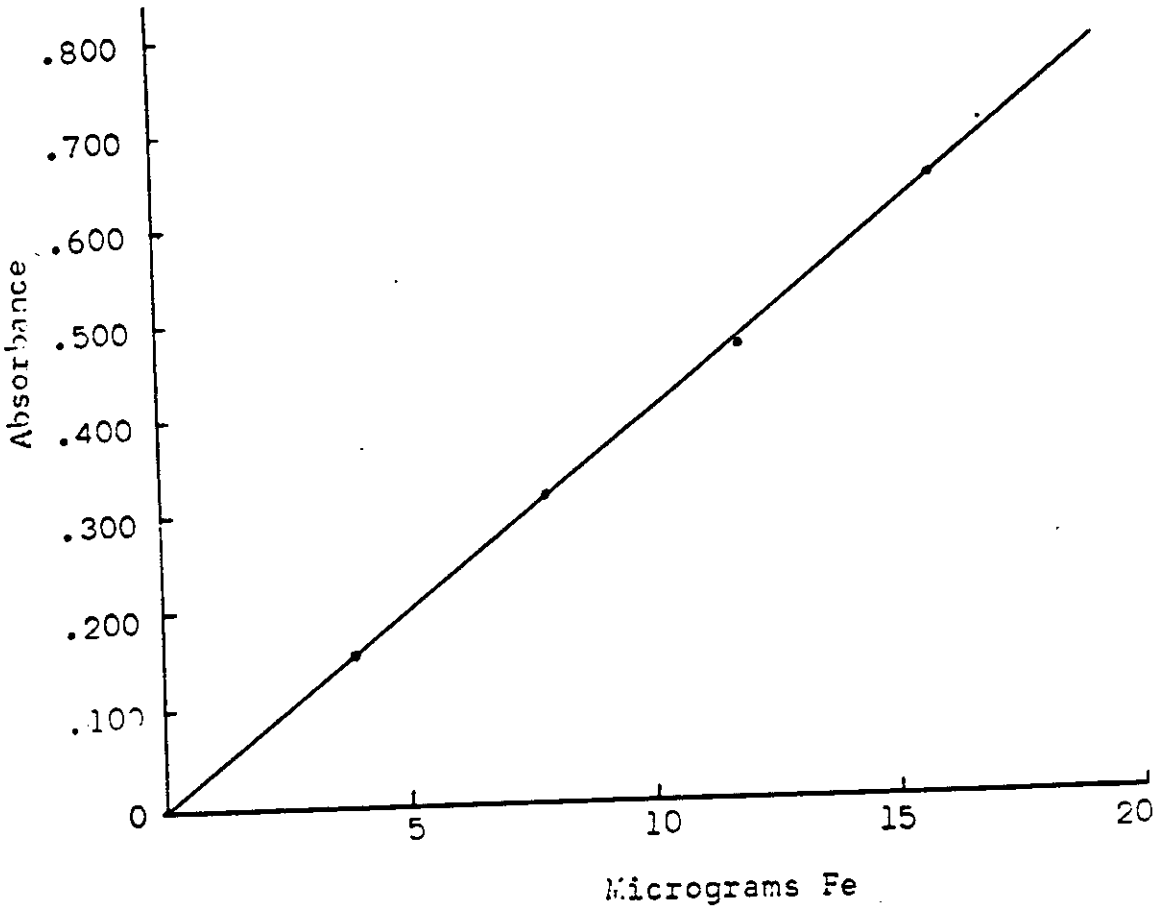

Figure 3: Iron Standard Curve.

APPENDIX B

Tissue Cutting and Staining

I. Alcohol Dehydration Method for Paraffin Embedding

Reagents

10% Formalin - Dilute 10 cc of commercial formalin (40% formaldehyde) to 100 cc with tap water.

50% Alcohol - Dilute 50 cc of absolute alcohol to 100 cc with distilled water.

70% Alcohol - Dilute 70 cc of absolute alcohol to 100 cc with distilled water.

80% Alcohol - Dilute 80 cc of absolute alcohol to 100 cc with distilled water.

95% Alcohol - Dilute 95 cc of absolute alcohol to 100 cc with distilled water.

100% Alcohol - Absolute alcohol can be kept at 100% concentration by mixing it with pulverized copper sulphate which has been previously dehydrated. The copper sulphate falls to the bottom of the bottle, the 100% alcohol remaining above.

Xylol - Purchase chemically pure xylol (xylene water-and acid-free)

Xylol-paraffin Mixture - Mix 1 ounce of pure xylol with 1 ounce of special paraffin, and keep in a warm place.

Pure Paraffin - Used pure paraffin. Melting point 56°-57°C, made by Fisher Scientific Company.

Tissue Embedding Molds - Used disposable plastic tissue embedding molds manufactured by Peel-A-Way Scientific, Calif..

Technic

1) Remove the portions of tissue of lungs for examination to be not thicker than ¼ inch. Keep in formalin solution at least two hours.

2) Wash one hour in tap water to remove the formalin.

3) Immerse in alcohol in the following series

50% Alcohol ---- 1 hour.

70% Alcohol ---- 1 hour.

80% Alcohol ---- 1 hour.

95% Alcohol ---- 1 hour.

100% Alcohol ---- not more than 1 hour.

4) Xylol one hour to clear. If not clear, immerse for a longer period. The section is opaque until placed in xylol, when the edges become clear. If there are milky or chalky spots in the tissue, put it back in 95% alcohol, then absolute alcohol, then xylol.

5) Xylol-paraffin. Immerse over-night with just enough heat to keep liquid. Do not put in the paraffin oven.

6) Next morning. Place the section in pure paraffin for two to two and one-half hours at 58° to 60°C.

7) Pure paraffin again. Tissues can be left here a day if necessary. Four to five hours is all that is necessary. The oven must not be hotter than 58° to 60°C.

8) Embed or orient. Fill plastic embedding molds almost full with paraffin. Transfer the tissue into container with aid of a warm spatula. Arrange it in the center of the container and dip the container into cold water for congealment of paraffin. In a few minutes the paraffin is rigid and plastic molds may be removed. The paraffin block with the enclosed object may be kept for any length of time.

2 . Cutting Paraffin-Embedded Sections

Spencer No. 820 rotary microtome was used for cutting paraffin-embedded sections.

Metal holders were used to mount the paraffin block on the microtome. Warm the holder enough to melt the paraffin. Press the block onto the holder. When the object holder and paraffin block have cooled, proceed with the cutting in sections 5 microns thick. Place the pieces of the ribbon onto warm water of the tissue bath with automatic temperature regulation for floating and spreading of tissue sections embedded in paraffin. Mount the ribbons on slide glass and dry for several hours at room temperature.

3 . Staining Technic for Paraffin Sections

Reagents

1) Delafield's Hematoxylin - Hematoxylin Stain Solution (Delafield) made by Fisher Scientific Company.

2) Acid Alcohol - Add 1 cc of chemically pure concentrated hydrochloric acid 70% alcohol to make 100 cc total.

3) Alkaline Alcohol - Dissolve 2 grams of sodium-bicarbonate in 100 cc of 70% alcohol.

4) 0.5% Alcoholic Eosin - Dissolve 500 mg of eosin in 100 cc of 95% alcohol.

5) Permount - A permanent mounting medium for covering histological sections mounting on microscopic slide, made by Fisher Scientific Company.

Technic

1) Immerse in xylol five minutes to dissolve the paraffin.

2) Immerse in alcohol in the following series

Absolute alcohol ---------- 1 minute

95% alcohol ---------- 1 minute

80% alcohol ---------- 1 minute

70% alcohol ---------- 1 minute

50% alcohol ---------- 1 minute

Tap water ---------- 1 minute

3) Hematoxylin, five minutes or longer. If tissue is not correct shade of purplish blue, replace in the hematoxylin. Look at the section uder the microscope to determine the correct intensity of the stain.

4) Rinse with tap water until no more color comes off.

5) 50% alcohol. Wash. Just put the slide in and out.

6) Acid alcohol. Dip the slide in the jar, then hold it above until the tissue is salmon pink. Do not decolorize too long.

7) Alkaline alcohol until blue. Look at tissue under microscope to ascertain whether nuclei are sufficiently blue. If they are not, replace the slide in acid alcohol, then 50% alcohol then water, then hematoxylin.

8) Immerse in 80% alcohol for 1 minute.

Immerse in 95% alcohol for 1 minute.

9) 0.5% alcoholic eosin. Dip in about ½ minute or longer.

10) Wash in 95% alcohol, not too long as the eosin becomes decolorized. Wash in 100% alcohol, not too long otherwise eosin may disappear.

11) Immerse in xylol until clear, usually 3 to 10 minutes. Look at the tissue under the microscope; if it is not red enough, go through the alcohols and eosin steps again; if not blue enough, go through the process to the hematoxylin.

12) Put a drop of Permount over the tissue and mount with a cover glass without air bubbles.

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APPENDIX E

A Comparison of Observed Incidences of Lung Cancer in Hamsters Exposed to Nickel Oxide and Nickel-Containing Coal Fly Ash with Incidences Predicted Using Unit Risk Estimates for Rats Exposed to Nickel Subsulfide

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1. Introduction

Section 7.6 of the EPA draft Health Assessment Document for Nickel (Draft) describes a set of procedures and uses them to produce a quantitative estimate, based on the data from an animal study (Ottolenghi et al. (1974)), of the unit risk of lung cancer in humans from continuous lifetime exposure to 1 μg Ni_3S_2/m^3 in ambient air. The present report compares similar quantitative risk estimates, obtained by using the same procedures and data, with the observed incidences of lung cancer in hamsters exposed to nickel oxide and nickel-containing coal fly ash, as reported by Wehner et al. (1975), and Wehner et al. (1981) respectively.

Use of these procedures should not be construed as an endorsement of their scientific validity. Indeed, the large discrepancies reported herein between predicted and observed incidences of lung cancer in hamsters call that validity into serious question. In particular, the assumption that the carcinogenic potencies in rodents of nickel oxide and nickel-containing coal fly ash are the same as that of nickel subsulfide, after adjusting only for the compounds' relative nickel content, appears to be totally inconsistent with the experimental data.

2. Review of Draft's Procedures for Quantitative Estimation of Lung Cancer Risk from Nickel Subsulfide Exposure

This section 1) reviews the procedures followed in the Draft for deriving a unit risk estimate for nickel subsulfide based upon animal studies and 2) uses those procedures to derive maximum likelihood and lower bound estimates, as well as an upper bound estimate, of the unit risk to rats and humans from exposure to nickel subsulfide (Ni_3S_2).

In the Draft, the incidences of adenomas, adenocarcinomas, and squamous cell carcinomas among male Fischer-344 rats, as reported by Ottolenghi et al. (1974), were pooled to yield combined lung tumor incidences of 1/108 in controls and 16/110 in rats exposed to 970 μg Ni_3S_2/m^3. These combined lung tumor incidences are also used in the present report.

For the special case of just one treatment group in addition to controls, maximum likelihood estimates of the parameters of the one-stage model, whose form is given by

$$P(D) = 1 - \exp(-(Q0 + Q1*D)),$$

may be obtained analytically:

$$Q0 = -\ln((N0-N0^+)/N0),$$

$$Q1*D = -\ln((N1-N1^+)/N1) - Q0,$$

where D is exposure level in the treated group in appropriate units, N0 and N1 are the numbers of animals in the control and treated groups, and $N0^+$ and $N1^+$ are the numbers of animals that exhibited lung tumors in each of those groups. Thus, with the concentration of Ni_3S_2 unadjusted for duration and intermittency, i.e., expressed in μg Ni_3S_2/m^3, 6 hours/day, 5 days per week, for 78 weeks, the maximum likelihood estimates of Q0 and Q1 are

$$Q0 = -\ln(107/108) = 0.930239E-02;$$

$$Q1 = -(1/970)*[\ln(94/110) - \ln(107/108)] = 1.52457E-04.$$

It should also be noted that for this special case, these estimates provide an exact fit to the data.

The procedure described in the Draft for computing an upper 95% confidence bound on Q1 is to increase its value and reestimate the other model parameter (Q0) by maximum likelihood such that at the increased value, $Q1_u$, the log-likelihood has decreased, relative to its highest value, by 2.70554/2 = 1.35277 units. This is a standard likelihood ratio test based on χ^2 with one degree of freedom whose validity is contingent upon the asymptotic normality of the parameter estimates. Use of this procedure yields

$$Q0_u = 0.716023E\text{-}02,$$
$$Q1_u = 2.29842E\text{-}04.$$

It was also deemed useful to place a lower 95% confidence bound on Q1 and on the corresponding human unit risk estimates. Using the log-likelihood ratio test procedure, one simply decreases the value of Q1 and re-estimates Q0 by maximum likelihood until the difference in log-likelihoods is again 1.35277 units. This procedure yields

$$Q0_\ell = 1.730308E\text{-}02,$$
$$Q1_\ell = 0.90992E\text{-}04.$$

Conversion of these unit risk estimates for rats to equivalent unit risk estimates for humans then involves two scaling factors. The first is presumed to account for the differences in exposure regimens, e.g., 970 μg Ni_3S_2/m^3 for 6 hours per day, 5 days per week, for 78 weeks (with an assumed lifespan of

110 weeks), versus a continuous lifetime exposure to an equivalent concentration, i.e., 24 hours per day, 7 days per week, for 110 weeks. The Draft, p. 127, assumes that the effects of exposure for a given species under these two protocols are the same if the exposure concentration x time products are the same. Thus, the equivalent continuous lifetime exposure concentration is taken to be

$$970\ \mu g\ Ni_3S_2/m^3 * [6/24 * 5/7 * 78/110] = 122.8\ \mu g\ Ni_3S_2/m^3.$$

A second factor is presumed in the Draft, p. 128, to account for across-species differences in continuous lifetime exposure level attributable to across-species differences in weight, inhalation rate, and air intake. To convert from rat exposure to human exposure, the Draft uses

$$122.8\ \mu g\ Ni_3S_2/m^3 * [.64/.29 * (.35/70)^{1/3}] = 46.3\ \mu g\ Ni_3S_2/m^3.$$

Thus, the overall scaling factor to go from exposure of rats using the Ottolenghi et al. protocol to continuous lifetime exposure of humans is

$$970\ \mu g\ Ni_3S_2/m^3 / 46.3\ \mu g\ Ni_3S_2/m^3 = 20.95.$$

The unit risk estimates for rats must be multiplied by this scaling factor to obtain the corresponding unit risk estimates for humans exposed continuously for a lifetime. Table 1 shows the upper bound, maximum likelihood, and lower bound estimates of the unit risk for rats and humans exposed to nickel subsulfide. Note that the upper bound result for humans presented in the Draft, p. 128 namely, $Q1_u$ = 4.8E-03, is in near perfect agreement with the one presented herein.

3. Comparison of Observed Incidences of Lung Cancer in Hamsters Exposed to Nickel Oxide and Nickel-Containing Coal Fly Ash with Incidences Predicted Using Unit Risk Estimates for Rats Exposed to Nickel Subsulfide.

It was deemed instructive to use the estimates of Q0, Q1, and their 95% confidence bounds derived from the Ottolenghi et al. study to predict lung tumor incidence among male Syrian golden hamsters under the conditions of the studies of nickel oxide, coal fly ash, and nickel-enriched coal fly ash reported by Wehner et al. (1981) and (1975). Comparison of observed and predicted incidences provides a test of the assumption that nickel oxide and the nickel species present in coal fly ash possess the same carcinogenic potency for rodents as does nickel subsulfide.

Wehner et al. (1975) exposed male Syrian golden hamsters by inhalation to 53.2E+03 μg NiO/m^3 for 7 hours per day, 5 days per week for up to 22 months. The nickel concentration of this exposure was thus 4.18E+04 μg Ni/m^3. Wehner et al. (1981) also exposed male Syrian golden hamsters by inhalation to 70E+03 μg/m^3 and 17E+03 μg/m^3 nickel-enriched coal fly ash (NEFA) for 6 hours per day, 5 days per week for up to 20 months. They similarly exposed hamsters to 70 E+03 μg/m^3 coal fly ash (FA). The nickel content of NEFA was approximately 6% while the nickel content of FA was approximately 0.30%. Thus, the concentrations of airborne nickel were 4.20E+03 μg Ni/m^3 and 1.02E+03 μg Ni/m^3 for the NEFA experiments, and 2.10E+02 μg Ni/m^3 for the FA experiment.

In order to predict the cancer risk for hamsters from the Ottolenghi et al. rat data using the one-stage model, the above concentrations of nickel

must be converted to equivalent concentrations of nickel subsulfide for rats. The Draft cited data on rats from the Biology Data Book, 2nd edition, v. 3 (FASEB, 1974), to the effect that 113 gram rats inhale 105 liters of air per day. Using the formula given on p. 119 of the Draft, this was converted to an equivalent statement that a 350 gram (W_r) rat inhales 224 liters (I_r) per day. The Biology Data Book also yields the fact that 92 gram (W_h) Syrian golden hamsters (Mesocricetus auratus) inhale 86.4 liters (I_h) per day. These data were used with the procedure outlined in the Draft on p. 127 to convert the nickel exposure levels for hamsters to equivalent nickel exposure levels for rats. The procedure assumes that the absorption fraction is the same in the both species, i.e.,

$$v_r = (I_h/W_h)/(I_r/W_r)(W_h/W_r)^{1/3} * v_h = 0.939981\ v_h.$$

The equivalent nickel concentrations are thus:

	Hamster, μg Ni/m^3 lifespan	Rat, μg Ni/m^3 110 weeks	78 weeks
53.2E+03 μg NiO/m^3	4.18E+04	3.93E+04	5.54E+04
70E+03 μg NEFA/m^3	4.20E+03	3.95E+03	5.58E+03
17E+03 μg NEFA/m^3	1.02E+03	0.96E+03	1.35E+03
70E+03 μg FA/m^3	2.10E+02	1.97E+02	2.78E+02

The figures in the column for 78 weeks of exposure are obtained from those in the column for 110 weeks of exposure by scaling up by the factor (110/78).

To convert the above concentrations of nickel to concentrations of nickel subsulfide they must be multiplied by the reciprocal of the nickel content of

Ni_3S_2, namely 73.3% by weight. In the case of Ni_3S_2 equivalent of nickel oxide exposure, the concentrations of Ni_3S_2 must be also multiplied by 7/6 because Wehner et al. exposed the hamsters to nickel oxide for 7 hours per day whereas Ottolenghi et al. exposed the rats to Ni_3S_2 for only 6 hours per day. The equivalent concentrations of Ni_3S_2 to be used for predicting incidences are presented in Table 2.

The prediction equation is

$$P(D) = 1 - \exp(-(Q0' + Q1'*D)),$$

where Q0' is either Q0, $Q0_\ell$, or $Q0_u$, and Q1' is either Q1, $Q1_\ell$, or $Q1_u$ for rats as presented in Table 1. The concentration (D) to be used in each case is the value in the third column of Table 2.

The observed incidences of lung cancer in hamsters exposed to nickel oxide and nickel-containing coal fly ash and the incidences predicted using the unit risk estimates for rats exposed to nickel subsulfide are presented in Table 3. The large discrepancies between observed and predicted incidences of lung tumors are totally inconsistent with the assumption that nickel oxide and nickel-containing coal fly ash possess the same carcinogenic potency for rodents as does nickel subsulfide, after adjusting only for the compounds' relative nickel content.

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Table 1. Unit risk estimates for rats and humans exposed to 1 μg Ni_3S_2/m^3

	Rats 6 hrs/day, 5 d/week 78 weeks	Humans continuous lifetime
Upper 95% bound, $Q1_u$	2.30E-04	4.82E-03
Best estimate, Q1	1.52E-04	3.19E-03
Lower 95% bound, $Q1_\ell$	0.91E-04	1.91E-03

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Table 2. Nickel subsulfide concentrations for rats under the Ottolenghi et al. (1974) protocol equivalent to the concentrations of nickel oxide and coal fly ash for hamsters under the Wehner et al. (1975,1981) protocols.

Hamster, $\mu g/m^3$ lifespan	Rat, $\mu g\ Ni_3S_2/m^3$ 110 weeks	78 weeks
53.2E+03 NiO	6.25E+04	8.82E+04
70E+03 NEFA	5.39E+03	7.60E+03
17E+03 NEFA	1.31E+03	1.84E+03
70E+03 FA	2.69E+02	3.80E+02

Table 3. Comparison of observed incidences of lung cancer in hamsters exposed to nickel oxide and nickel-containing coal fly ash with incidences predicted using unit risk estimates for rats exposed to nickel subsulfide

Exposure	Lung Tumor Incidence			
	Observed	Predicted		
		Lower 95%	Best Estimate	Upper 95%
53.2E+03 µg NiO/m^3	0/51[a]	51/51	51/51	51/51
70E+03 µg NEFA/m^3	2/61[b,c]	31/61	42/61	50/61
17E+03 µg NEFA/m^3	0/62[c]	10/62	16/62	22/62
70E+03 µg FA/m^3	0/61[c]	3/61	4/61	6/61

[a] additionally, one osteosarcoma was observed (Wehner et al. (1975))

[b] the two tumors consisted of one pulmonary adenocarcinoma and one mesothelioma (Wehner et al. (1981))

[c] denominator is the number of hamsters that died or were killed at final sacrifice (20 months) excluding those autolyzed, periodically sacrificed, or withdrawn from exposure

APPENDIX F

NICKEL AND ITS INORGANIC COMPOUNDS

(INCLUDING NICKEL CARBONYL)

A Supplementary Submission to the

National Institute for Occupational

Safety and Health

by

International Nickel (U. S.) Inc.

October, 1976

C00033

5. Clydach Calcining Plant

a) Total Dust Concentrations

Nickel carbonyl was not discovered until 1888 yet the Mond Nickel Company launched a commercial refinery employing carbonyl chemistry in 1902. The technology was rapidly evolving at the same time the demand for the product required equal increments of new capacity in 1907, 1911, 1916, 1923, 1928 and 1930. It is not surprising that the Clydach works was reputed by employees to be extremely dirty in its early years.

The calcining sheds were the dustiest part of the operation and were known locally as "Hell's Kitchens". The dust was generated by crushing and grinding fresh matte, by the handling of finely divided residues returned from the nickel extraction process, and by calcining with insufficient draft and dust collecting equipment. A general manager of the Clydach plant who worked in the calciner buildings in 1929 was of the opinion they were dirtier than the Copper Cliff sinter plant which he visited in 1951.

The first measurement of airborne dust in the calciner sheds was not made until 1932. Although a gravimetric technique was employed, the filter was only a plug of wool and the amount of air sampled was only 0.1 m^3 so very small weights of dust had to be determined by difference. Furthermore, 1932 was a poor year commercially (no matte was shipped to Clydach from Canada that year) so the plant was running at greatly reduced capacity. Finally, the installation of a central grinding plant and new calciners with improved flues and dust collecting equipment was already underway. These changes were completed in 1935 and produced a dramatic improvement in the working environment of the calciner sheds. The figures presented in Table 45 probably understate the dustiness that existed in the early years at Clydach.

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TABLE 45

CONCENTRATIONS OF TOTAL DUST* IN TWO CLYDACH CALCINER SHEDS

Location	Dust Concentration, mg/m^3
Calciner Shed #3	
Near ball mill stage	14
West end	8
Calciner Shed #4	
Near ball mill	42
East end	13
West end	12

* A tube containing a plug of wool was weighed after drying at 40°C for 1 hour. 100 liters of air were aspirated through the tube at a height of about 5 feet. The tube was again dried and reweighed.

C00400

The crushing and grinding of matte appears to be dustier than the operation of the calciners per se. Calciner shed #3, where the first new calciner was installed, appears to have been less dusty than shed #4. Further evidence of the improved working conditions provided by the new calciners is shown by comparing the sulfur dioxide concentrations in sheds 3 and 4. Fifteen to thirty liters of air were absorbed in a neutralized solution of hydrogen peroxide which was then titrated with 0.1 N sodium carbonate. The concentrations of sulfur dioxide thus determined in 1932 are given below:

Location	No. of Samples	Concentration of SO_2, ppm	
		Range	Mean
Calciner shed #3	4	0.2 - 3.8	1.5
Calciner shed #4	12	3.8 - 54	25.4

The data show that the changes being effected in #3 shed produced an acceptable level of sulfur dioxide in the atmosphere whereas shed #4 was essentially unbearable by today's standards. This improved draft would also have helped reduce the amount of airborne dust.

Measurements of dust concentrations were also recorded in 1945 and 1949. These are important because the modifications begun in the calciner sheds had been completed by then and other improvements had been effected as well. Comparing data from this period with the 1932 data should indicate whether the earlier dust measurements were indeed unrealistically low. Furthermore, Doll et al[10] indicate the hazard causing increased risk of respiratory cancer had essentially disappeared after 1930. Data from this period will thus provide information relevant to safe chronic exposure.

Unfortunately the reported concentrations of airborne dust were characterized by counting the particles in a measured volume of dusty air (sampled with an Owens jet), the results being expressed as millions of particles per cubic foot (MPCF). These measures of dust concentration cannot be compared with modern measurements and standards without a knowledge of the densities and particle size distributions of the dusts. This is so because all sizes of counted particles contribute equally to the particle count but the fine particles contribute very little to the weight of collected dust. The dusts of interest to Inco are no longer available so information on similar dusts must be used to convert these historical data to gravimetric units.

The conversion factor to be applied to particle counts (MPCF) is derived by assuming all the particles are spherical and have the same diameter, specifically the volume mean diameter d_v. The factor is then given as follows:

$$\frac{4}{3}\pi\left(\frac{d_v}{2}\right)^3 \times \rho \times 35.31 \times 10^{-3} \quad \frac{cm^3}{\mu m^3} \quad \frac{ft^3}{m^3} \quad \frac{mg}{g}$$

d_v is entered in μm and ρ, the density, in g/cm^3. Multiplying the dust count in MPCF by this factor will give the gravimetric dust concentration in mg/m^3.

Clearly a knowledge of d_v is most important because its cube is used in the conversion factor. An estimate of d_v for Clydach calciner dusts has been made using data from Inco's existing fluid bed roasting plant at Copper Cliff (FBR). The FBR dusts are primarily nickel oxide produced during roasting fine impure nickel sulfide (ground to 50% -18 μm and pelletized) at 1100°C in a fluidized bed. Clydach was then calcining nickel oxide containing about 0.7% S made by sintering impure nickel sulfide at Port Colborne or Copper Cliff. The sinter was only ground to 50% -100 μm and was calcined at only 780°C so very little fume was generated.

The size distributions of these two dusts may reasonably be expected to be similar.

Two samples of ambient FBR dust were obtained during the testing of Clydach gauze masks. Their size distributions were determined microscopically and are reported in Table 48. d_v was calculated for each sample by evaluating the expression:

$$d_v = \left(\frac{\Sigma n_i d_i^3}{\Sigma n_i}\right)^{1/3}$$

where n_i is the number of particles with diameter d_i. The average value of d_v for the two samples was 5.4 μm. Since Clydach counted only particles smaller than 10 μm, d_v was evaluated for the FBR dusts using only those particles $\leq$ 10 μm. This is a conservative approach to the conversion factor because it will sometimes be applied to particle counts made at Clydach on atmospheres containing particles > 10 μm. Even if the large particles were ignored in counting, they would have contributed to the weight of solids in the Clydach atmosphere. For instance, including even the few particles in the 10 - 20 μm range in the FBR dusts increased d_v to about 8 μm and would have increased the conversion factor over threefold.

A similar finding is made in analyzing the data for an open hearth fume[22] in which the majority of the particles are less than 0.1 μm in diameter. The mass mean diameter of particles < 10 μm (these comprise 68 percent of the weight) is about 4 μm but this doubles if all particles up to 40 μm (comprising 93 percent of the weight) are included.

The other parameter needed to evaluate the conversion factor is ρ, the density of the dust. A detailed study of flue dusts from nickel calciners was made at the Orford works in Bayonne, N.J. in 1915-1917. The density of these dusts was determined to be 2.4 g/cm^3 using petroleum ether

C00100

in a pyknometer. However, these calciners were treating impure nickel sulfide so the dusts probably contained a great deal of sulfate (ρ = 3.7 g/cm^3). Since Clydach was calcining nickel oxide with very little sulfur in it, not much sulfate could be formed and the density of the dust would be closer to the true density of nickel oxide. Nevertheless, a value of 2.4 will be used as a conservative approach. Evaluating the conversion factor with d_v = 5.4 µm and ρ = 2.4 g/cm^3 gives the following result.

Dust Concentration (mg/m^3) = 7 x Dust Concentration (MPCF)

Huntington recently derived an empirical conversion factor of 5.2 by comparing simultaneous gravimetric sampling with sampling for subsequent particle counting. The agreement is reassuring because their measurements were made mainly around the melting shop where the dust would have been finer due to a higher fume content.

Bloomfield and DallaValle[23] found some empirical correlation between particle counts and gravimetric concentrations by weighing 611 impinger samples on which counts had been made. These are included in the table below.

Conversion Factor	Dust	Method	Correlation Coeff.
7	FBR	Theoretical	
5	Huntington melt shop	Empirical	
2.85	Open hearth fume	Theoretical	
2.35	Cement	Empirical	0.69
1.86	Metal grinding and polishing	"	0.7
1.15	Granite	"	0.76
1.15	Bituminous coal	"	0.85
0.8	Anthracite coal	"	0.77

C00104

The conversion factor becomes smaller as the dust becomes finer. It is appropriate to use different conversion factors throughout the flowsheet to reflect the expected changes in size of the Clydach dusts. The factors selected in the table below were conservatively chosen in an effort to avoid the common error of overestimating gravimetric concentrations.

Factor	Where Applied
5	Storing, grinding and handling sinter
3	Calciner sheds
1	Nickel sheds

The reported dust concentrations in MPCF and their estimated equivalents in mg/m^3 are both reported in Table 46. The 1949 data indicate the central grinding plant was cleaner than it had been in 1945 and, in contrast with 1932, cleaner than the calciners per se. The calciner sheds were still the dustiest part of the entire plant. The estimated gravimetric conversions indicate the 1932 concentrations reported in Table 45 are definitely too low. All things considered, it is estimated that the total dust concentrations in the calciner plants at Clydach during the hazardous period ranged from 40 to 100 mg/m^3.

TABLE 46

CONCENTRATIONS OF TOTAL DUST
AT THE CLYDACH WORKS

Sample Source	Dust Concentrations MPCF		Dust Concentrations est. mg/m^3	
These measurements were reported in 1945.				
Samples were taken in the central grinding plant. Dust was mainly in the 1-10 µm size range. The minimum and maximum observed in each location were reported.	1.8	13.7	9	68.5
	2.6	19.1	13	95.5
	1.4	7.5	7	37.5
	1.9	16.8	9.5	84.0
The next measurements were reported in 1949.				
8 locations (mostly in central grinding plant) where sinter was crushed, ground, seived, sampled, stored, transported, etc. Most of the dusts observed were 1-10 µm.	1.7 - 8.1		8.5 - 40.5	
	Range Observed			
	5 ± 3.7		25 ± 18.6	
	Mean ± 2 std. dev.			
4 locations in the calciner buildings. Dusts were in the 1-15 µm size range.	9.5 - 11.8		28.5 - 35.4	
	10.5 ± 2.2		31.5 ± 6.6	
17 locations around the reducers and volatilizers in the nickel sheds. About one-third of the dusts observed were 1-10 µm, the remainder were 1-15 µm or coarser.	3.1 - 10.6		3.1 - 10.6	
	6 ± 5.2		6 ± 5.2	

C33403

b) Composition of the Dust

No chemical analyses of airborne dusts from the early Clydach operations are available. The feed to the process then was a nickel-copper sulfide containing about 35% Cu and 45% Ni. This material was calcined and leached in acid to dissolve copper before reducing and extracting nickel by carbonylation. Recent analysis of a 1929 sample of this leached material gave its composition as 15.5% Cu, 55.8% Ni and 3.4% S. This same general composition would persist through reduction but the nickel content would decrease during the carbonylation process. The residue from carbonylation may have been recycled through this entire process several times. An annual composite for 1929 of material that had been through this cycle three times was recently analyzed to give 27.6% Cu, 26.9% Ni and 6.1% S. A 1929 monthly composite that had been processed four times analyzed 20.5% Cu, 39.0% Ni and 5.5% S.

The nickel and copper contents of the feed and intermediate products in this period ranged from about 25 - 55% Ni and 15 - 35% Cu. These products and the dust they gave rise to were moved back and forth through the plant. It is assumed for simplicity that the dust averaged 45% Ni and 25% Cu throughout the plant.

Since the volatilization process extracted nickel very selectively, the recycled residues became increasingly enriched in the tramp elements originally present in the feed. This may be seen by comparing the arsenic, lead and selenium content of the three samples recently analyzed and mentioned above.

	Analysis, %		
Sample	% As	% Pb	% Se
Copper extracted matte	0.025	0.060	0.004
Concentrate #3	1.19	1.21	0.026
Concentrate #4	10.9	4.0	0.048

An early report states that the calciner flue dusts analyzed about 2.5% Se. This process obviously created material rich in tramp elements but the principal mechanism was different from that operating in the sintering plants. The weight of these materials was small compared with the feed to the process but they were finely divided and were moved repeatedly through the plant where they could have contributed to the airborne dust.

Beginning in 1930, the copper was essentially removed from the Clydach feed, first by the Orford process and, after 1948, by Inco's matte separation process. The dusts were assumed to be about 70% Ni after this time. The sulfur content of the feed was also lowered over the years by sintering or calcining the feed in Canada. From 1945 on, the feed was nickel oxide prepared first by sintering at Port Colborne and, after 1961, by fluid bed roasting at Copper Cliff. These oxidation processes also removed substantial amounts of the tramp elements from the feed, thus minimizing their concentration in the volatilizer residues at Clydach.

The information in parts (a) and (b) may be combined to estimate the amount of airborne nickel in various parts of the Clydach works at various times.

Location	Period	Concentration, mg Ni/m^3
Calciner sheds	1902-1930	20 - 50
Grinding plant	1945	5 - 50
Grinding plant	1949	5 - 35
Calciner sheds	1949	20 - 25
Nickel sheds	1949	3 - 10

NiPERA INC.
Nickel
Producers
Environmental
Research
Association

October 19, 1990

Ms. Genevieve Shiroma
Chief, Toxic Air Contaminant
Identification Branch
California Air Resources Board
Sacramento, CA 95812

Dear Ms. Shiroma:

Enclosed are the revised comments of NiPERA on the State of California's Proposed Identification of Nickel as a Toxic Air Contaminant. Like our earlier submission, these comments pertain strictly to the calculation of the unit risk number for nickel.

As you will recall, at the August meeting in which I presented NiPERA's earlier results, requests were made for raw data back-up of these results. I agreed to provide such information. In addition, during the course of the meeting, reference was made to the Department of Health Services' (DHS) efforts to contact EPA (specifically Dr. Steven Bayard) for clarification of the estimates of unit risk derived by the EPA. As the DHS relied heavily upon EPA's data and methods for calculating the unit risk, it was suggested that it would benefit DHS to talk to Dr. Bayard, given the importance of the methods used and DHS's self-professed inability to understand the unit risk based upon the Maximum Likelihood Estimate (MLE). Having worked with Dr. Bayard in the past, I offered to contact him for further clarification of the issues.

The enclosed submission reflects NiPERA's efforts to follow through on these commitments. Equations and methods for calculating unit risk estimates are provided; comments reflect extensive communications with Dr. Bayard over the past two months. Based upon these communications, we have recalculated our original estimates to reflect a better understanding of the approaches taken by EPA and a greater knowledge of the key issues that drive the selection of the most appropriate risk model for use in estimating the unit risk. Our attempts to clarify EPA's approach have led us to confirm our initial beliefs that maximum likelihood estimation is, indeed, the best approach to take. We have also learned where EPA erred in its calculations, undoubtedly leading to some of the difficulties DHS had in using

C00403

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this approach. We have discussed these issues in greater detail in the enclosed comments.

I do apologize for the lateness of this submission, but trust that in the interest of the better knowledge gained and better estimate of the unit risk derived both CARB and DHS will carefully consider these comments.

Sincerely,

Donna J. Sivulka

Donna J. Sivulka
Executive Director

DJS/cl

Enclosure

000410

COMMENTS OF THE NICKEL PRODUCERS ENVIRONMENTAL RESEARCH ASSOCIATION, INC. ON THE STATE OF CALIFORNIA'S PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT

OCTOBER 19, 1990

C00111

COMMENTS OF
THE NICKEL PRODUCERS ENVIRONMENTAL RESEARCH ASSOCIATION, INC.
ON THE STATE OF CALIFORNIA'S
"PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT"

I. INTRODUCTION

In August, NiPERA proposed modifications to the risk assessment procedure that was used in the California Air Resources Board's (CARB) Proposed Identification of Nickel as a Toxic Air Contaminant. We made the following recommendations at the public comments meeting held in Sacramento:

- New information on the Copper Cliff Sinter Plant workers should be utilized.
- Adjustments for lack of follow-up should be eliminated based on the reliability of tracing methods used in updating this cohort.
- The use of the proportionate mortality ratio to estimate background lifetime risk is questionable.
- Maximum likelihood (ML) estimation of the slope of the dose-response curve should be investigated.
- The U.S. EPA should be contacted to ascertain the reasons for large differences between the ML-based risk estimate and that obtained by the Average Relative Risk approach.

NiPERA has investigated the EPA's risk assessment procedures in depth. We found no problems with the maximum likelihood estimates of dose-response slope parameters, and were able to replicate these estimates for the Copper Cliff and Huntington cohorts. The reason for CARB's use of weighted least squares in preference to the maximum likelihood approach is therefore unclear. Maximum likelihood estimation of the dose-response parameter is a more statistically rigorous approach than weighted least squares in that it explicitly utilizes the assumed Poisson error structure of the data. This is particularly important in estimating the upper 95% confidence limit for the slope parameter that drives the risk assessment.

The reason given in the CARB document for use of weighted least squares was that the unit risks estimated by the ML and Average Relative Risk approaches were greatly disparate. This is not

related to ML estimation *per se*. For example, the ML estimate for the Chovil et al. data presented in the EPA NiHAD (4.19×10^{-5}) is similar to that obtained from the Average Relative Risk Estimate ($8.9 \times 10^{-5} / (.026 \times 70) = 4.89 \times 10^{-5}$). The reason for the differences in the unit risk estimates from these two approaches was in the estimation of lifetime risk of lung cancer in the presence of competing risks (presented in mathematical form on page 8-205 of the HAD). When we discussed this with Dr. Steven Bayard of the U.S. EPA, he investigated further and found that the computer program that performed this calculation was in error. There were other errors in the EPA Nickel HAD that also surfaced. In particular, on page 8-210, the background risk of lung cancer for white males in 1976 was given as 0.036. This is really closer to the background risk of the population (males and females, all races) that Dr. Bayard re-estimated as 0.038. Dr. Bayard's corrected ML multiplicative model unit risk estimate from the Copper Cliff Sinter Plant cohort data is 1.1×10^{-4} (based on 1976 U.S. population lung cancer mortality rates).

Because of the errors in the EPA analysis, and the points previously discussed with the CARB, NiPERA has undertaken another risk assessment based on lung cancer mortality data from Copper Cliff sinter plant workers, reported in the Doll et al. "Report of the International Committee on Nickel Carcinogenesis in Man (1990). This assessment differs from that provided to the CARB in August in the following ways:

- Maximum likelihood estimation is used to obtain slope and variance estimates for the dose-response curve.
- Lifetime unit risk is estimated using a conditional hazard function.
- Adjustments are made to more accurately estimate nickel exposure.

II. ADJUSTMENTS TO EXPOSURE ESTIMATES

In its submission to the CARB in August, NiPERA provided a risk assessment that was based on recently published data on the Copper Cliff Sinter Plant workers from the Doll et al. study. The exposure estimates in the August risk assessment were obtained by multiplying the midpoints of duration of exposure categories in Doll et al. Table 51 by 100 $\mu g/m^3$. However, this

CC3436

approach results in exposure estimates that are low relative to those used by the CARB. For example, the highest exposure category in the Chovil et al. (and CARB) analysis was 1.65, while that from the NiPERA analysis was 1.2, a difference of over 35%.

To adjust for this underestimate of exposure, we have now used the original exposure estimates in conjunction with the numbers of men hired by year, as presented in Table 4 of Chovil et al. Mean cumulative exposure associated with each duration of exposure category in Table 51 of Doll et al. was estimated as the weighted average of cumulative exposures occurring from each hire year. For example, the midpoint of the 10-14 years of employment category is 12.5 years. Given that the plant was open until the beginning of 1963, the only men who had 12.5 years or more of employment were those that were hired from 1948 to 1951. Cumulative exposure associated with 12.5 years of work for the 39 men hired in 1948 was estimated as 1650 mg Ni/m^3 x years (4 x 200 + 8.5 x 100). Similarly, men hired in 1949, 1950, and 1951 were estimated to have had cumulative exposures of 1550, 1450, and 1350 mg Ni/m^3 x years, respectively. The weighted average of the 12.5 year cumulative exposures for these four hire years is:

(39x1650 + 83x1550 + 43x1450 + 114x1350)/279=1467

Average cumulative exposures for 0.5, 2.5, and 7.5 years of employment were estimated in this way to be 78, 393, and 881 mg Ni/m^3 x years.

Admittedly, this is a crude approach to estimating cumulative exposure. However, in the absence of the raw data, it is a viewed as a reasonable attempt to reflect the composition of the work force relative to the changing exposure levels over the plant's operating period. The tacit assumption in the approach is that the distributions of durations of exposure (up to the midpoint of the exposure) for the hire years were similar. One might question this assumption, thinking that men hired during the period when the conditions were worst (pre-1952) might be more likely to leave after one or two years than those who were hired later. This does not seem to be the case since 65 of the men had an average weighted duration of exposure of about 16.5 years (Chovil et al., Figure 2), implying at least 2.5 years experience prior to 1952.

C33112

III. RISK ASSESSMENT APPROACH

The authors of the CARB TSD discuss the difficulty of empirically discriminating between additive and relative risk models, concluding that "*a priori* considerations clearly favor a relative risk model for quantitative risk assessment for nickel and lung cancer." They then seem to argue against this position when they present the results of Magnus et al. (1982), which clearly suggest that the effects of nickel exposure and smoking are closer to additive than multiplicative. The truth of the matter is that one can not estimate additive risks with either the Chovil et al. (or Doll et al.) data since the person-years associated with the observed lung cancer deaths are unavailable.

The TSD's authors seem to believe that application of relative risk estimates to background rates for the period during which the Copper Cliff cohort was followed provides reasonable estimate of additive risk. It is not clear that this is true. Nevertheless, we will proceed with this approach since the data that would allow us to estimate unit risk using an additive risk model are unavailable. To properly perform the risk assessment, we feel that it would be desirable to obtain the raw data and apply the additive model.

In our analysis we utilize a conditional hazards function. It is based on the background lifetime risk of lung cancer, which can be estimated from statistics which summarize mortality rates by age intervals:

$$P_0 = \sum_{i=1}^{n} \frac{c_i}{d_i}(1-\exp(-d_i t_i)) \prod_{j=1}^{i-1} \exp(-d_j t_j)$$

where:

c_i = lung cancer mortality rate in age interval i

d_i = overall mortality rate in age interval i

t_i = number of years in age interval i

n = number of age intervals covering a lifetime

C00115

In this expression,

$\frac{c_i}{d_i}$ = proportion of lung cancer deaths in age interval i

$1-\exp(-d_i t_i)$ = probability of death in age interval i

$\prod_{j=1}^{i-1} \exp(-d_i t_i)$ = probability of survival to age interval i

Under the assumption of a multiplicative risk model, the age specific risk, conditional upon continuous exposure to 1 $\mu g/m^3$ nickel, is estimated by:

$$c_i' = (1+\Delta age_i)\, c_i$$

where:

Δ = ML estimate for incremental (unit) relative risk

age_i = midpoint of age interval i

The age-specific death rate, adjusted by increased lung cancer risks is given by:

$$d_i' = d_i + (c_i' - c_i)$$

Thus, the lifetime risk of lung cancer, conditional on lifetime exposure to 1 $\mu g/m^3$ is estimated by:

$$P_c = \sum_{i=1}^{n} \frac{c_i'}{d_i'} t_i (1-\exp(-d_i' t_i)) \prod_{j=1}^{i-1} \exp(-d_j' t_j)$$

The incremental lifetime (unit) risk is estimated by:

$$IR = P_c - P_0$$

C00413

IV. RESULTS OF RISK ASSESSMENT

The relationship between relative lung cancer risk and estimated exposure to nickel is displayed in Figure 1. Under the assumption that the observed values are Poisson-distributed, the maximum likelihood estimate for the slope of the line (δ) is 5.573, with an asymptotic variance estimate of 0.932. Thus, the upper 95% confidence limit for the slope (δ_{ucl}) is 7.466. The fit of the model to the data is good, as indicated below:

Lung Cancer Deaths in Copper Cliff Sinter Workers
Estimated Using a Relative Risk Model

Cumulative Exposure ($1000 mg/m^3$ x years)	Observed	Predicted	Expected (Background)
0.78	15	17.27	12.04
3.93	15	13.65	4.28
8.81	12	9.51	1.61
14.67	21[a]	23.58[a]	2.57[a]

[a] includes duration of exposure categories 10-14, ≥15 years

$\chi^2_{(3\ d.f.)} = 1.36$, $p=0.71$

The ML estimates in the relative risk model, δ and δ_{ucl}, were based on cumulative exposure calculated from the original 200 and 100 mg/m^3 (pre- and post-1952) concentration estimates from Chovil et al., with no adjustment to reflect continuous exposure or the possible overestimation of airborne nickel concentrations in the Copper Cliff sinter plant. Consistent with the CARB approach, δ and δ_{ucl} were divided by 165 to adjust them to continuous exposure equivalents (in milligrams). The number 165 is the product of the following adjustment factors: Unit cumulative exposure level (1,000 mg/m^3 x years); adjustment for full day exposure (8/24); adjustment for weekly exposure (5/7); adjustment for yearly exposure (48/52); adjustment for lower exposure than Chovil et al. estimate (0.75). An additional adjustment factor of 1000 was applied to obtain the increment to relative risk per $\mu g/m^3$ x year cumulative exposure. That is,

$$\Delta = \delta/165{,}000 = 5.573/165{,}000 = 3.4 \times 10^{-5}$$

$$\Delta_{ucl} = \delta_{ucl}/165{,}000 = 7.466/165{,}000 = 4.5 \times 10^{-5}$$

C00547

These values were used to estimate lifetime lung cancer risk, conditional on continuous exposure to 1 μg Ni/m^3 (defined above as P_c). Canadian lung cancer and all-cause death rates in 5-year age intervals (averaged over the period 1965-1984) were used to obtain the following lung cancer risk estimates:

Lifetime (75-year) Lung Cancer Mortality Risk
With Conditional and Incremental Estimates
Based on Continuous Exposure to 1 μg/m^3 Nickel

Relative Risk Estimator	Lung Cancer Risks		
	Background (P_0)	Conditional (P_c)	Incremental (IR)
Δ= 3.4x10-5	4.085×10^{-2}	4.094×10^{-2}	8.83×10^{-5}
Δ_{ucl}= 4.5×10^{-5}	4.085×10^{-2}	4.097×10^{-2}	1.18×10^{-4}

The highest reported average ambient air nickel concentration in California is 0.0105 μg Ni/m^3 (see INCO's September 5, 1990 comments to CARB, p. 4). Thus, it is unlikely that the number of lung cancer deaths due to nickel exposure would exceed 1.3 per million ($0.0105 \times 118 \times 10^{-6} = 1.24$). A "best" estimate for a nickel-related increase in lung cancer mortality would be this highest average exposure applied to the estimated unit risk (as opposed to its upper 95% confidence bound). This computation ($0.0105 \times 88 \times 10^{-6}$) gives an estimated risk of less than 1 per million.

There is a strong possibility that even these small risks are overestimated. For example, a linear extrapolation of the Copper Cliff-derived dose-response function to the lifetime exposure of California residents may overestimate risk because of the existence of a low-level exposure threshold. If such a threshhold exists, it would be difficult to detect in occupationally exposed workers whose lowest cumulative nickel exposures (500 μg Ni/m^3 x years x 0.165 = 82.5 μg Ni/m^3 x years) were 50 times higher than those of California residents who might be continuously exposed for 70 years to the state's highest reported ambient concentrations (0.0236 x 70 = 1.6 μg Ni/m^3 x years).

C00113

IV. CONCLUSIONS

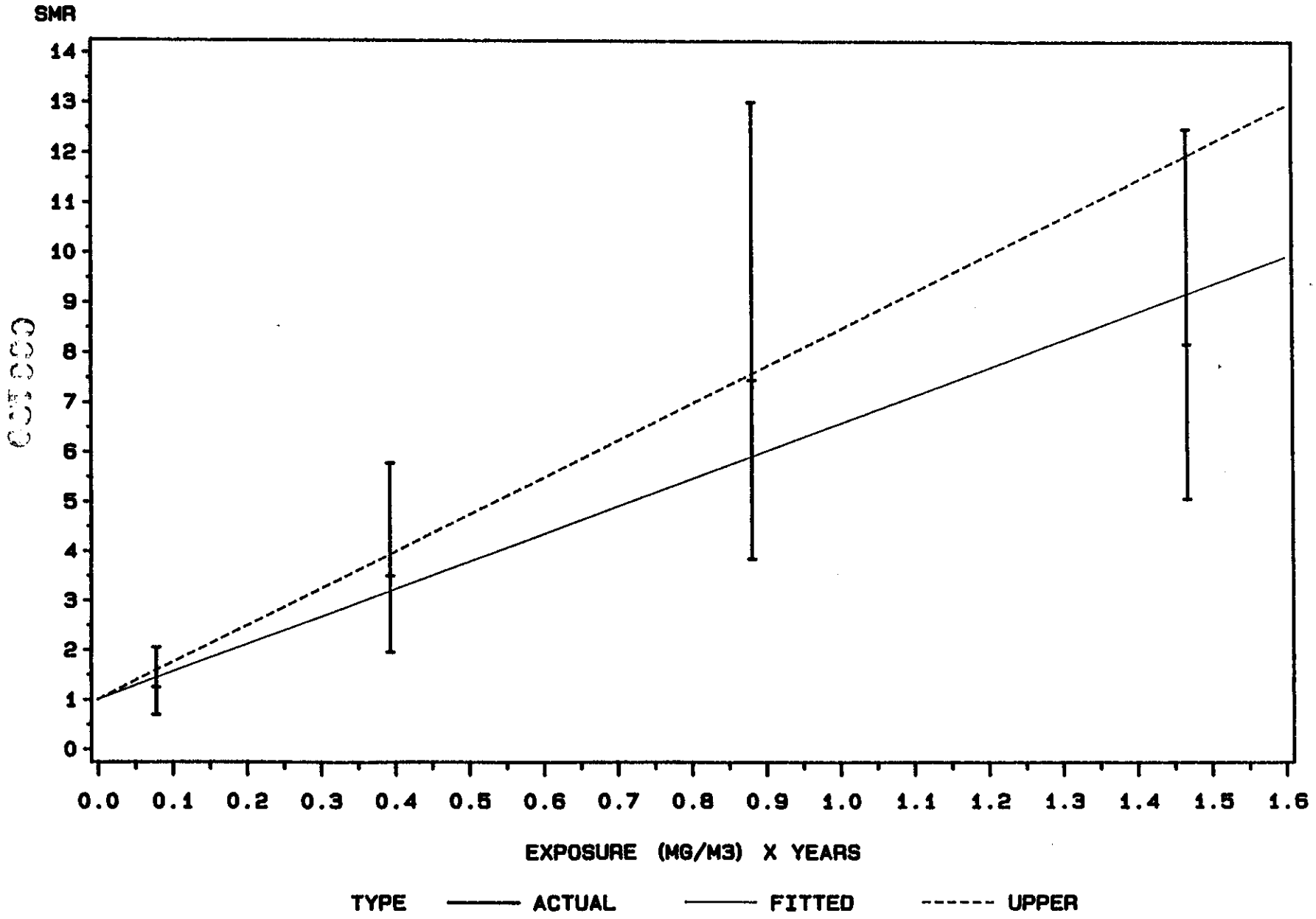
We have performed a risk assessment that addresses the issues that we raised with the CARB in August. Our analysis indicates that lung cancer risks associated with nickel exposure are low. Based on the highest observed average nickel concentration at a California air monitoring site, the lifetime (75 year) risk of lung cancer associated with continuous exposure to nickel in California's air is estimated to be less than 1.3 per million.

We recognize that this risk assessment is based on two approaches that are less than optimal. First, cumulative exposure values were crudely estimated from duration of exposure category midpoints. Second, a multiplicative model was used to approximate what is believed to be an additive process. Changes in either of these approaches could result in different risk estimates. To some extent, the use of the upper 95% confidence bound for unit risk should protect against biases which might be associated with these approaches. However to fully address these issues, we recommend examination of the basic lung cancer mortality data from the updated study of Copper Cliff sinter plant workers.

C33113

Figure 1

COPPER CLIFF SINTER PLANT WORKERS
LUNG CANCER MORTALITY RELATIVE TO ESTIMATED NICKEL EXPOSURE



PRELIMINARY COMMENTS OF THE NICKEL PRODUCERS ENVIRONMENTAL RESEARCH ASSOCIATION, INC. ON THE STATE OF CALIFORNIA'S PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT

AUGUST 13, 1990

C00121

I. Introduction

The June 1990 report, Proposed Identification of Nickel as a Toxic Air Contaminant, has been prepared by the Air Resources Board and Department of Health Services of the State of California to assist the State in determining if nickel should be identified as a toxic air contaminant. That is an important decision and must be supported by the best available scientific evidence and by the most objective interpretation of that evidence. In NiPERA's review of the report, we have identified several major areas in the report that we believe require further attention.

The comments presented below pertain solely to the quantitative risk assessment portion of the report. These comments discuss (1) the availability of new information, (2) the selection of an appropriate cohort for risk assessment purposes, (3) the assumptions associated with the risk assessment presented in the report, and (4) the calculation of a new risk estimate based upon more recent data and improved assumptions. More detailed comments on other parts of the report will be submitted at a later date.

We hope that these comments prove useful to California in meeting its objective to produce a report of high scientific merit and to make regulatory decisions that are scientifically sound.

II. New Information on Existing Cohorts

CARB's choice of studies for quantitative risk assessment is predicated on the assumption that no new cohort studies have been published since the U. S. Environmental Protection Agency (EPA) published its Health Assessment Document (HAD) on Nickel and Nickel Compounds in 1986. Because CARB believes that there is no new information available, it has evaluated the cohorts chosen by the EPA for risk assessment in order to decide whether these cohorts would be suitable for determining risks in the state of California. Ultimately, CARB chose the study of Copper Cliff sinter workers by Chovil et al. (1981) as the basis of its carcinogenic risk assessment.

It is unfortunate that CARB was unaware that the results of the International Committee on Nickel Carcinogenesis in Man (ICNCM) were recently published in a special issue (February, 1990) of the Scandinavian Journal of Work, Environment and Health. This international collaborative research project sponsored by six different organizations, including NiPERA, was undertaken, in part, in response to

C03192

the initial findings of the EPA NiHAD. These findings suggested that further follow-up, additional exposure information, and comparative analyses would be required for key nickel cohorts in order to better understand the nickel species and concentrations to which workers were exposed in the past. Only with this information could more reliable inferences be drawn regarding the risks associated with exposure to nickel compounds.

The cohorts reanalyzed by the Committee included those studied earlier by Cox et al., Cooper and Wong, Cragle et al., Enterline and Marsh, Goldberg et al., Magnus et al., Peto et al., Roberts et al. (including the Copper Cliff Sinter workers), and Shannon et al. In most instances, including the Copper Cliff workers, valuable follow-up information was added to the studies. The analysis of the Committee is detailed and somewhat complex. This is due to the complexities of the actual workplace environment to which workers were exposed. With rare exceptions, workers were exposed to mixtures of nickel compounds. Despite its complexities, CARB is advised to review this information carefully as it does represent the most recent data on these cohorts. Of likely particular importance to CARB will be the Committee's conclusion that:

> "....it is possible to comment on the cancer risks associated with the level of airborne nickel to which the general population is exposed....it can be concluded that the risk to the general population from exposure to the extremely small concentrations (less than 1 μg Ni/m^3) to which it is exposed in the ambient air is minute, if indeed there is any risk at all."

III. Selection of Cohort for Risk Assessment

Any effort to develop quantitative dose-specific models of risk from any of the nickel cohorts must first and foremost recognize the limitations of such an exercise. This limitation is due to the uncertainty in the estimates of the types and levels of nickel that workers were exposed to in the past. If models are to be used, they should not be used to the exclusion of exercising sound judgment on the basis of the qualitative and semi-quantitative information provided by these studies.

With this in mind, it would appear that the cohorts that provide the most reliable information for risk assessment are the Huntington and Ontario cohorts. This is due to the fact that actual exposure estimates, albeit limited, are available for these workers. In regard to the Huntington cohort, the problems noted by the CARB regarding the

CC0120

precision and accuracy of the relative risk estimates are not unfounded. Nevertheless, these problems must be weighed against the utility of this cohort for risk assessment purposes. As the EPA noted, the value of this cohort for risk assessment lies with the fact that the workers were exposed to concentrations that approximate environmental conditions.. Determining whether this study provides useful dose-response information at low doses is also critical to the evaluation process. It is recommended that the CARB reexamine this issue in greater detail, taking into account the new updated information within this study, before summarily dismissing this cohort for use in assessing risks.

Given that the CARB has chosen to use the Copper Cliff cohort for risk assessment, the remaining discussion will focus on the importance of using the most current information on these workers and determining whether CARB's underlying risk assumptions are appropriate.

IV. Assumptions Associated with CARB's Risk Assessment

There is no question that the CARB should use the more recent data presented on these workers. As noted in both EPA's HAD and CARB's report, the Chovil et al. study (1981) is not without its limitations. In particular, the issue of loss to follow-up of 25 percent of the cohort seems to present a particular problem in analyzing these data. In the more recent reports of Roberts et al. (1984, 1989) and the ICNCM (1990), it is noted that it is not only reasonable, but prudent to assume that those lost to follow-up in this cohort are likely to be alive at the end of the follow-up period. The reason that this assumption can be made is because deaths are ascertained through the use of a highly reliable death certificate registry in Canada (far better than that available through the Social Security Administration in the U. S.). Absence of any recording of death in this registry, coupled with statistics that reveal infrequent emigration, have been considered sufficient proof that a worker <u>has not died</u> and can therefore "justifiably contribute person-years to the analysis to the end of the follow-up period" (ICNCM, 1990). CARB's 25 percent adjustment for "fraction lost to follow-up" is therefore overly conservative and unjustifiable.

In regard to the background lifetime rates of lung cancer employed by the CARB in analyzing the Copper Cliff workers, it should be noted that the figure of 0.049 is inappropriate. CARB notes that this rate was derived by dividing the total number of cancer (lung?) deaths for the years 1963 to 1978 by the total number of deaths in those years. CARB further notes that "this estimation method

C00424

gives the lifetime risk of dying from lung cancer for a cohort experiencing the mortality rates from lung cancer from all other causes which occurred in the period 1963-1978." The calculation yields the proportionate mortality rate (PMR) for lung cancer, which does not directly measure the lifetime risk of death from lung cancer. In fact, if this calculation is carried out for the U.S. population in 1979, one obtains a "lifetime" risk for white males of approximately 0.071, whereas an estimate based on the age distribution of the population in 1979 is 0.038.

Canadian lung cancer mortality risks during the period 1960-1965 and 1975-1979 were similar, if not somewhat lower, than those of the U.S. population (Figure 1). In addition, the rates increased in both popuplations at a similar rate, as evidenced by the increases between the two time periods shown in Figure 1. The increase in Canadian lung cancer mortality risk across the 1960-1979 time period encompassing the Chovil study is shown in Figure 2.

In the EPA HAD document, the 1976 "lifetime" lung cancer risk (0.036) was adjusted downward to 0.026 to reflect the lower risks in earlier years. For a longer follow-up period, i.e. 1963-1984, this estimate would change somewhat due to the increased risks in the years 1979-1984. When the trend from 1953-1976 (reported by EPA) is taken into account, and projected forward, the risk estimate increases to 0.029. We recognize that this estimate, like the one given by EPA, may be imprecise. However, it is certainly more accurate than the 0.049 risk used by CARB.

Because the background rate is such an important component of the risk estimate, its estimation for a specific period of interest deserves more comprehensive effort than making simple adjustments to one year's data (or worse yet, using the proportionate mortality ratio). We would therefore recommend a careful examination of Canadian mortality statistics to calculate this rate for use in any risk assessment procedure.

V. Risk Assessment Calculations

A recalculation of the unit risk estimate based upon available recent data from Copper Cliff sinter workers and the modified risk assumptions noted above is presented below.

Table 1 presents the most recent data available on the Copper Cliff sinter workers as presented in the ICNCM report. These data reflect an additional six years of follow-up beyond that of the Chovil et al. study, with approximately 70 percent more lung cancer deaths

000125

(63 vs. 37). Most of these deaths occurred in men with less than five years of employment at Copper Cliff. The 33 deaths reported in the ICNCM study for men with 5 or more years exposure is virtually identical to the 34 reported by Chovil et al. as occurring in men with at least 650 (mg/m^3) * years of weighted cumulative exposure (i.e., at least 3 years of exposure). Thus, the additional follow-up resulted in no new deaths in the most highly exposed men. This, in turn, results in reduced relative risk estimates for these men.

A weighted least squares regression line (forced through 1) for these data is shown in Figure 3. Because cumulative exposure information is not available in the ICNCM report, cumulative exposures were based upon exposures to 100 mg Ni/m^3. This value represents the lower range of nickel exposure (100 to 400 mg Ni/m^3) in workers first exposed prior to 1952.[1] While this value clearly underestimates cumulative exposures prior to 1952, it likely overestimates cumulative exposures after 1952 (range: 20 to 100 mg Ni/m^3).[2] In order to correct for this overestimation, a unit risk estimate based upon the upper 95 percent confidence limit of this slope has been adjusted by 0.75 as was done in CARB's analysis of the Chovil et al. data (Table 2).

Comparisons of the unit risk estimate derived by the different methods are presented in Table 2. From this table it is evident that the slope of the lung cancer line has changed. This change reflects the reduction in estimated lung cancer mortality risk for the Copper Cliff sinter plant workers based on additional follow-up. In particular, workers in the two highest nickel exposure categories used by Chovil et al. had relative risks of 13 and 17 based on less than 1 expected death in each

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[1] The upper range of this exposure has been reported to vary from 250 to 400 mg Ni/m^3 depending on the source of the information. In the most recent report of the ICNCM, the upper limit is given as 100 mg Ni/m^3, expressed as a converted value for a personal gravimetric sampler operated in the "closed face" mode. This converted value corresponds to 250 mg Ni/m^3 as actually measured by the roof monitors. As the conversion to equivalent personal gravimetric samples was merely undertaken to facilitate comparisons between studies within the ICNCM report, the actual measured values have been used in the analysis herein. Use of the measured rather than the derived value facilitates a direct comparison to the analysis carried out by the CARB.

[2] See Appendix to ICNCM report.

C03429

category. With additional follow-up, the expected deaths rose by a factor of two. No additional deaths occurred, and the relative risk estimates dropped significantly.

Using adjustments that are more appropriate (i.e. scientifically based), the unit risk number comes to 9.6 x 10^{-5} or 96 lung cancer deaths per million, based upon the 95 percent upper confidence limit of the slope. The "best estimate" of the unit risk would be 73 lung cancer deaths per million [96 x (6.9 - 1)/(8.77 - 1)].

VI. Additional Considerations in Deriving a Unit Risk Estimate

A major consideration that has not been discussed up to this point is the choice of mathematical approach to risk estimation. The calculations presented above (and those done by CARB) were similar to the "average" relative risk (ARR) approach employed by the EPA. The CARB approach differs from the ARR approach only in that uses more than one data point to estimate the slope of the dose-response line. Weighted least squares is used to fit the line through these points (and unity), while the EPA approach simply calculates the slope of a line through the overall risk at the average exposure and unity. Neither of these approaches directly addresses the probability structure of the data. In this sense, the Maximum Likelihood estimation approach is a more rigorous method.

It would appear that the CARB's choice of an estimation method that is similar to EPA's average relative risk approach over one based on Maximum Likelihood estimation was predicated on the ease with which it could be implemented rather than on its scientific merit. That is to say, because the CARB could not replicate the calculations derived in the MLE model, it merely chose an approach that was more simplistic and easy to replicate. This hardly constitutes a scientific decision.

NiPERA's efforts to calculate the EPA's reported fitted values using the Maximum Likelihood estimate for incremental unit risk were also unsuccessful. However, this does not invalidate the approach, nor the estimates that it provides. The clue to the difficulty in replicating EPA'S results may lie in the fact that the MLE model purportedly took "the presence of all other competing risks" into account, whereas the ARR model does not account for such competing risks. Given that competing risks will undoubtedly factor into any risk assessment based upon nickel exposures alone, the CARB would be well-advised to contact the EPA for further clarification of this issue. From the results of the Huntington and Copper Cliff cohorts, it would appear that the MLE approach gives

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consistently lower risk estimates. Without fully understanding why this is so, the CARB's use of an approach similar to an ARR model may not be warranted and may result in an overestimation of the risks.

Another major consideration that has not been taken into account is the risk attributable to individual nickel species. The calculations presented above are for total nickel. There is no question, based upon the results of the ICNCM report, that exposure to different nickel compounds will likely yield different unit risk estimates. Further, there is no evidence that exposure to metallic nickel is associated with any increased lung and nasal cancer risks. A thorough evaluation of the compound-specific risks was not possible given the limited time available to respond to the CARB report and the complexities associated with such an evaluation. Nevertheless, the issue of speciation and associated risks is pertinent to the deliberations of the CARB and deserves further attention on the part of the Board.

VII. Conclusions

Based upon the information presented above, the importance of using the most recent data available and assumptions that are scientifically well-grounded becomes clearly evident. The unit risk estimate calculated by the CARB and the estimate presented above differ by at least a factor of two. Given that the risk estimate presented above is conservatively based, i.e. the exposure estimates at high doses are known to be underestimated, the true risks are likely even lower than stated.

It can be concluded that the estimated risk to residents of California from inhalation of atmospheric nickel is not likely to be higher than 0.08 ($0.0011\ \mu g\ Ni/m^3 \times 73 \times 10^{-6}$) to 2 ($0.0236\ \mu g\ Ni/m^3 \times 96 \times 10^{-6}$) lung cancer deaths per million, and may well be lower. This is, as the ICNCM report predicted, indeed, a minimal risk due to exposures to nickel and its compounds.

C00423

Table 1

Lung Cancer Mortality of the Copper Cliff Sinter Plant Workers with 15 or More Years Since First Exposure at the INCO, Ontario, Copper Cliff Sinter Plant by Years of Exposure Based on ICNCM (1990) Study

(O=observed number of deaths, E=expected number of deaths, SMR=standardized mortality ratio, CI=95% confidence interval)

Duration of Copper Cliff Sinter Plant Exposure (Years)	Lung Cancer			
	O	E[a]	SMR	95% CI
<1	15	12.04	125	
1-4	15	4.28	350***	
<5	30	16.32	184**	124-263
5-9	12	1.61	744***	
10-14	20	2.18	916***	
≥15	1	0.39	256	
≥5	33	4.18	789***	543-1109
Total	63	20.51	307***	238-396

[a]Based on the Ontario mortality rates.

* P<0.05
** P<0.01
*** P<0.001

Table 2

Risk Assessment Calculations for Lung Cancer Mortality
Based on the Copper Cliff Sinter Workers

	CARB DATA	RECENT DATA
Slope of lung cancer	9.22	6.91
Upper 95% CI of slope	11.26	8.77
Fraction lost to followup	0.25	----
Upper 95% CI of slope adjusted for loss to followup	15.02	----
Adjustment for equivalent lifetime exposure level		
Unit cumulative exposure level (mg/m^3 yrs)	1000	1000
Exposure adjustment per day (8/24)	0.33	0.33
Adjustment per week (5/7)	0.71	0.71
Adjustment per year (48/52)	0.92	0.92
Adjustment for lower exposure than initial estimate	0.75	0.75
Combined adjustment factors	0.165	0.165
Corresponding 70 yr lifetime exposure (mg/m^3)	2.35	2.35
Calculation of 95% upper confidence limits of lifetime risks for environmental exposure to 1 $\mu g/m^3$		
RR estimate for adjusted exposure	15.02	8.77
Excess RR estimate (RR-1)	14.02	7.77
Excess RR estimate for lifetime exposure at 1 mg/m^3	5.96	3.31
Background lifetime lung cancer mortality risk	0.049	0.029
Lifetime added risk for exposure at 1 $\mu g/m^3$	2.9×10^{-4}	9.6×10^{-5}

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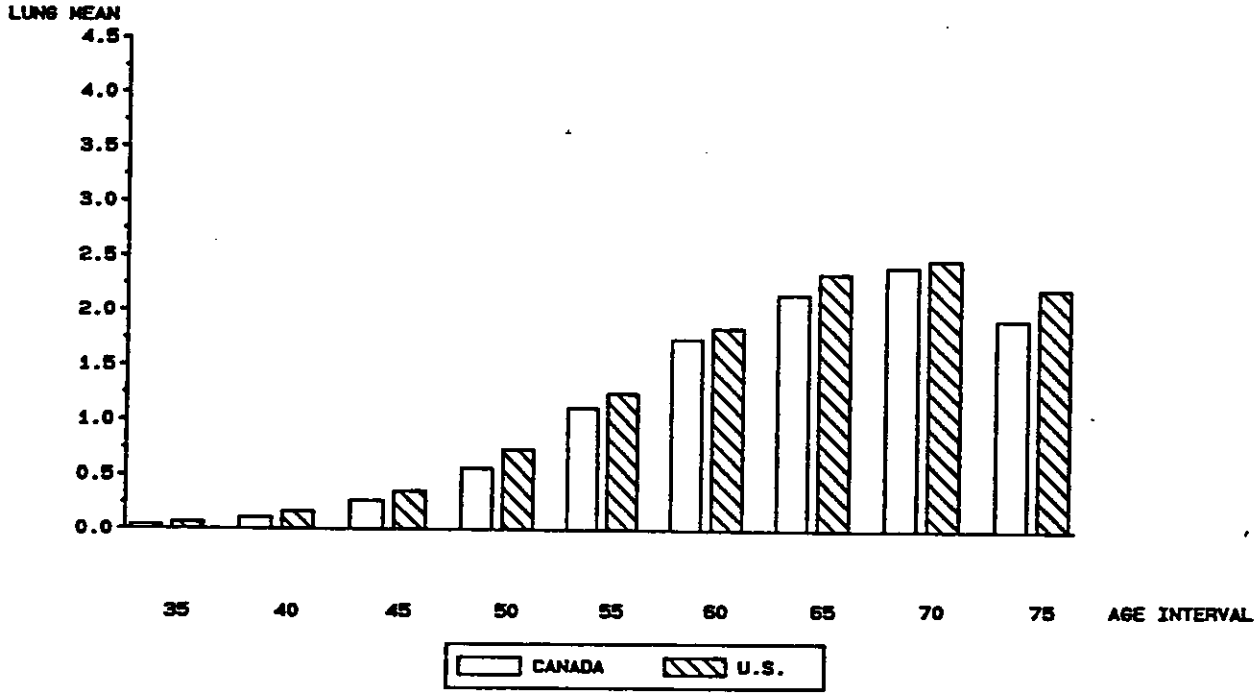
FIGURE 1

LUNG CANCER MORTALITY (PER 1000)
BY AGE CATEGORIES
YEAR=60-64



YEAR=75-79

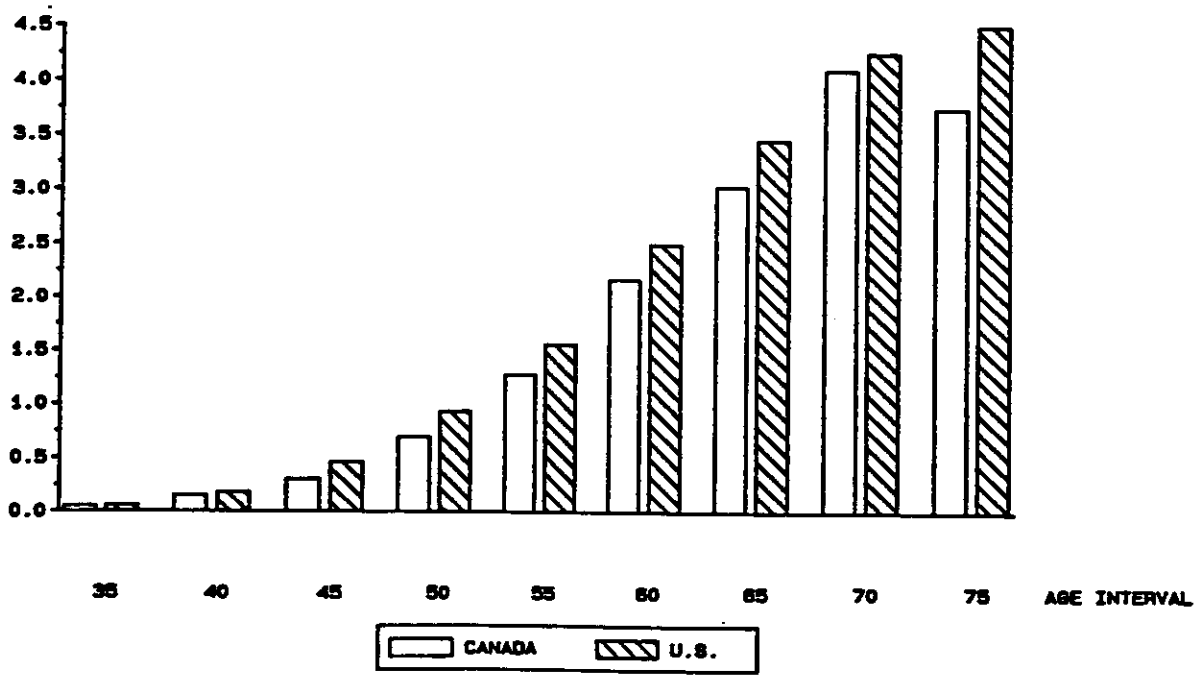


FIGURE 2

CANADIAN LUNG CANCER MORTALITY (PER 1000)
BY 5 YEAR AGE AND CALENDAR TIME CATEGORIES

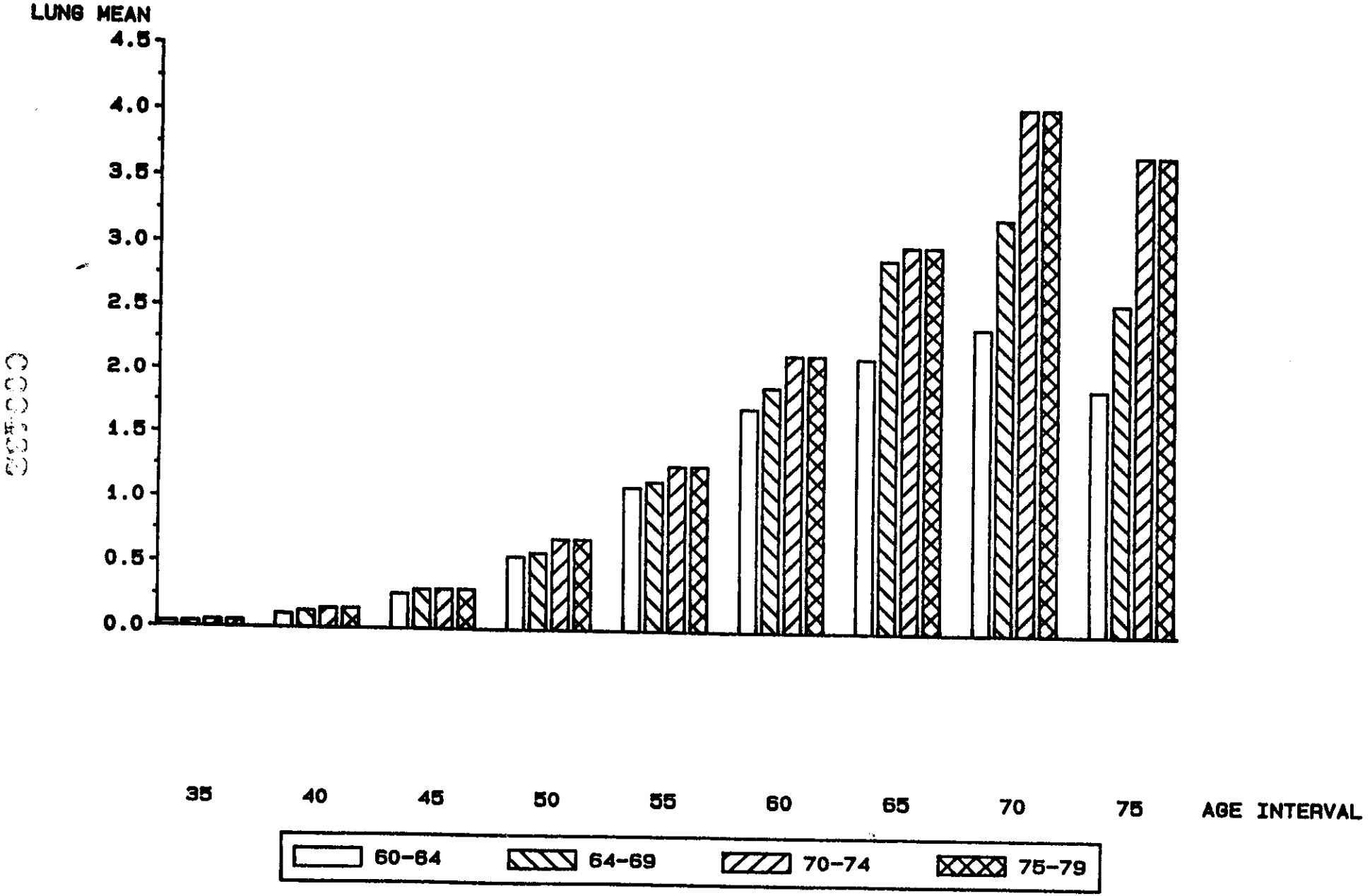
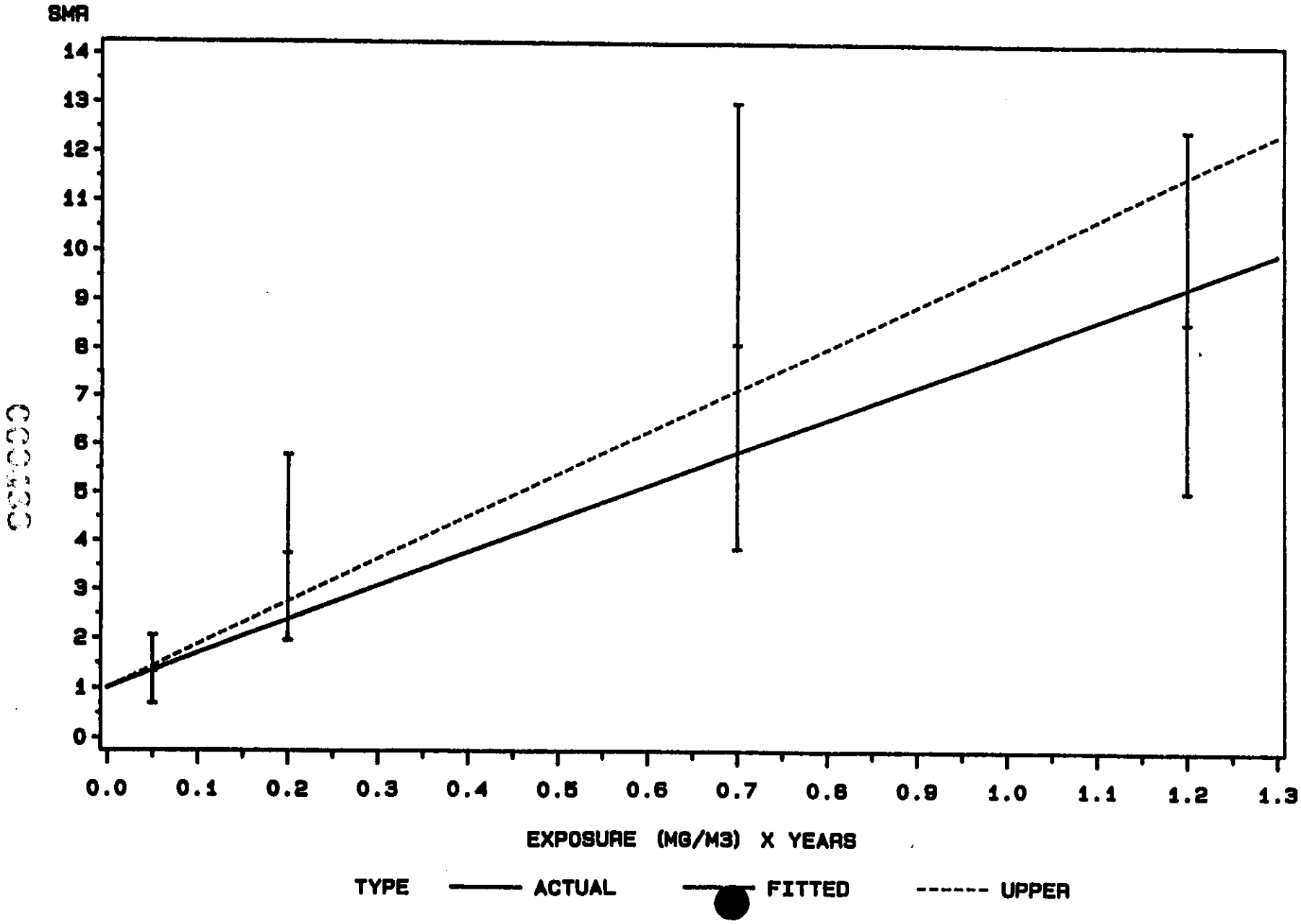


FIGURE 3

COPPER CLIFF SINTER PLANT WORKERS
LUNG CANCER MORTALITY RELATIVE TO ESTIMATED NICKEL EXPOSURE



Southern California Edison Company

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August 22, 1990

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminants Identification
Branch
Stationary Source Division
Air Resources Board
Attention: Nickel
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma:

Thank you for the opportunity to comment on the draft DHS report, "Proposed Identification of Nickel as a Toxic Air Contaminant." The report recommends that nickel subsulfide, nickel oxide, and all other forms of "insoluble nickel" be considered as capable of causing cancer in humans, and that their potencies are equal to that of nickel refinery dust. We believe this conclusion is not supported by the current state of knowledge regarding nickel toxicity.

Only nickel subsulfide, nickel refinery dust, and nickel carbonyl have shown evidence of carcinogenicity from environmental exposures. There is no evidence to support the conclusion that other forms of nickel can cause cancer by inhalation or ingestion routes of exposure. Despite this lack of data, the DHS report assumed that other forms of nickel are carcinogenic.

An EPA review of nickel toxicity (Health Assessment Document for Nickel and Nickel Compounds, 1986), which included the studies reviewed by the DHS, concluded that only three forms of nickel could be classified as having sufficient evidence for carcinogenicity; namely, nickel subsulfide, nickel refinery dust, and nickel carbonyl. Of these, the risk of cancer to humans could only be estimated for nickel subsulfide and nickel refinery dust. There was not enough evidence to classify other forms of nickel as carcinogens. This report was reviewed by the EPA's Science Advisory Panel.

Further, the National Toxicology Program is currently conducting studies on the carcinogenicity of nickel oxide and nickel sulfate (National Toxicology Program, Chemical Status Report, July 1990). The results from these studies will be available in the near future providing the necessary data to determine whether these compounds are cancer causing. Since the needed data for a carcinogenicity determination for nickel oxide and nickel sulfate is near at hand, it makes more sense to wait so that an appropriate decision regarding whether or not to list these compounds can be made at that time.

Highlighting the need to wait for the National Toxicology Program data is that the information used by the DHS to conclude that nickel oxide has the same carcinogenic potency as nickel subsulfide was from studies where the nickel compound was given by injection to experimental animals. However, exposure by injection is not relevant to assess the risk of cancer to humans by inhalation or by ingestion. The results of the relevant studies cited by the DHS are either negative or inconclusive regarding whether nickel oxide can cause cancer when inhaled, and do not give scientific support to the conclusion that nickel oxide can cause cancer in humans.

We recommend that the draft DHS report be revised to accurately reflect the scientific data and the EPA's review of the data. The only forms of nickel for which there is sufficient evidence at this time to list as toxic air contaminants are nickel subsulfide and nickel refinery dust. Listing other forms of insoluble nickel is not currently supported by the data.

Sincerely,

Janet Baas, D. Env.
Environmental Specialist

17 August 1990

Genevieve Shiroma
Toxic Air Contaminant Identification Branch
Stationary Source Division
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Ms. Shiroma,

The following comments are submitted on the February 1990 draft report, PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT, PART B--HEALTH RISK ASSESSMENT. My comments address two major issues which seem to limit the validity and usefulness of the report as the scientific basis for the regulation of nickel.

1. Omission of the Doll Report

Sir Richard Doll, of Oxford University, presented a re-analysis of nickel epidemiology studies to the International Agency for Research on Cancer in summer 1989. His research was also published as the "Report of the International Committee on Nickel Carcinogenesis in Man," Scandinavian Journal of Work, Health and Environment 16: 1-82, 1990.

The purpose of Doll's analysis was to clarify the exposure of individual workers to specific nickel species, i.e., nickel oxide, nickel subsulfide, soluble nickel, metallic nickel, and total nickel.

The CARB draft report mentions neither the existence of this important work nor its results. The Carcinogenesis section of the CARB draft report should be revised to include the Doll report, and, as appropriate, new unit risk factors should be developed for the different nickel species.

2. Apparent contradiction between the amount of nickel required by humans as an essential nutrient and the amount of nickel estimated to pose a cancer risk

Chapter 4 discusses the scientific data which support a dietary requirement of nickel for humans. Indeed, the values

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derived by Nielsen (35-50 micrograms/day) and by Bennett (120 micrograms/day) are presented as the possible daily human dietary requirement.

In contrast, breathing the air of California, which contains 0.0011-0.0236 micrograms nickel/cubic meter, seemingly puts one at risk for cancer. At the standard breathing rate of 20 cubic meters/day, this amounts to 0.022-0.472 micrograms nickel/day--quantities several orders of magnitude lower than the daily requirement!!!

This issue should be thoroughly addressed, possibly in conjunction with a more detailed discussion of tissue distribution and route of exposure for soluble and insoluble nickel species.

I appreciate this opportunity to provide technical comments in the spirit of ensuring the best scientific basis for regulations in California.

Sincerely,

Kathleen A. Hazer

Kathleen A. Hazer, Ph.D.
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18 August 1990.

SUMMARY OF MAIN ISSUES

For various regulatory toxicity evaluations which will rely on Part B of the Nickel Document as their PRIMARY SOURCE of information, the following data will be required (where possible) following inhalation, oral and dermal routes of exposure (multi-route risk assessments):

1. Amounts absorbed (percentages), retained (half-lives) and excreted
2. Metabolism, including essentiality and detoxification mechanisms
3. One day NOAEL/LOAEL data and/or LD/LC50s
4. Ten day NOAEL/LOAEL data
5. Sub-chronic - 3-9 months - NOAEL/LOAEL data
6. Chronic/Lifetime NOAEL/LOAEL data
7. Reproductive effects data - NOAEL/LOAEL levels and
8. Data on genotoxicity and carcinogenicity - risk assessment(s), potency, etc.

On limited examination of the sections pertaining to points 1-7, it was found that many references had been omitted. Some of the more obvious ones (32) have been included in the line by line critique attached, but it is strongly suggested that an in-depth literature review, both on-line and by hand (of key articles, the in press IARC document, etc.) be performed prior to draft No. 2.

With regard to the section on genotoxicity, review data to improve this section are attached. Any additional references in the in press IARC document should also be considered.

For the section on animal model carciogenicity, recent literature should be reviewed using the on-line data-bases and additional information should be obtained from the in press IARC document, as well from key NTP experiments, completed or nearing completion.

Since the Carcinogenic Risk Assessment on Nickel is based on human cohort(s), it is imperative to use the latest and most detailed mortality and exposure data that are available, namely, Doll et al. (FEBRUARY, 1990) and Roberts et al. (1989). This has not been done, leading to a document that is out-dated and which does not reflect the current state of scientific knowledge.

Consideration should also be given to whether more than a single Carcinogenic Risk Assessment should be developed for nickel and its various compounds.

In addition, the new IARC classification of nickel and nickel compounds, should be taken from the in press IARC document, for example, metallic nickel is no longer classed as Group 1.

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17 August 1990.

COMMENTS ON THE ARB/DHS DOCUMENT ON NICKEL AS A TOXIC AIR CONTAMINANT

Part B: SUMMARY
Part B: Page 1, Paragraph 3, Line 7:
The word "tested" should be clarified - this was not a normal population, but rather a set of persons with skin sensitivity/problems.

Part B: Page 2, Paragraph 2, Line 7:
The oral and inhalation dose units should be put in a form to show that the LOELs are comparable.

Part B: Page 2, Paragraph 4, Lines 5-8:
This statement should be reconsidered after reading the Doll Report (Doll et al., 1990).

Part B: Page 2, Paragraph 5:
It should be noted that there was only ONE DOSE LEVEL in this inhalation study.

Part B: Page 3, Paragraphs 1 and 2:
These statements should be reconsidered after reading the Doll Report (Doll et al., 1990) and RECOMPUTING A NEW RISK ASSESSMENT.

Part B: Page 3, Paragraph 5, Lines 7-10:
This statement should be reconsidered after reading the Doll Report (Doll et al., 1990).

Part B: Page 3, Paragraph 7, Line 2 and on:
These statements should be reconsidered after reading the Doll Report (Doll et al., 1990) and RECOMPUTING A NEW RISK ASSESSMENT.

Part B: Page 4, Paragraphs 2-5:
These statements should be reconsidered after reading the Doll Report (Doll et al., 1990) and RECOMPUTING A NEW RISK ASSESSMENT.

Part B: Page 7, Section 3:
Under this section the following 3 references should be included:

1. Sunderman and Selin (1968) - Rats, nickel carbonyl, inhalation, 15mins at 200mgNi/m3 - significant absorption.

2. Mikehyer (1971) - Rabbits, nickel carbonyl, inhalation, 100mgNi/m3 for 1hr., 28% of dose retained, half-life in lung 7.8 and 21 hours.

3. Tanaka et al. (1985) - Rats, nickel oxide, inhalation, 0.5 or 55mgNi/m3, 7hrs/d, 5d/wk for over 1 month - half-life in lung, 11.5 months for small particles and 21 months for large particles.

Part B: Page 29, Section 4.2:
This section deals with deficiencies not with normal level interactions and this should be clearly stated in the heading.

In addition, there should be a section dealing with metal-nickel interactions at "normal" levels and ALSO one on the interaction of nickel and other metals in carcinogenesis, for example, the nickel-manganese interaction (Sunderman and McCully, 1983).

Part B: Page 31, Section 5:
The following 22 references on acute, sub-chronic and chronic animal and human toxicity should be included under the various sub-sections:

1. Dadrup et al. (1983) - Acute, human toxicity - Stated by ATSDR/EPA to be a key study.

2. Adkins et al. (1979) - Mice, inhalation, nickel chloride (0-0.9mgNi/m3 for 2hrs) or nickel sulfate (0-0.46mgNi/m3 for 2hrs) - LOAEL levels obtained.

3. Dunnick et al. (1987) - Mice and rats, inhalation, 12 days - comparative toxicity - nickel oxide, subsulfide and sulfate - Stated by ATSDR/EPA to be a key study.

4. Bingham et al. (1972) - Rats, inhalation, nickel chloride or oxide, 2 weeks - Stated by ATSDR/EPA to be a key study.

5. Weischer et al. (1980a) - Rats, inhalation, nickel oxide, 0.2, 0.4 or 0.8mgNi/m3, 23hrs/d, 7d/wk, 28 days.

6. Yelfimova et al. (1976 and 1977) - Rats, inhalation, nickel oxide, 1, 5, 50 or 500ugNi/m3, continuous for 3 months - LOAEL 5ugNi/m3.

7. Weischer et al. (1980b) - Rats, inhalation, nickel oxide, 0.2, 0.4 or 0.8mgNi/m3, 23hrs/d, 7d/wk, 180 days.

8. Curstedt et al. (1983 and 1984) - Rabbits, inhalation, nickel dust, 3-8 months - NOEL 0.13mg/m3 - Stated by ATSDR/EPA to be a key study.

9. Itskova et al. (1978) - Rats, inhalation, nickel chloride, 0.2, 1, 5, 50ugNi/m3, continuous for 6 months - weight gain effects.

10. Kosova (1979) - Rats, inhalation, nickel sulfate, 0, 1.1 or 2.2mgNi/m3, 4hrs/d, 7d/wk, 9 months - LOAEL 1.1mgNi/m3.

11. Clary (1975) - Rats, intratracheal, nickel chloride, 1 dose of 2.8 or 5.6mgNi/kg - effects on glucose and insulin.

12. Mastromatteo (1986) - Rats, oral, nickel hydroxide, sulfate, oxide, sulfide and subsulfide, LD50s.

13. Haro et al. (1968) - Rats, oral, nickel acetate, LD50.

14. Itskova et al. (1969) - Rats, oral, nickel chloride, LD50s and other effects.

15. Kosova (1979) - Rats, oral, nickel sulfate, LD50 and other effects.

16. Weischer et al. (1980a) - Rats, oral, nickel chloride, 0, 2.5, 5 or 10ppm Ni, 28 days - effects observed at 2.5ppm.

17. Whanger (1983) - Rats, oral, nickel acetate, 100, 500 or 1000ppm Ni for 6 weeks - NOEL 100ppm, LOAEL 500ppm.

18. Dieter et al. (1987) - Mice, oral, nickel sulfate, 44, 108 or 150mgNi/kg/day, 180days - LOEL 44mg/kg/day.

19. Itskova et al. (1969) - Rats, gavage, nickel chloride, 0.5, 5, 50, 500 or 5000ug/kg for 7 months, effects at 5mg/kg level.

20. O'Dell et al. (1970) - Calves, oral, nickel carbonate, 62.5, 250 or 1000ppm, 8 weeks - NOAEL 250ppm or LOAEL 1000ppm.

21. Kosova (1979) - Rats, dermal, nickel sulfate, 25% or 50% solns., 14 or 30 days - effects noted.

22. Mathur et al. (1977) - Rats, dermal, nickel sulfate, 0, 40, 60 or 100mgNi/kg for 15 or 30 days - effects noted.

Part B: Page 31, Section 5.1, Lines 6-7:
Under "... cause of human" ACUTE "systemic toxicity", the word ACUTE has been omitted.

Part B: Page 53, Section 5.5:
The following 7 references should be included in this reproductive effects section:

1. Weischer et al. (1980a) - Rats, nickel oxide, inhalation, 0.8, 1.6 or 3.2mg/m3 - dose-dependant effects.

2. Berman and Rehnberg (1983) - Mice, nickel chloride, oral, 500 or 1000ppm Ni, days 2-17 - NOAEL 500ppm.

3. Nadeenko et al. (1979) - Rats, nickel chloride, oral, 0.01, 0.1 or 10ppm Ni for 7 months, male and female, prior to mating and through pregnancy - 0.1ppm embryo lethal, 10ppm infertility.

4. Phatak and Patwardham (1950) - Rats, nickel carbonate, oral, 0, 8, 15 or 25mgNi/kg bd. wt., 8 week prior to mating and through pregnancy - reduced litter sizes at all levels (small groups).

5. Tsujii and Hoshishima (1979) - Mice, nickel chloride, parental, 1ug in 1ml water, 11 doses during pregnancy - behavioral effects.

6. Costa and Mollenhauer (1979) - Rats, nickel subsulfide, i.m., 15mgNi on day 6 - animals kept 26 months - tumors and other effects observed.

7. Gilani and Marano (1980) - Chick eggs, nickel chloride, injection, 5-17ugNi/egg - dose related malformations.

Part B: Page 69, Section 5.5.5, Paragraph 2, Lines 10-12:
Please give the original reference and state whether these were and are official EPA extrapolation values.

Part B: Section 5.5.5, Page 70, Paragraph 1:
Please state:
1. The year after Ottolenghi et al.,
2. The page on which the calculations for the dose 122.8ugNi3S2/m3 can be found,
3. How the value of 60ugNi/kg-day was obtained,
4. What is the lowest reproductive effect level being quoted, plus reference,
5. "An exposure of 24ngNi/m3 per day (based on the maximum level" of what, and
6. What is the LOAEL for the rat and again the reference.

Part B: Page 70, Section 6:
A genotoxicity tabular summary would be most helpful. Since apparently the data consulted were from the reviews by Sunderman (1989) and IARC (1987a), it is suggested that the relevant table (copy attached) from a third review, namely that by Fairhurst and Illing (1987), be precised, added to, brought up to date and used.

Part B: Page 72, Section 7.1, Lines 6-8:
Please state WHEN the "check" was made, thus showing how current this statement is.

Part B: Page 72, Section 7.1, Lines 8-10:
Since these studies were to be completed in 1988 or 1989, please report on what the status is in late 1990 and if in press, please sumarize the findings.

Part B: Page 72, Section 7.1.1.1:
In Paragraph 1, do the third and fourth sentence refer to Hueper (1958)? Do Paragraphs 2-4 refer to Hueper (1958)?

Part B: Page 72, Section 7.1.1.4:
In the first paragraph, Fisher et al. (1986) is noted but is not mentioned again in this section. Their findings should be described and it should be noted that this was an intratracheal experiment.

Part B: Section 7.1.2, Page 88:
The first four paragraphs on page 88 need to be deleted, since they are a repeat of what is already on page 85.

Part B: Page 90, Section 7.1.4:
The second sentence is technically incorrect, for example, Kosova (1979) tested nickel sulfate by the inhalation route for a period of 9 months at a dose level of up to 2.2mgNi/m3 for 4 hours per day.

Part B: Page 94, Section 7.2, Line 3:
It is stated, ".. increased risks of lung cancer and NASAL SINUS cancers." Please explain why this appears to be the last time NASAL cancers are referred to. In addition to the cohorts of nickel refinery workers mentioned later, the following articles may prove helpful:

Andrews (1983), Heinberg et al. (1983), Kicharin (1970), Rousch et al. (1980), Torjussen (1979) and Virtue (1972).

It would also seem important, at some stage, to discuss the possible involvement of nickel with other types of cancer and why this is improbable. Some references are: Burch et al. (1981), Olsen and Sabroe (1984), Roberts et al. (1989) and Doll et al. (1990).

Part B: Page 96, Section 7.2, Line 5:
In spite of Stern's statement it would be helpful to review certain welding studies, such as:
Gerin et al. (1984) and Becker et al. (1985), Polednak (1981) - nickel pipe welders and Sjogren (1980) and Cornell (1984) - stainless steel welders and workers.

Also, why are only refineries and welders mentioned for possible worker exposures? It may be helpful to review, for example, the following cohorts and to show that the resultant risks were low, not statistically significant or negative:

1. Swedish Ni/Cd battery workers - Kjellstrom et al. (1979), Andersson et al. (1984) and Elinder et al. (1985)
2. British Ni/Cd battery workers - Sorahan and Waterhouse (1983)
3. US aircraft engine factor workers - Bernacki et al. (1978)
4. Metal polishing and plating industry - Blair (1980)
5. Die-casting & electroplating - Silverstein et al. (1981)
6. Nickel platers - Burges (1980)
7. Ni/Cr platers - Sorahan et al. (1987)
8. US alloy plant - Redmond (1984)
9. Ni/Cr alloy foundry workers - Cornell and Landis (1984)
10. British alloy plant - Cox et al. (1981) and Doll et al. (1990)
11. Oak Ridge Gaseous Diffusion Plant - Godbold and Tompkins (1979), Cragle et al. (1984) and Doll et al. (1990)

For completeness it would seem appropriate to also review, briefly, the following studies:

1. Germany - Rockstroh (1958)
2. Czechoslavakia - Olejar etal. (1982)
3. Russia - Znamenskii (1963), Tatarskaya (1965 and 1967) and Saknyn and Shabynina (1970 and 1973)
4. Japan - Tuchiya (1965)

Part B: Page 96, Section 7.2, Line 8:
In this document DHS states that no new cohort studies have been published since the EPA Risk Assessment, this is incorrect. THREE groups of studies have been published:

1. Goldberg et al. (1987) and Leclerc et al. (1987),
2. Roberts et al. (1989a and b) and
3. Doll et al. (1990) - one of the most complete and complex studies ever to have been undertaken. It should be noted that EPA, CEC and two departments of the Canadian government were among the 6 sponsors of this study. This study, known as the Doll Report was published in FEBRUARY, 1990 and pre-publication copies had been available in 1989.

In addition, several reviews are worthy of consideration and inclusion in Part B of this document:

1. The IARC Review of Nickel, Chromium and Welding - In Press, (Meeting held June, 1989 and they had draft copies of the Doll Report made available to them)
2. Recent papers by Bozec (1989), Sunderman (1989b) and Grandjean et al. (1988) and
3. Earlier reviews by Doll (1980), Doll (1984) and Peto (1985).

In addition, to the 4 cohorts of refinery workers discussed by DHS, the following cohorts need at least to be mentioned:
1. Hydrometallurgical nickel refinery in Alberta - Egedahl and Rice (1984)
2. Falconbridge, Canada - Shannon et al. (1980 and 1984) and Doll et al. (1990)
3. New Caledonia - Lessard et al. (1978), Langer et al. (1980), Goldberg et al. (1985a and b), Goldberg et al. (1987), Leclerc et al. (1987) - New Guinea - and Doll et al. (1990)
4. Finland - Doll et al. (1990) and
5. Hanna Mining, Oregon - Doll et al. (1990).

Part B: Page 96, Section 7.2.1.1:
When considering this West Virginian cohort, data from Enterline and Marsh (1980) and more importantly, those from Doll et al. (1990) are worthy of consideration, as well as the study by Enterline and Marsh (1982) cited by DHS.

Incorrect data are given in Section 7.2.1.1 and Table 7.8. The 8 lung cancer deaths observed versus 6.96 expected, were from a sub-cohort of 109 calcine workers, NOT the total cohort of 1855 workers hired before 1947. There were 72 lung cancer deaths in the cohort of 1855, whereas 74.12 were expected. In the cohort of 1353 hired after 1946 there were 19 lung cancer cases versus 19.37 expected. Also the AVERAGE total nickel for the calciners was estimate to be 5.00mg/m3, not a range of 0.01-5.00mg/m3 as stated. This was made up of metallic Ni: 0.4mg/m3; oxidic Ni: 0.5mg/m3; soluble Ni: 0.05mg.m3 and sulfidic Ni: 4.0mg/m3 (Doll et al., 1990). This makes the values calculated for cumulative exposure in this section invalid. (The calciners were dismantled in 1947 not 1948).

Table 63 in Doll et al. (1990) is of particular interest, since SMRs have been calculated for lung cancer versus cumulative exposure for metallic nickel, oxidic nickel, sulfidic nickel, soluble nickel and total nickel.

The choice of cohort and/or sub-cohort and exposure data should be discussed, <u>in detail</u>, in further drafts of this document.

Part B: Page 96-8, Section 7.2.1.2:
When considering this INCO, Ontario, Canadian cohort (really 3 cohorts - Copper Cliff, Coniston and Port Colborne), in addition to the studies mentioned by DHS, namely, Chovil et al. (1981), Roberts et al. (1984), Muir et al. (1985) and Warner (1985), the data from Mastromatteo (1967), Roberts et al. (1980), Roberts and Julian (1983) and more importantly those from Roberts et al. (1989a and b) and Doll et al. (1990) need to be considered <u>in detail</u>.

The total size of this INCO-Canadian cohort is 54,746 workers, of whom 50,977 were classed as "non-sinter" workers and 3,769 as sinter workers.

The study by Chovil et al. (1981), which has been used by DHS for the nickel risk assessment, is now out of date for this purpose, since their follow-up period ended in 1978, whereas in the newer references the follow-up was brought up to 1984. Chovil et al. use on a sub-cohort taken from the Copper Cliff sinter plant and reports on 495 workers with 37 lung cancer deaths, whereas Roberts et al. (1989) and Dole et al. (1990) cite 67 lung cancer deaths out of 1744 workers from this SAME Copper Cliff sinter plant.

It should be noted that in this study by Chovil et al. (1981), it was thought that 25% of the cohort was lost to follow-up. In the later studies, including the Doll Report and Roberts et al. (1989b), the method of tracing ex-workers (via the Canadian death records system) is such, that it is highly unlikely that any of the untraced workers have died. This latter comment also applies to Section 7.2.5, Page 112, Paragraph 5.

Thus, since so much NEW data are now available, this Section 7.2.1.2 PLUS the TOTAL RISK ASSESSMENT (Sections 7.2.2, 7.2.3, 7.2.4, 7.2.5 and 8, as well as Tables 7.8 and 7.9 and Figure 2 and also probably Figure 1) will need to be <u>reconsidered, rewritten and recomputed</u>.

However, the very availability of so much new data may cause problems of choice. For example, when considering ONLY the INCO - Ontario cohort, what data should be used? Some of the choices among <u>sinter workers</u> are as follows:

1. From Port Colborne (electrolysis, leaching, calcining and sintering) Doll et al. (1990), Tables 53 and 55 and Roberts et al. (1989b), Table 2 - 72(73) lung cxancers were observed in a sub-cohort of 1671 or

2. From the sinter cohort at Copper Cliff and Coniston, Roberts et al. (1989b), Table 1 and Doll et al. (1990), Tables 52 and 54 - observed 67 lung cancers in a sub-cohort of 1744 and 8 in a sub-cohort of 336, respectively or

3. Should the combined data from the 3 sub-cohorts, as given in Doll et al. (1990), Table 50, be used?

Considering Doll et al. (1990), Table 9 and other available exposure data, how should these exposure levels be used? For example:

1. How should exposure levels be averaged, if mortality data were to be combined from the 3 sinter worker sub-cohorts from Copper Cliff, Coniston and Port Colborne, see Doll et al. (1990), Table 9?

2. Should total nickel (different for each plant and for each time period) be used?

3. Or how should risk due to oxidic nickel, sulfidic nickel and soluble nickel be apportioned? It would seems that with our present state of

knowledge that apportioning risk would be inappropriate, in spite of Doll et al. (1990), Table 63.

A detailed discussion on Doll et al. (1990) pp. 5-6 and 69-75 is also of critical importance.

The choice of cohort and/or sub-cohort and exposure data should be discussed, in detail, in further drafts of this document.

Part B: Pages 98-100, Section 7.2.1.3:
In this INCO, Clydach, Welsh cohort, in addition, to the studies mentioned by DHS, namely, Doll et al. (1977), Peto et al. (1984), Morgan (1985) and Kaldor et al. (1986), data from Anon. (1932a and b), Bridge (1933), Amor (1939), Doll (1958), Morgan (1958), Doll et al. (1970), Cuckle et al. (1980) and more importantly those from Doll et al. (1990) need to be considered, in detail.

The overall cohort qualification period was 1902-1960 (not 1910 as stated on line 1, page 99) with a follow-up period in the Doll et al. (1990) study of 1907-1984.

The plant at Clydach is of interest for a couple of reasons:
1. The history of the plant is know in a great deal of detail, since there is little turn-over in the population of the plant or in the village and
2. The present medical director, Dr. Lindsay Morgan grew up in the village and succeeded his father, who only fairly recently died in his mid-nineties, whereas his mother is still alive in her late nineties. Both had a very keen interest and knowledge of the history of the area and community and plant affairs. Dr. Lindsay Morgan's maternal grandfather was an associate of Dr. Mond, whose process (the Mond process) was used in setting up the plant originally.

Thus, the estimates of exposure given in Doll et al. (1990), Tables 2 and 3 should be fair and accurate and since Dr. Morgan has done further research, his newer data in the Doll Report should supercede his earlier estimates (Morgan, 1985), quoted in Part B: Section 7.2.1.3, Paragraph 5 on page 99.

The problems with the cohorts and SMRs stated in Part B: Section 7.2.1.3, Paragraph 6 on page 99 and the top of page 100, no longer exist, see for example Doll et al. (1990), Table 17. The size of the cohort post-1930 was 1173, with 44 lung cancer deaths, hence it can no longer be stated, "...the number of workers in the cohort .... are too few....". The cohort pre-1930 is 1348 not 967 (as stated in Part B: Table 7.8, page 101) and the number of cancer deaths is 172 not 145.

The choice of cohort and/or sub-cohort and exposure data should be discussed, in detail, in further drafts of this document.

Part B: Page 100, Section 7.2.1.4:
In this Falconbridge, Norwegian cohort, in addition, to the reports considered by DHS, namely, Pederson et al. (1973), Kreyberg (1978) and Magnus et al. (1982), data from Loken (1950) and more importantly that in Doll et al. (1990) should be considered.

The mortality data given in Doll et al. (1990), Tables 41, 43 and 44 are of particular interest. It should be noted that the total cohort size is now 3250 with 77 deaths from lung cancer versus 2247 with 82 lung cancers quoted in Part B: Table 7.8, page 101.

Exposure data are now available, see Doll et al. (1990), Table 6. Thus extrapolations from other plants, see Part B: Page 100, Section 7.2.1.4, Lines 11-13, should not be used. For comparisons with exposures in other plants see Doll et al. (1990) pages 6, 18 and 20 and elsewhere.

The choice of cohort and/or sub-cohort and exposure data should be discussed, in detail, in further drafts of this document.

Part B: Pages 100-101, Section 7.2.2:
It is important that the Falconbridge, Ontario, Canadian cohort of 11,594 workers be included with the above 4 cohorts in any Risk Assessment cohort choices discussed by DHS in future drafts of this document. References for this Falconbridge, Ontario cohort are as follows: Shannon et al. (1980 and 1984) and Doll et al. (1990). Exposure estimates also exist for this cohort - Doll et al. (1990), Table 11, as well as for several sub-cohorts - Doll et al. (1990), Table 70. One of the sub-cohorts is a "sinter workers" group of 1602 workers with 24 lung cancer deaths.

Part B: Section 7.2.2 - Choice of Risk Assessment Cohorts - CANNOT be adequately commented on until a NEW Table 7.8 is contructed and a TOTAL RE-EVALUATION of the cohorts and/or sub-cohorts to be used for risk assessment is made by DHS.

Very nearly all the observations made about the 4 cohorts in Part B: Section 7.2.2 are no longer applicable, following the publication of Doll et al. (1990) and Roberts et al. (1989b). Many of the necessary changes have been discussed above.

Part B: Pages 103-5, Section 7.2.3.1:
Because of the Doll Report, Part B: Page 104, Table 7.9 needs to be recalculated.

Also because of the Doll Report, with its new follow-up periods, Part B: Page 105, Lines 8-10 need to be recalculated. In addition, the change in background population cancer rates with time needs to be adequately addressed. This latter comment also applies to Section 7.2.5, Page 115, Paragraph 5.

Part B: Page 105, Section 7.2.3.3:
Because of the Doll Report, this section is now only of historical interest.

Part B: Pages 105-7, Section 7.2.3.4:
Because of the Doll Report, most of Page 107, Paragraph 2, although of historical interest, should not be relevant to the necessary NEW 1990 Risk Assessment for Nickel.

Part B: Pages 108-9, Section 7.2.4:
Page 108, Paragraph 1, Line 5: The new follow-up periods from the Doll Report should be used.

Part B: Pages 109-11, Section 7.2.4.1:
Page 111, the last Paragraph, Line 5, this statement may not be true for non-US cohorts. Smoking became increasingly popular in European and UK during WWI and after 1918, blue collar workers, particularly ex-soldiers, were seldom without their cigarettes.

Part B: Pages 112, Section 7.2.4.2:
This section needs to be made relevant to the cohorts used in the necessary NEW 1990 Risk Assessment.

Part B: Pages 112-5, Section 7.2.5:
This section and Tables 7.11 and 7.12 need to be made relevant to the cohorts used in the necessary NEW 1990 Risk Assessment.

Part B: Pages 116-7, Section 8:
Paragraphs 1 and 2 need to be up-dated to reflect the data in the Doll Report.

Paragraph 3, Sentence 1 needs to be up-dated to reflect the data in the Doll Report, including Table 63.

Paragraph 3, Sentences 4 and 5 are incorrect, the negative study (Fisher et al., 1986) was intratracheal NOT inhalation.

Paragraph 3, Sentences 6 and 7 will need to be updated following a NEW Risk Assessment, using the data available in the Doll Report.

Paragraphs 3 and 4, it would be instructive to compare the doses used by Ottolenghi et al. (1974) and Glaser et al. (1986) in rats and Wehner et al. (1975 and 1984) in hamsters and then convert them to human equivalency doses. Ottolenghi et al. (1974) exposed rats to 0.7mgNi/m3, 6hrs/d, 5d/wk for 78wks as nickel sulfide, that is a weekly dose of 21mgNi or a total dose of 1638mgNi in 78wks. Whereas, Glaser et al. (1986) exposed rats to 0.2mgNi/m3, 23hrs/d, 7d/wk for 78wks as nickel oxide, that is a weekly dose of 32.2mgNi or a total dose of 2511.6mgNi in 78 wks. This is about 150% of Ottolenghi et al. (1974) dose. The data for Wehner et al. (1975 and 1984) are: hamster exposed to 42mgNi/m3, 7hrs/d, 5d/wk for life, that is a weekly dose of 1470mg.

Paragraphs 5 and 6 need to be re-thought after detailed review of the Doll Report, particularly pages 71-5.

Paragraph 7 needs to be re-thought after reading the Doll Report, particularly pages 70-1 and 73-5. With regard to Sentence 4 and 5, is it official DHS policy to compare the potency of inorganic compounds of a particular element by comparing times of residency in the lung?

Paragraph 8 needs to be re-thought following study of the Doll Report.

Part B: Pages 117-8, Section 9:
Although the conclusions of this paragraph are correct, certain

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statements should be clarified.

1. "There are no animal or human studies which produce" SCIENTIFICALLY VALID "evidence that nickel is carcinogenic when ingested"; the words scientifically valid should be added.

2. The degree of absorption of nickel oxide and nickel subsulfide from the alimentary tract will not be zero.

3. Sentence 6, as it stands, is not logical. Concentration build-ups of inorganic compounds in body organs do not necessarily lead to cancer.

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August 20, 1990.

Ms. Genevieve Shiroma,
Chief - Toxic Air Contaminant Identification Branch,
Stationary Source Division,
Air Resources Board,
Attn: Nickel,
P.O. Box 2815,
Sacremento, CA 95812,
U.S.A.

Dear Ms. Shiroma:

We have reviewed the preliminary draft report on nickel prepared by the staffs of the Air Resources Board (ARB) and the Department of Health Services (DHS), dated June, 1990. Our comments are recorded below and are restricted to Part B of the report:

P.3: In the second to last paragraph, the DHS states that there is at present no way to quantitatively determine a carcinogenic threshold for nickel. Nevertheless, the DHS considers the mechanism of nickel's carcinogenicity as a nonthreshold process in the absence of compelling evidence of a threshold. We feel that the report looses credibility on the basis of this assumption.

P.5 : Item IB2: IARC recently classified nickel compounds as Class I carcinogens and metallic nickel in the Class 2B category. The final report should be revised to reflect this change.

P.7 : Item 3 - Pharmacokinetics: This paragraph should be expanded to indicate that nickel absorption depends on the amount inhaled and breathing rate, as well as the chemical form.

P.25 : Item 4 - Essentiality: The report recognizes that nickel deficiency has not been described in humans but has recently been established as an essential trace element in a number of microorganisms, plants and experimental animals. This statement is not compatible with the assumption that nickel carcinogenicity is a nonthreshold process referred to in the comment on P.3 given above.

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Pgs. 79 vs 92 and 94: In the last paragraph, in Section 7.1.1.1, on metallic nickel (P.79), the report recognizes that lung reactions can vary dramatically between the rat and hamsters, the latter showing scarcely any chronic affects, due to exposure, suggesting this species may be non-responsive to nickel. Nevertheless, in Section 7.1.5.1, Pg.92, metabolic factors are assumed to be equal across species and the fraction absorbed is assumed to be the same for all species in the calculation of the human equivalent continuous exposure on P.94. The adoption of a cross-species equality approach is considered to be a serious weakness in the report.

Pg.95 : Table 7.7: The application of a One-Hit Model to determine the risk estimates is not appropriate, since it has been demonstrated that concinogenicity is a multi-stage event. See ref. attached in Appendix 1, Grisham (1989) CIIT Activities, 9, 1-9.

P.112 : Risk Assessment Calculations in Section 7.2.5: The use of the Chovil et al., 1981, paper to make risk assessment calculations for lung cancer mortality (Table 7.12) is suspect, since the study is not considered useful for the determination of the magnitude of the increased risk. The fundamental weaknesses of the study are associated with the following:

(a) A very significant 25 percent of the cases were untraced, which is considered too high and reason to reject the study.

(b) It was assumed that the 25 percent untraced had the same cancer incidence as the balance of the cohart, which is unacceptable.

(c) It appears that the cause of death for 37 of the primary lung cancer cases was determined from pathology or clinical reports and not on death certificates alone. The corresponding Ontario vital statistics were based on death certificate information only and such a comparison is unacceptable epidemiologic practice.

(d) The approach used to determine the adjustments for equivalent lifetime exposure could be improved. Work periods were longer and vacation times shorter prior to the 1950 time-frame, resulting in longer exposure periods than those considered. Improvements could be made by obtaining more detailed information on work schedules for the study period.

These and other shortcomings of the Chovil study were summarized by Wong et al. and the relevant critique is attached in Appendix 2.

Finally, the conclusion by the DHS, based on the findings of nickel-induced carcinogenesis in humans and animals, that nickel is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness or which may pose a present or potential hazard to human health is at odds with the conclusions expressed in the Report of the International Committee on Nickel Carcinogenesis in Man, published in a special issue of the Scand J. Work Environ Health 1990, 16:1-82. The evidence from the Committee study suggests that respiratory cancer risks are primarily

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related to exposure to soluble nickel at concentrations in excess of 1 mg Ni/m^3 and to less soluble forms at concentrations greater than 10 mg Ni/m^3. With excess risks being confined to these high levels of exposure and the absence of any evidence of hazard from metallic nickel, it was concluded that the risk to the general population from exposure to the extremely small concentrations (less than 1 g Ni/m^3) to which it is exposed in the ambient air is minute, if indeed there is any risk at all.

Yours very truly,

FALCONBRIDGE LIMITED,

Dr. Larry A. Morris,
Director,
Product Environmental &
Regulatory Services.

Dr. Albert G. Cecutti,
Director,
Occupational Health & Hygiene.

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Attachs.

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Appendix 1.1

CIIT ACTIVITIES
Chemical Industry Institute of Toxicology

Vol. 9, No. 2 February, 1989

The First Leon Golberg Memorial Lecture
January 13, 1989

Current Insights Into the Mechanisms of Carcinogenesis, with Implications for Mesothelioma

Joe W. Grisham, M.D.

I am honored to be the first Leon Golberg Memorial Lecturer. Dr. Golberg epitomized to me the ideal modern toxicologist. He was broadly trained in mathematics and chemistry (bachelor's degrees); in physical chemistry and anatomy/physiology (master's degrees); and in biochemistry, organic chemistry, and medicine (doctoral degrees or equivalent). He had extensive practical experience in toxicology and metabolism at many levels, including working scientist, college professor, drug company executive, and research institute director. Although Dr. Golberg held several notable positions, including directorship of the British Industrial Biological Research Association, I believe his most outstanding accomplishment was made as Founding President of the Chemical Industry Institute of Toxicology.

It was during his tenure at CIIT that I knew Leon Golberg. I first met him in 1976, when he came to Chapel Hill to enlist my help in bringing about his goals for CIIT. That he succeeded in involving me is attested by the fact that I served continuously on the CIIT Scientific Advisory Panel from 1976 to 1988. The opportunity to work with Leon Golberg for five years of that period was personally rewarding. His mission was to establish CIIT as the premier research institution on mechanistic toxicology in the world, a goal he pursued with single-minded intensity.

Leon considered his major scientific interest to be "mechanisms of toxic action of environmental chemicals." Not only did he want to understand toxic mechanisms, but he also wanted to see that knowledge applied to improving the safe manufacture, use, and disposal of toxic chemicals. Leon's faith in the utility of mechanistic insights into toxicology can be stated succinctly by paraphrasing *John 8:32*: "Know the mechanism, for the mechanism will set you free." He sincerely believed that accurate knowledge of toxic mechanisms could help free the public of its generalized fear of chemicals.

To undertake this mission, Dr. Golberg quickly gathered a staff of imaginative young scientists, and he imbued them with his sense of purpose. A research program was started almost immediately in the old Corning Glass building in north Raleigh and expanded in the state-of-the-art facility in Research Triangle Park. Today CIIT is a highly regarded international center of research on mechanisms of toxicity of chemicals. Reflecting this stature, I have previously characterized CIIT as "the jewel of the chemical industry." If that metaphor is apt, then so is this: Leon Golberg faceted and polished that jewel. CIIT is a living memorial to his accomplishment.

To know this man, to observe his achievements, and to sense how he wrought them—by combining awesome intellect and sound common sense with total commitment and intense personal effort—was a powerful experience for me. I dedicate my lecture today to the memory of this singular man and to his accomplishments as a scientist and a leader.

A distinguished leader in the field of chemical carcinogenesis, Joe Wheeler Grisham is a natural choice to introduce the Leon Golberg Memorial Lecture Series. Dr. Grisham's continued pursuit of an increased understanding of the mechanisms through which chemicals induce tumors has spanned twenty-five years, from early work in the whole animal to today's emphasis on understanding this process at the molecular level. His current research interests focus on oncogenes and tumor suppressor genes as determinants of susceptibility to chemically induced cancer.

Dr. Grisham earned both his undergraduate and M.D. degrees at Vanderbilt University in Nashville, Tennessee. A lieutenant commander in the U. S. Naval Reserve, he served with the U. S. Naval Radiological Defense Laboratory in San Francisco from 1961-63. He taught pathology and anatomy at Washington University School of Medicine, St. Louis, Mo., for many years. Since 1973, Dr. Grisham has been Professor and Chair of Pathology and Professor of Medicine, University of North Carolina at Chapel Hill.

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App 1.2

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Activities is published monthly by the Chemical Industry Institute of Toxicology. All correspondence should be directed to Willanna Griffin, Information Services, Chemical Industry Institute of Toxicology, P.O. Box 12137, Research Triangle Park, North Carolina 27709. Telephone (919) 541-2070.

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Stedman, D. B., and Welsch, F. (1989)

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App 1.3

Lecture (from page 1)

A member of numerous professional organizations, Dr. Grisham has served on numerous governmental and professional committees. He has been chairman of CIIT's Scientific Advisory Panel since 1976. He serves on the editorial boards of ***Experimental and Molecular Pathology, Laboratory Investigation, Cancer Research, Environmental Health Perspectives,*** *and* ***American Journal of Pathology****. Dr. Grisham has authored or coauthored more than 100 publications.*

The Golberg Lecture series is intended to promote a better understanding of mesothelioma, the cancer that led to Leon's untimely death. While I am not an expert on mesothelioma, I have spent much time studying carcinogenesis as a generalized biological process. In this lecture, I will summarize some current insights into the mechanism and process of carcinogenesis in general and then survey recent studies that bear on the mechanism of development of mesothelioma. I will focus on new aspects of the molecular genetics and cell biology of cancer -on proto-oncogenes, tumor suppressor genes, growth factors and receptors, and on the behavior of the cells in which these genes and molecules have been altered. The broad overview that I will present necessarily will lack much important detail.

Genes and Cancer

Our current understanding indicates that cancer is a disease (or rather, a group of diseases) of the cellular genome (Knudson, 1986; Bishop, 1987). Development of cancer by affected cells occurs in response to aberrant expression of genes, leading to abnormal elevation or suppression of production of a normal gene product (a protein), or to the production of an abnormal (mutated) gene product. Full development of cancer is associated with the aberrant expression of multiple genes, which causes the cancer cell to project an abnormal phenotype. A cell's phenotype results from the interplay of that cell's actively expressed genes (genotype) and its microenvironment; the cancer phenotype allows an affected cell and its progeny to reproduce free of the constraints normally imposed on cells in an organized, highly regulated tissue, and to move across tissue barriers to establish colonies (metastases) at distant sites. Numerous epigenetic microenvironmental influences play important roles in cancer development by producing conditions that enable the selective growth of genetically altered cells.

Cancer begins, in the vast majority of instances, as a genetic change in one individual cell. A population of cancer cells is clonal (Woodruff, 1986), the entire mass of aberrant cells being derived by the sustained reproduction of the progeny of a single altered cell. In fact, most cancers undergo multiple clonal evolutions to generate several new cell populations, each more abnormal than the previous (Nowell, 1986). Sustained reproduction of cells is an essential feature of cancer development. In the past, we believed erroneously that all cancer cells reproduced more rapidly than normal cells, and most of the current chemotherapeutic strategies are still based on that former presumption. Reproduction of cancer cells differs from that of normal cells not by being more rapid, but by being unregulated by the needs of the body, which allows huge populations to accumulate.

We know the properties of only a few of the many genes that control cell reproduction, whose aberrant expression may play a role in cancer development (Bishop, 1987). In a few instances, specific genes involved in carcinogenesis have been cloned and sequenced, their locations on chromosomes precisely ascertained and the functions of their gene products determined. However, much remains to be learned about the involvement of genes and their protein products in producing the cancer phenotype.

Proto-oncogenes and Tumor Suppressor Genes

Two major categories of genes appear to have essential roles in carcinogenesis mechanisms— so-called proto-oncogenes and tumor suppressor genes or anti-oncogenes (Knudson, 1986; Bishop, 1987; Friend *et al.*, 1988). The use of the term oncogene (or tumor gene) may seem to imply that these types of genes are directed specifically to the causation or prevention of cancer. However, the genes that are involved in carcinogenesis also have essential roles in the reproduction and differentiation of normal tissue cells. Their names reflect their involvement in cancer, which is accidental. It is only when these genes are expressed incorrectly —at the wrong time in a cell's life, in the wrong amount, or after they have been altered to yield an incorrect product or no product at all— that they confer the cancer phenotype.

At this time, strong evidence indicates that more than thirty proto-oncogenes and possibly four or five tumor suppressor genes may be involved in cancers in humans (Bishop, 1987; Friend *et al.*, 1988; Sager, 1986; Klein, 1987). In addition, there is less substantial evidence of a similar role for several more genes of each category. In general, proto-oncogenes act to stimulate cell reproduction while tumor suppressor genes act to inhibit reproduction of cells, although this overly simple description obscures much mechanistic complexity. Thus, uncontrolled cell reproduction is facilitated by activated proto-oncogenes and by inactivated tumor suppressor genes. Hypothetically, the activation of one or more proto-oncogenes may need to be combined with the inactivation of both alleles of a relevant anti-oncogene for cancer to develop from a normal diploid cell.

Even though this theory may be generally correct in its broad implications, it will need much modification as more is learned about the genetics of cancer. Already we know that it is too simple and the distinctions between proto-oncogenes and tumor suppressor genes too sharply drawn. For example, the normal allele of certain proto-oncogenes appears to be able to block the action of the mutated allele, giving such a gene both oncogenic and anti-oncogenic functions (Klein, 1987). Furthermore, in cells from different tissues, carcinogenesis may require different combinations (possible lineage-specific) of proto-oncogenes and/or tumor suppressor genes, which may have to be expressed or not expressed during limited states ("windows") of differentiation in order to produce the cancer phenotype (Klein, 1987). Terminal differentiation is a potent suppressor of cancer development.

The protein products of genes that are involved in carcinogenesis include various growth factors, growth factor receptors, tyrosine kinases, G-proteins, DNA binding proteins, and other molecules that take part in the transmission of a signal from the surface of a cell to that cell's interior, as well as products of other genes that regulate the cell cycle, cell differentiation, and gene translation/transcription. Many of these gene products are components of a cell's signal transduction pathways. Peptide growth factors, which regulate the growth of cells by exerting positive or negative influences on cell proliferation,

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participate in the first step of a signal transduction pathway. Growth factors produce a cellular response by binding to a specific receptor (Deuel, 1987; Earp *et al.*, 1988), which typically stimulates a protein kinase to phosphorylate a tyrosine residue on the cytoplasmic end of the receptor molecule, thereby causing it to activate the next step in the signal transduction pathway.

For example, in the phosphoinositide signal transduction pathway (Berridge, 1987), the growth factor receptor is linked through a so-called G-protein to a specific phospholipase, which hydrolyzes phospholipids in a cell's membrane to yield inositol phosphates and diacyl glycerol (Berridge, 1987). Both of the latter molecules function as so-called second messengers to stimulate specific metabolic responses, the former to mobilize calcium and the latter to exchange protons, among other things. The resulting changes in intracellular pH and level of ionized calcium stimulate further alterations in cellular metabolism, ultimately leading to the expression of a set of genes that causes the cell to reproduce. Products of various proto-oncogenes appear to participate at various levels of this signal transduction pathway (Bishop, 1987; Klein, 1987). Abnormal components of the signal transduction pathways, such as those produced by activated proto-oncogenes, lead to the transmission of incorrect information, which may cause the cell to reproduce inappropriately.

Numerous growth factors have been identified, each of which can stimulate a response in a limited range of cells by binding to specific receptors (Deuel, 1987). A normal cell generally does not express both cognate growth factors and growth factor receptors (Sporn and Roberts, 1985). Typically, one type of cell in a tissue provides the growth factor that binds to its specific receptor on and regulates a response of another cell in that tissue, or the regulatory growth factor may come from another tissue located elsewhere in the body. Interdependence of cells and tissues for regulatory growth factors is a physiological strategy that serves to balance and integrate the needs of the body for the products of various cells and tissues. As a crucial part of the cancer phenotype, a cell may acquire the ability to produce a growth factor for which it already has a receptor (or vice versa), thereby escaping an important control on reproduction. When a cell makes both a growth factor and its receptor, it is said to be under autocrine growth control, a condition which results in positive regulatory feedback and stimulated continuous reproduction (Sporn and Roberts, 1985). Autocrine control has been shown to occur in several cancers. Paracrine functions of growth factors, including actions on vessels and connective tissue, are of major importance in development of cancer.

Aberrant expression of proto-oncogenes can be activated by several mechanisms (Bishop, 1987; Nowell, 1986; Friend *et al.*, 1986; Sager, 1986; and Klein, 1987). Activation of some oncogenes can occur by specific single-base mutations of the DNA of the affected gene, by translocation of the gene to another site on the chromosome where it is controlled by an active promoter, by amplification (that is, by formation of several additional copies of the gene), and by over-expression through post-translational mechanisms.

The activating effect of mutations is well illustrated by the *ras* group of oncogenes (Barbacid, 1987). The normal protein product of the *ras* gene is localized to the cell membrane, where it may function as a G-protein in a signal transduction pathway. Single-base mutations, most commonly in either the 12th or 61st codons of the *ras* genes, activate them by causing the replacement of one amino acid in the protein product. These mutations appear to yield a protein product that has reduced GTPase activity and impaired function in signal transmission.

A well-studied example of oncogene activation by genomic translocation involves the *myc* gene in the malignant tumor of lymph glands known as Burkitt's lymphoma (Haluska *et al.*, 1987). Burkitt's lymphoma is a cancer of B-lymphocytes, cells which normally produce immunoglobulins at high levels when confronted with a foreign antigen. Actively expressed immunoglobulin genes are located on human chromosome 2 at band p12 (kappa chain), on chromosome 14 at band q32 (heavy chain), and on chromosome 22 at band q11 (lambda chain); the *myc* gene is located at band q24 of chromosome 8. In the Burkitt's lymphoma, the *myc* gene is translocated to a site near one of the immunoglobulin genes (or vice versa), which places it under control of the highly active enhancer-promoter sequences of an immunoglobulin gene. Translocation of either the *myc* gene or one of the immunoglobulin genes results in reproducible structural changes in the involved chromosomes (Haluska, *et al.*, 1987). Characteristic, nonrandom structural changes also are found in the chromosomes of many other types of cancers (Heim and Mitelman, 1987). Many of these chromosome structural changes occur at breakpoints that involve oncogene loci (Haluska *et al.*, 1987).

Combinations of activated oncogenes, whose products act at different points in the signal transduction pathway, sometimes may be required to produce the cancer phenotype (Bishop, 1987; Klein, 1987; Weinberg, 1985). For example, an oncogene that codes for a nuclear protein, such as *myc*, may act in concert with an oncogene that codes for a product that is a part of the signal transduction system located in the cell membrane, such as *ras*. We have studied a liver epithelial cell line which has acquired autocrine growth regulation by aberrantly expressing transforming growth factor-alpha, a growth factor almost identical in function to epidermal growth factor (Lui *et al.*, 1988). Expression of the TGF-alpha gene alone is insufficient to produce the cancer phenotype in these cells, which requires elevated expression of both the *myc* gene and the gene for TGF-alpha. Increased expression of the *myc* gene appears to sensitize the cells to the effects of TGF-alpha.

The normal functions of the products of tumor suppressor genes (anti-oncogenes) and the inactivation of these genes in the development of the cancer phenotype is currently under intensive study. There is now considerable evidence for the participation of genetically recessive tumor suppressor genes in predicating the cellular phenotypes of several types of cancers. Cells from such cancers are typified by the loss or inactivation of both alleles of these gene loci. The first evidence for tumor suppressor genes came from studies in which cancer cells and normal cells were fused to form a hybrid offspring and the ability of the progeny of that hybrid to form a tumor was tested (Sager, 1986; Stanbridge, 1984). These studies have shown that when a normal, diploid cell of a particular lineage is fused with a tumor cell from the same lineage, the ability of the hybrid progeny cell to form a tumor generally is suppressed. Further studies with unstable hybrids which lose chromosomes have shown that tumor suppression can be traced to specific chromosomes, the exact chromosome seeming to vary with the specific lineage of the cancer cell (Sager, 1986; Stanbridge, 1984).

For example, human chromosomes 1, 4, 11, 13, and 14 are associated with tumor suppression in hybrids formed between

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tumorigenic and normal human cells of some lineages. In addition, studies on nonrandom chromosomal aberrations in cancer cells have identified consistent deletions in additional chromosomes that may reflect the location of recessive tumor suppressor loci for other human cell lineages, including tumors of endocrine glands, kidney, lung, and mammary glands (Sager, 1986; Stanbridge, 1984). Recent studies have shown that a single copy of chromosome 11, incorporated into Wilms' tumor cells by minicell fusion, is able to suppress the cancer phenotype (Weissman *et al.*, 1987). Such results imply that these chromosomes contain gene loci, the products of which suppress the expression of the cancer phenotype.

The Rb locus ("RB" for retinoblastoma, a cancer of the eye), located on human chromosome 13 at band q14, is the most completely elucidated human tumor suppressor gene (Knudson, 1985; Lee *et al.*, 1988; Huang *et al.*, 1988). The involvement of the Rb locus was first detected by astute interpretation of epidemiologic studies on familial retinoblastoma, which suggested that the Rb gene is recessive (Knudson, 1985). These epidemiologic studies indicated that the cells of children who have a familial susceptibility to the development of retinoblastoma contain only one active Rb allele, acquired loss or inactivation of this remaining allele resulting in the development of the cancer. The mechanisms by which the remaining Rb allele may be inactivated were suggested to include mutational or nonmutational inactivation of the Rb locus, nondisjunctional deletion of the chromosome containing the active Rb locus, nondisjunction of the normal chromosome followed by reduplication of the copy that lacks the active Rb locus, and deletion of the Rb locus by mitotic recombination (Knudson, 1985).

Subsequent laboratory research on tissues from patients with sporadic and familial retinoblastoma has corroborated the clinical studies. Recent research studies have identified the precise chromosomal location of the Rb gene, the gene has been cloned, and the gene product has been characterized as a DNA-binding phosphoprotein (Lee *et al.*, 1988). Furthermore, transfection of the cloned Rb gene into cultured retinoblastoma cells has been shown to suppress the cancer phenotype (Huang *et al.*, 1988). Loss of function of the Rb gene appears to be effective in causing retinoblastoma only during a limited period of retinal growth (Knudson, 1985; Lee *et al.*, 1988), but the Rb locus also may have a role in the development of osteosarcoma at a later time in the lives of retinoblastoma-prone children (Lee *et al.*, 1988).

Cell Reproduction

Control of the cellular reproductive cycle (or cell cycle) is the crucial feature that distinguishes normal and cancer cells. The cell cycle encompasses the complete and accurate replication of the genome (DNA synthesis) during the S phase, the precise splitting of the genomic DNA into two identical sets, and the distribution of these identical sets as chromosomes to the two progeny cells during the M (mitosis) phase (Prescott, 1987). The genome is most susceptible to damage that leads to cancer (gene mutations and numerical and structural aberrations of chromosomes) while it is being replicated and distributed to daughter cells (Grisham *et al.*, 1983). Genes, including proto-oncogenes, are replicated in an ordered sequence during the period of DNA synthesis; first the genes that are actively expressed in that cell lineage, followed by the numerous genes that are not actively expressed (Doggett *et al.*, 1968). We have found that the point of maximal susceptibility of a cultured mouse cell to chemically induced transformation coincides with the time of replication of the Harvey *ras* gene (Grisham *et al.*, 1979), and that the transformed phenotype is associated with activation of the same gene (Smith and Grisham, 1987). Many mutagenic agents are also clastogens, that is, they induce structural abnormalities (translocations, inversions, duplications, deletions) in chromosomes (Oshimura and Barrett, 1986). In addition, abnormalities of the microtubules of the mitotic spindle may lead to the maldistribution of entire chromosomes to the two daughter cells (nondisjunctional errors), which may play a role in the development of cancer by "unbalancing" gene dosage (Sachs, 1986). In any event, chromosomal abnormalities as reflected by aneuploidy are associated closely with the cancer phenotype (Nowell, 1986; Friend *et al.*, 1988; Sager, 1986; Klein, 1987).

It is unfortunately true that genomic errors occur spontaneously with a reproducible probability each time a cell replicates, splits, and distributes its DNA during a reproductive cycle, even in the absence of a carcinogenic agent. Spontaneous errors in base sequence leading to gene mutation occur randomly at every gene locus approximately once in every 10^7 to 10^9 reproductive cycles (Lewin, 1980). Some of these spontaneous mutations may be expected to activate oncogenes and inactivate anti-oncogenes. If the participation of two gene loci, including a recessive tumor suppressor gene, is required for the full expression of the cancer phenotype, the overall probability of the spontaneous development of cancer in diploid cells would be reduced to about once in every 10^{14} to 10^{18} cell births. Whatever the combination of genes involved in carcinogenesis, the probability of spontaneous acquisition of the cancer phenotype appears likely to lie between about once in 10^8 cell births to once in 10^{12} cell births. This may seem to represent a very small risk. However, during a 70-year span following conception, more than 10^{16} new cells are produced in the human body (Prescott, 1987). In the face of such an awesome level of cell reproduction, even events of such low probability will occur with reasonable frequency. Doubtless our somatic tissues contain numerous cells that have spontaneously developed alterations in individual proto-oncogenes or tumor suppressor genes that permit the entrainment of the carcinogenic process. Certainly, clinical experience demonstrates that cancers occur most often in those tissues that are the sites of the most extensive cell reproduction (Foulds, 1958). Any situation that augments cell reproduction in a tissue or acts to increase the genomic error rate during DNA replication (such as a familial DNA repair deficiency and/or exposure to carcinogens) will increase the probability that cancer will develop in that tissue. In the mouse cell line to which I previously referred, the tumorigenic phenotype is spontaneously acquired (along with activation of the H*ras* gene) at the rate of about 10^{-7} per cell per division (Grisham *et al.*, 1988b). Exposure of these cells to a potent mutagen/carcinogen (methyl-N'-nitro -N- nitrosoguanidine) while they are replicating the H*ras* gene increases the probability that they will develop the tumorigenic phenotype by about 100-fold (Grisham *et al.*, 1988a).

The Process of Carcinogenesis

Cancer is a slowly developing disease that encompasses multiple stages and may require decades to evolve in humans (Foulds, 1958). A major hypothesis depicts the process of carcinogenesis as a linear sequence comprising at least three stages, termed initiation, promotion, and progression (Yuspa and Poirer, 1988). These discrete stages may reflect the temporal involvement of

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different genes. Initiation, as the name implies, is conventionally viewed as the first event in the process occurring either spontaneously or from the damage incurred by a carcinogen. As the result of the initiation step, the affected cell acquires an altered ("initiated") phenotype. This new phenotype is expressed as a changed pattern of response to stimuli for growth and differentiation that gives the cell a selective growth advantage over uninitiated cells. In at least some instances, the initiating mutation-like lesion involves a proto-oncogene, causing its aberrant expression and reducing the stringency with which the reproductive cycle of the initiated cell is regulated.

During the promotion stage, the initiated, response-altered cell is caused to replicate selectively by the influence of certain agents or environments to form a clonal population of similar initiated cells (Yuspa and Poirer, 1988). Promoting influences are varied, some being chemicals that act through epigenetic, reversible pathways. Promoters may not be complete carcinogens, and agents that have only promoting activity cannot initiate the process of carcinogenesis. Different chemical promoters have entirely distinct chemical properties, tissue specificities and, probably, mechanisms of action. The chemical promoter which has been most intensively studied experimentally, tetradecanoyl phorbol acetate, acts by binding to protein kinase C and affects one limb of the phosphoinositide signal transduction pathway (Blumberg, 1988). Some growth factors also have promoter activity for some cell lineages. Even though the mechanisms of different chemical promoters are diverse, the outcomes are the same—selective expansion of the clonal population of initiated cells (Yuspa and Poirer, 1988). The elevated cell proliferation that typifies many promoting environments also can facilitate the spontaneous development of additional genetic changes.

The progression stage of carcinogenesis is characterized by the acquisition of the malignant cancer phenotype by some of the cells in the expanded clone of initiated cells (Nowell, 1986; Yuspa and Poirer, 1988). During the progression stage, cells with increasingly aberrant genotypes and phenotypes appear. Although little is known about the mechanisms underlying progression, this stage is characterized by escalating levels of genetic instability, which may include the deletion or inactivation of both alleles of a tumor suppressor gene as the critical event. Other gene alterations that also may occur in cells during the progression stage include activation of an additional, cooperative oncogene, deletion of the normal allele of a mutated oncogene, and amplification of an oncogene (Klein, 1987), or reassortment of chromosomes to alter gene dosage (Sachs, 1986). Whatever the genetic mechanisms, new clonal populations that are able to metastasize to distant sites arise during the progression stage.

Initiation of a cell by a carcinogen, and even initiation followed by promotion, does not necessarily yield a cancer. The initiated cell will not advance further in the carcinogenic process unless it encounters an environment that enables it to escape the normal regulatory constraints on cell growth, *i.e.*, that allows it to express the phenotype made possible by its altered repertoire of active genes. Large populations of initiated cells resulting from promoter action will not grow autonomously and metastasize unless additional genomic changes occur. Production of cancer requires the concatenation of several necessary but individually insufficient propabilistic events. New therapeutic strategies are based on blocking the process of carcinogenesis by interdicting cellular mechanisms. Reducing the probabilities for any one of the linked mechanistic events reduces the overall probability of cancer, and may prevent its occurrence even when one or more of the permissive cellular lesions have been induced and the process has been carried nearly to completion. From the therapeutic point of view, this complexity offers many points at which evolution of the carcinogenic process potentially may be terminated. In order to take full therapeutic advantage of this situation, however, we must yet learn the details of the mechanisms of carcinogenesis in every cell lineage and tissue.

New Insights into Mesothelioma

The mechanism of development of mesothelioma is still obscure (Yuspa and Poirer, 1988). This is not surprising when it is understood that mesothelioma was not recognized until about fifty years ago (Craighead, 1987). Although reasonably diligent television viewers and newspaper readers now are aware that certain types of asbestos fibers may play a causal role in mesothelioma, identification of asbestos as a causal factor did not take place until 1960 (Craighead, 1987). The recognition of asbestos as a carcinogen greatly stimulated research into the causes and development of mesothelioma (Craighead, 1987).

Not only have many epidemiological studies of human populations with known exposures to particular forms of asbestos been performed, but the carcinogenic potential of asbestos and other mineral fibers has been evaluated in experimental animals under controlled conditions, using defined amounts and types of fiber given by different routes. I will leave the discussion of these valuable studies to future Golberg Lecturers. However, I want to mention in the context of my talk today that epidemiologic studies of human populations indicate that numerous patients with mesothelioma report no known exposure to asbestos (Peterson *et al.*, 1984), and show that individuals from some families are more susceptible to the development of mesothelioma than are persons from the general population (Lynch *et al.*, 1985). These observations suggest that mesothelioma may occur spontaneously and from causes other than asbestos, and that susceptibility to mesothelioma from any cause, as for retinoblastoma and some other cancers, may be genetically conditioned. The cellular and molecular basis for increased susceptibility to mesothelioma must continue to be explored.

Recent studies have demonstrated that cultured normal human mesothelial cells proliferate in response to an unusually large number of individual growth factors of different types, including epidermal growth factor (and, by analogy, TGF-alpha), platelet-derived growth factor, fibroblast growth factor, transforming growth factor-beta, interleukin-1, interleukin-2, interferon-beta, and interferon-gamma (Lavek *et al.*, 1988). Certain combinations of growth factors, especially a combination of EGF (or TGF-alpha) with either PDGF or TGF-beta or a combination of FGF with PDGF or IL-1 or IFN-gamma, stimulate sustained rounds of cell proliferation in cultured normal human mesothelial cells (Lavek *et al.*, 1988). This broad pattern of response to different growth factors suggests that mesothelial cells could be affected by activation of an equally wide range of proto-oncogenes. Mesothelioma cells of one cultured line have been shown to synthesize and secrete PDGF and, possibly, TGF-alpha (Gerwin *et al.*, 1987), suggesting that they have acquired an autocrine growth factor/receptor pathway.

Combined observations from several studies involving cells from more than 25

human mesotheliomas show that virtually all are aneuploid, with either hypodiploid or hypotetraploid numbers of chromosomes, and contain a nonrandom pattern of chromosome numerical and structural abnormalities (Gibas *et al.*, 1986; Popescu *et al.*, 1988). The most common structural abnormalities in mesothelioma cells involve deletions, translocations, and inversions of one or both arms of chromosomes 1, 3, 7, 9, 17, and 22. These chromosomes are the sites of several proto-oncogenes and of genes for some of the growth factors that stimulate proliferation of mesothelial cells, most notably the *sis* gene (chromosome 22q13) which codes for the B chain of PDGF. Although a mesothelioma-specific karyotype has not yet been identified, it seems reasonable to hypothesize that these chromosome structural alterations reflect the genomic lesions that lead to the development of autocrine stimulation of growth of mesothelial cells, and, therefore, to the cancer phenotype.

Exposure of cultured human mesothelial cells to asbestos fibers *in vitro* causes reproducible abnormalities in the distribution and structure of chromosomes in progeny (Lechner *et al.*, 1985), which may resemble those found in mesothelioma cells (Popescu *et al.*, 1988). Mesothelial cells in which aneuploidy has been induced by exposure to asbestos fibers demonstrate altered growth characteristics, including some growth properties that suggest that the affected cells have partially acquired the cancer phenotype (Gibas *et al.*, 1986).

These and other recent studies (Moalli *et al.*, 1987) provide the basis for hypothesizing a mechanism of asbestos-induced mesothelial carcinogenesis. Asbestos fibers injure mesothelial cells and activate macrophages which accumulate at the sites of injury. Activated macrophages excrete several growth factors that cause sustained proliferation of normal mesothelial cells, and they also produce reactive species of oxygen which may mutate genomic DNA. Furthermore, asbestos fibers may cause abnormalities of chromosome structure and number in injured mesothelial cells, possibly leading to activation of the *sis* or another oncogene. The combination of sustained cell proliferation, mutation-like lesions, and chromosomal aberrations would facilitate the production of clonal cell populations that contain activated oncogenes and lack tumor repressor loci, causing them to express the cancer phenotype. Tentative though it be, this hypothesis offers a framework for further studies that should provide more substantial knowledge of the mechanism of mesothelioma development.

Envoi

I hope that my lecture is a worthy reflection of Leon Golberg's intense interest in toxicological mechanisms, and that it will provide a base on which future Golberg Lecturers can build. As I was constructing this lecture, one of my recurring ideas was of what Leon would have thought about its contents. I am confident that he would be proud of the fact that much important research on carcinogenic mechanisms, including the carcinogenicity of asbestos and other fibers, had been accomplished at institutions in the Research Triangle, especially his beloved CIIT. However, I am certain that he would be dissatisfied with our current state of mechanistic knowledge about general carcinogenesis and development of mesothelioma. In my reverie, I imagined I con with that typical bright twinkle in his eyes and his characteristic, somewhat enigmatic smile, as he said, "Joe, excellent progress has been made on this problem, but there is much more that must be learned. It's now time to get back to work in the laboratory."

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Weinberg, R. A. (1985). The actions of oncogenes in cytoplasm and nucleus. *Science* 230, 770-776.

Weissman, B. E., Saxon, P. J., Pasquale, S. R., Jones, G. R., Geiser, A. G., and Stanbridge, E. J. (1987). Introduction of a normal human chromosome 11 into a Wilms' tumor cell line controls its tumorigenic expression. *Science* 236, 175-180.

Woodruff, M. F. A. (1988). Tumor clonality and its biological significance. *Adv. Cancer Res.* 50, 197-229.

Yuspa, S. H., and Poirier, M. C. (1988). Chemical carcinogenesis: From animal models to molecular models in a decade. *Adv. Cancer Res.* 50, 25-70

Animal Care Technicians Receive Local Awards

Carl U. Parkinson, Work Leader, Animal Care, and Kathy B. Chambers, Animal Care Technician, were honored December 16 at a banquet sponsored by the Research Triangle Branch of the American Association for Laboratory Animal Science.

Mr. Parkinson received the "Supervisor/Technician of the Year" award for his contributions to the field of laboratory animal science and his active participation in AALAS. Recently certified as an AALAS Laboratory Animal Technologist, he represented the interests of the local Animal Care Technicians as the Technician Branch Representative for the national AALAS organization.

Ms. Chambers was presented the "President's Award" for outstanding dedication and service to the field of laboratory animal care. She is certified as an AALAS Assistant Laboratory Animal Technician and was recently an assistant editor for the RTB-AALAS newsletter.

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Publications (from page 2)

Inhibition of DNA synthesis in mouse whole embryo culture by 2 methoxyacetic acid and attenuation of the effects by simple physiological compounds. *Tox. Lett.* 45, 111-117.

Swenberg, J. A., Koch, S.A.M., and Walker, V. E. (1988). Formation and accumulation of ethenoguanine in the target tissue for acrylonitrile carcinogenesis. *J. Cell. Biochem.*, Suppl. 12A, 353. [Abstract].

Tan, W.-Y., and Starr, T. B. (1989). Estimating times to initiation onset and malignancy using a two-stage model of carcinogenesis. *Toxicologist* 9(1), 1. [Abstract No. 1].

Walker, V. E., and Swenberg, J. A. (1988). Hydroxyethylation of rat brain DNA after multiple exposures to ethylene oxide or a single dose of hydroxyethylnitrosourea. *J. Neuropath. Exp. Neurol.*, 47,350. [Abstract].

Welsch, F., Duignan, J. M., and Mebus, C. A. (1989). The role of sarcosine in 2-methoxyethanol-induced developmental toxicity. *Toxicologist* 9(1), 268. [Abstract No. 1075].

Working, P. K. (1988). Male reproductive toxicology: Comparison of the human to animal models. *Environ. Health Perspect.* 77, 37-44.

New Fellows, Visiting Scientist

Three postdoctoral fellows began appointments at CIIT on January 1. Julia S. Kimbell received her Ph.D. in differential geometry from Duke University in 1988. In 1989, Dr. Kimbell was the recipient of a three-year fellowship from ALCOA, which sponsored her work on optimal sheet metal deformation. During that same year, she received the J. P. Smith Award for Excellence in Teaching from the Duke mathematics department. At CIIT, Dr. Kimbell will be working with Dr. Thomas B. Starr of CIIT's Department of Risk Assessment on the disposition of inhaled reactive gases such as formaldehyde.

Marc Bonnetoi, Assistant Professor in Pharmacy and Toxicology at the Veterinary School of Toulouse, France, begins a CIIT fellowship this month with the Department of Experimental Pathology and Toxicology. Dr. Bonnetoi received a D.V.M. in 1981 from the University of Toulouse. In 1988, he received the French *Agrégation* in Pharmacy and Toxicology at the Veterinary School of Toulouse. His research, carried out in collaboration with the French National Institute for Agricultural Research, focused on sporidesmin, a mycotoxin which causes facial eczema in ruminants. Under the direction of Dr. Kevin T. Morgan, he will study the neurotoxicity and olfactory toxicity of monohalomethanes.

Also beginning an appointment with the Department of Experimental Pathology and Toxicology is Sandra R. Lidridge. Dr Lidridge recently earned her Ph.D. in environmental toxicology from the University of Wisconsin, Madison, where her dissertation research involved the measurement of mutagenic effects of chemicals in human mammary cells. She will be working with Dr. Byron Butterworth, Department of Experimental Pathology and Toxicology, on the development of a human mammary epithelial cell DNA repair assay.

Kenji Funaki, a Visiting Scientist with the Department of Cellular and Molecular Toxicology, received his D.Sc. from Hokkaido University in 1983 in cytogenetics and teratology. Dr. Funaki is a member of the Japanese Society of Anatomy, the Japanese Society of Congenital Anomaly, and the Japanese Society of Human Genetics. He joins the human cell transformation program of Dr. Craig J. Sorsiko, where he will investigate cytogenetic changes associated with exposure to human carcinogens and the malignant transformation of human cells.

Videotape Available

A videotape of Dr Gisham's presentations, *Current Insights into the Mechanisms of Carcinogenesis, with Implications for Mesothelioma*, is available on loan from CIIT. Contact:

Mrs. Elizabeth Barnhill
CIIT
P.O. Box 12137
Research Triangle Park, N.C. 27709
919/541-2070

Present for the First Leon Golberg Memorial Lecture were (left to right): Dr. Donald A. Hart, Vice President, Administration; Mrs. Leon Golberg; Dr. Golberg's son Aaron, daughter Laura Golberg Hamilton, and son-in-law Michael Hamilton, of Washington, D.C.

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Appendix 2

Critical Evaluation of Epidemiologic Studies of Nickel-Exposed Workers

Final Report

A Report to the
Nickel Producers Environmental Research Association

by

Otto Wong, Sc.D., F.A.C.E.
Donna Folliart, M.D., M.P.H.
Robert W. Morgan, M.D., S.M.Hyg.

Environmental Health Associates, Inc.
2150 Shattuck Avenue - Suite 414
Berkeley, CA 94704

7 February 1983

C03169

App 2.1

Critique:

This cohort study consisted of Copper Cliff nickel sinter plant workers with five or more years of employment, who worked sometime between 1943 and 1962 and who were alive in 1963. However, the cohort was "not a complete roll of all the sinter plant workers, but somewhat stratified random selection that included all durations of exposure." The report does not provide any details on the actual cohort selection, and it is not clear what the "somewhat stratified random selection" means. A search of death records for the entire Canada up to end of 1977 and for Ontario up to end of 1978 was made. As such, deaths in 1978 outside of Ontario would not have been identified. Incident cases were identified by Workmen's Compensation Board of Ontario claim records. The report did not discuss whether this source would identify cases among those who left Ontario after employment. Of the 495 included in the study, 124 (25%) were lost to follow-up. This proportion of unknown vital status was too high.

The method of calculating the expected number of deaths was rather unusual. The commonly accepted procedure for calculating SMR was based on the person-year concept or the modified life table. With the availability of computers, there is no reason not to count person-years at risk accurately. Probably because of their poor follow-up results, they

App 2.2

have taken three time periods and reduced the numbers in each cohort by applying expected deaths from the preceding period. This is a dubious practice.

Multiplying the number of expected deaths by 1.5 to obtain the number of expected incident cases was a gross oversimplification. The ratio of incidence to mortality is age-dependent, and age-adjustment is certainly necessary in calculating SIR. There are incidence rates available for Canada that could have been used as a more reasonable approximation for comparison.

Thirty-seven deaths were 'certified as dying from primary lung cancer, and the accuracy of diagnosis confirmed either by pathology reports or by review of clinical records to establish a best clinical diagnosis'. The wording is not clear, but it seems that the cause of death was based on pathology or clinical reports and not on death certificates alone. Such an approach is an unacceptable epidemiologic practice, since the corresponding Ontario vital statistics were based on death certificate information only. The result is an inflated number of observed deaths due to lung cancer. From the epidemiologic point of view, it is not important to establish a best clinical diagnosis, but to use the same criteria in diagnosis as the comparison data.

The report is not clear whether only those lung cancer deaths between 1963 and 1978 were included. The case

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App 2.3

diagnosed in 1962 was included; presumably, the case died subsequently in or after 1963. There were 7 cases diagnosed in 1977, who subsequently died, included in the study. Did all 7 cases die in 1977 or 1978? One case, diagnosed in 1978, was also included. Did the case die in 1978? Furthermore, for the incidence analysis, one case diagnosed in 1962 and four after end of study period were included. Including cases outside the study period in analysis is simply not acceptable.

The method used in the dose-response analysis, which is essentially an analysis by duration of exposure, might not be entirely appropriate. Based on the method of calculating expected deaths described earlier and Table 6, which presented the number of men in each duration sub-group, it appears that the expected was based on the number of men in each subgroup and not on person-years. It appears, for example, the 65 men in the 14+ year subgroup contributed all their person-years at risk to this subgroup even though their first 14 years should not have been included.

Table 6 indicates that there were 217 (67 + 78 + 72) in exposure subgroups of less than 5 years. On the other hand, it was stated earlier in the report that "exposure was recorded in terms of duration of employment in the plant" and the cohort definition required a minimum of 5 years of employment to be included.

Whether the decision to give double weight to exposure prior to 1951 with little supporting industrial hygiene data is justifiable is difficult to determine. Because the authors think there is a reduction of risk after 1951, they have multiplied 1948-1951 exposures by a factor of two for the purposes of a dose-response analysis. This reasoning seems to be somewhat circuitous. Other confounding factors such as the significant amount of PNA in the work environment and that over 90% of the workers smoked cigarettes further reduce the validity of the dose-response relationship.

In spite of the numerous methodologic flaws in the paper, it seems clear that these workers experienced an excess of lung and sinus cancer. Unfortunately, the paper is not useful in demonstrating the magnitude of the increased risk.

Roberts, 1982, Unpublished Report

Roberts, Julian and Muir (1982) studied cancer mortality in workers involved in mining, smelting, and refining nickel in Ontario, Canada. The cohort was defined as all male INCO process workers (or pensioners) in Ontario for 6 or more months on or after 1/1/1950. Sinter plant employees were included regardless of length of service. Of the 54,724 identified, 50,436 were from Sudbury area (includes Copper Cliff plant), and 4,288 from Port Colborne.

Job histories were obtained from company records. Fourteen occupational subgroups were defined, covering workers in mines, mills, smelters, sintering plants, matte processing, and copper and nickel refinery. The authors detailed

II.

Air Resources Board Staff Summary of Responses and Comments on the Preliminary Draft Part A.

A) Regulatory Compliance Consultants,(RCC) Inc, August 9, 1990.

1) **COMMENT:**

The RCC questions the basis of the data supplied by SCAQMD that 1.4 tons per year of nickel emissions are derived from the electroplating industry, since nickel can only be electroplated in the soluble form.

RESPONSE:

The SCAQMD derived the nickel emission inventory for electroplaters using the results of an industry materials usage survey compiled and provided in the report "Emissions of Potentially Toxic/Hazardous Air Contaminants in the South Coast Air Basin," September 30, 1984. Information regarding materials use, plating tank capacity, surface area exposed to the atmosphere and efficiency of control devices was used to generate a factor for total nickel emissions. If nickel is identified as a toxic air contaminant, the control phase will reassess the emissions estimates for industries affected by proposed regulations.

DHS staff conclude that based on available genotoxicity data, carcinogenicity data and physiochemical properties of nickel compounds, all nickel compounds should be considered potentially carcinogenic to humans by inhalation. In the revised report all forms of nickel are considered as carcinogenic substances, including the soluble forms emitted by the plating industry.

2) **COMMENT:**

EPA has classified "nickel dust" as a hazardous material.

RESPONSE:

We agree that EPA has placed "nickel refinery dust" into the Group A category (human carcinogen). However, the DHS has recommended that nickel and its compounds be considered as potential human carcinogens, regardless of the source.

B) Foss Plating Company,(FPC), Inc., August 22, 1990.

1) **COMMENT:**

FPC believes that the 1984 SCAQMD inventory vastly overstates the contribution of nickel from their industry, and that the study should be redone.

RESPONSE:

See the response to Comment A1.

2) **COMMENT:**

FPC believes that the nickel plating industry (which uses soluble nickel) should be removed from consideration as a source of harmful emissions.

RESPONSE:

As described in the response to Comment A1, in the revised report all forms of nickel are considered as carcinogenic substances, including the soluble forms emitted by the plating industry.

3) **COMMENT:**

FPC believes that the available evidence does not support the treatment of soluble nickel as a carcinogen, and therefore should be eliminated from the risk assessment.

RESPONSE:

See previous response.

C) Western States Petroleum Association,(WSPA), August 21, 1990.

1) **COMMENT:**

WSPA asks what nickel emissions factors were used to support Table II-6 on pg A29.

RESPONSE:

The nickel emission factor used to support the calculation in Table II-6 is 60 mg of nickel per kilogram of oil burned. This information has been clarified on page A31 of the revised report.

2) **COMMENT:**

WSPA is concerned with the use of old or inaccurate BTU information on oil use in steam generators in Kern County oil fields. They also state that raising the issue of potential "hot spots" is premature. The evaluation of "hot spots" would be better addressed by the AB 2588 process which ensures the generation of high quality information for this purpose.

RESPONSE:

The information used in this report is the most recent and comprehensive from the Kern County Air Pollution Control District. If WSPA can provide more accurate information on the amount of residual oil used in this area we would evaluate it for possible inclusion in the report.

The "hot spot" modeling study is intended to demonstrate that people near emission sources could be exposed to concentrations of nickel several times higher than ambient levels. We agree that the AB 2588 should provide high quality information on specific "hot spots." As this information becomes available, it will be used in the AB 1807 process to assisst us in the prioritizing of toxic air contaminants.

D) <u>California Technical Plating,(CTP), Inc., August 20, 1990.</u>

1) **COMMENT:**

CTP encourages CARB to distinguish between "soluble" and "insoluble" nickel with regard to carcinogenicity. Since the electroplating industry uses only "soluble" nickel, the industry should not be regulated.

RESPONSE:

See the response to Comment B2.

2) **COMMENT:**

CTP would like the reference for the South Coast Air Quality Management District (SCAQMD) study indicating that 1.4 tons per year of nickel emissions are from electroplating sources.

RESPONSE:

See the response to Comment A1.

3) **COMMENT:**

CTP questions the use of only 9 samples to represent the range of insoluble nickel in the air. They request justification for the use of 90% when the range was 50% to 90%.

RESPONSE:

The data on insoluble versus soluble nickel was presented in Appendix II of the draft report. The current version of the report does not include this appendix because all forms of nickel are considered to be carcinogenic, as discussed in the response to comment A1.

4) **COMMENT:**

Indoor air exposure to nickel from wood burning or cigarette smoke is not completely presented.

RESPONSE:

The indoor air exposure section includes all current references identified by extensive computer searches. If CTP has additional information or references, we would be happy to consider them for inclusion in the report.

5) **COMMENT:**

CTP feels that all available ambient monitoring data (two years) should have been used to estimate long term nickel exposure.

RESPONSE:

The ARB used the 12 month period of the most complete (at least one 24 hour sample/month) data from 1985 to 1986 to calculate the estimated population - weighted exposure to ambient levels of nickel.

6) **COMMENT:**

Nickel oxides are not quantified from various metal melting, production, and recovery operations.

RESPONSE:

Data are not available to estimate nickel oxides emissions. However, we would appreciate any data which CTP could provide for these operations.

7) **COMMENT:**

The range of 10.5 to 345 tons per year for nickel emissions from residual fuel oil seems too broad to prioritize the importance of this source.

RESPONSE:

The estimates of nickel emissions from fuel oil combustion were derived by using residual oil sample analysis rather than source test results. The nickel content of residual oil samples from throughout the USA ranged from 3 ppmw to 118 ppmw according to the information obtained from the literature search. The reason for the broad range in nickel content in the residual oil has not been determined. If nickel is identified as a toxic air contaminant and it is considered for control, it would be appropriate to determine an average nickel content of residual oil used in California and the emissions that result from its combustion.

8) **COMMENT:**

CTP questions the accuracy of the range (18 to 353 tons per year) of total nickel emissions from stationary sources.

RESPONSE:

As discussed in the response to the previous comment the range reflects the uncertainty in the nickel content of residual fuel combusted in stationary sources.

E) San Diego Gas and Electric,(SDG&E). August 14, 1990.

1) **COMMENT:**

SDG&E comments refer to part A, Appendix V, page 1 that states that the nickel content of residual fuel oil used in the continental U.S. has been found to be between 3 and 118 ppmw. SDG&E believes that since California utilities are now required to burn low sulfur oil (normally less than 5%), the higher value of 118 does not represent actual nickel content of California residual oil.

RESPONSE:

It is known that nickel content in oil is proportional to sulfur content, however, we do not have a quantitative estimate of nickel content in oils which have different percentages of sulfur. Liquid fuels in the South Coast Air Basin are required to contain a maximum of 0.25% sulfur while the sulfur content of liquid fuels in the Bay Area Air Basin can be as much as 0.50%. It is true that the power plants in these districts burn fuel oils with less than or equal to 0.50% sulfur. However, the sulfur content in residual oils burned in the rest of the state is unknown. Therefore, the staff has used a range of nickel concentrations in residual oil to estimate nickel emissions from oil combustion for the entire State. The low value of nickel concentrations may represent oils with much lower than 0.25% sulfur while the high value may represent oils with higher than 0.50% sulfur. We anticipate this range including the proportional relationship to be refined during the control phase should nickel be identified as a toxic air contaminant.

F) Calidria, August 14, 1990.

1) **COMMENT:**

The amount of estimated nickel emissions from asbestos mining and milling (0.65 tons/year) listed in the Table (III-1) on page A41, is

based on old data, and the information should not be considered accurate. Calidria estimates asbestos emissions are about 120 pounds per year. The estimated nickel emissions from chrysotile asbestos mining and milling would be 0.2 pounds per year.

RESPONSE:

The staff agrees with Calidria that the data used to estimate nickel emissions from chrysotile asbestos mining and milling are old. We are therefore revising the nickel emissions from asbestos mining and milling operations in Table II-1 to reflect more recent ARB data.

Based on ARB data from a survey conducted in 1988, chrysotile asbestos emissions from milling range from 150 to 330 pounds of asbestos (with a nickel content of 1.65 mg Ni/gram) per year which result in 0.25 to 0.54 pound of nickel per year. Chrysotile asbestos emissions from mining are estimated to be 4,500 pounds per year which result in nickel emissions of approximately 7.5 pounds per year. Total nickel emissions are therefore estimated to be from 7.8 to 8.0 pounds per year. Emissions at the mill are directly from the exhaust stacks while emissions at the mine are from screening activities and from storage piles. Note that the Calidria's nickel emission estimate is based on milling activities only. For the method of calculation see Appendix IV.

G) Metal Finishing Association of Southern California, (MFASC), Inc, August 6, 1990.

1)COMMENT:

To estimate long term nickel exposure, MFASC suggests that ARB use all 26 months of available data, rather than only 12 months of data.

RESPONSE

See the response to Comment D5.

2) **COMMENT:**

On page A41 of Part A, electroplating emissions of nickel are shown as 1.4 tons per year. MFASC believes that these are primarily water soluble nickel sulfate or nickel chloride droplets or mist, and thus should not be considered as carcinogenic.

C00134

RESPONSE:

See the response to Comment B2.

3) **COMMENT:**

MFASC recommends that grinding, polishing, and cutting of nickel parts be discussed separately from electroplating. In addition, MFASC recommends that the emissions from these operations be estimated separately from electroplating on page A41.

RESPONSE:

Nickel emissions from grinding, polishing and cutting operations are not available and were not included in the emissions estimates from the electroplating industry. Should nickel be identified as a toxic air contaminant, these emissions will be investigated during the control phase.

4) **COMMENT:**

MFASC is requesting that ARB remove electroplating from the table (Page A41) as a stationary source, since DHS considers only insoluble nickel compounds to be potentially carcinogenic to humans by inhalation.

RESPONSE:

See the response to Comment B2.

5) **COMMENT:**

ARB should identify what specific reports, methods and forms of nickel compounds were included in the 1984 SCAQMD report.

RESPONSE:

See the response to Comment A1.

H) Cal Bumper, August 15,1990.

1) **COMMENT:**

Cal Bumper expresses concern with using the 1.4 tons per year nickel emissions estimate by the SCAQMD because there is no distinction between soluble and insoluble nickel.

RESPONSE:

See the response to Comment B2.

2) **COMMENT:**

Cal Bumper questions the small number of samples used to predict soluble and insoluble concentrations as well as the use of only the highest end of the range (90% insoluble nickel concentration).

RESPONSE:

See the response to Comment D3.

3) **COMMENT:**

Cal Bumper is concerned about the lack of studies regarding the relative nickel exposure from wood burning, cigarette smoking and metal melting, production and recovery operations.

RESPONSE:

Should nickel be identified as a toxic air contaminant, during the control phase the relative risks of potential sources of nickel emissions will be further investigatd.

4) **COMMENT:**

The ranges are too large for the nickel emissions from all stationary sources (18.0 to 353.0 tons per year) and the fuel oil category (10.5 to 345.0 tons per year).

RESPONSE:

See the response to Comment D7.

C00183

I) Engelhard, August 6, 1990.

1) **COMMENT:**

Englehard asks ARB to reconsider the contribution of the electroplating industry to the nickel air emissions inventory, since the industry uses only water soluble nickel.

RESPONSE:

See the response to Comment B2.

2) **COMMENT:**

Based on the following comments, Englehard feels that the emissions inventory (1.4 tons per year) from the electroplating industry should be re-evaluated to reflect a decline in the use of nickel in California and before any further action to establish standards for the electroplating industry.

a. According to an INCO study, there has been a sharp nationwide decline (18%) in nickel electroplating from 1988 to 1989.

b. There is improved enforcement of OSHA standards in California for chemical processing which has reduced emissions.

c. Printed circuit board (PCB) manufacturing has been reduced in California due to movement of the industry to Mexico or offshore.

RESPONSE:

The staff agrees that nickel emissions from electroplating may be declining. Our emission estimates reflect the most current information presented by the SCAQMD. We have added a statement in the revised report on page A11 that these emissions may be declining. If nickel is identified as a toxic air contaminant we will re-evaluate emissions prior to developing controls. (Note: ARB does not establish air emission standards but develops suggested control measures based on best available control technology.)

3) **COMMENT:**

Engelhard states that the efficiency of nickel baths approaches 100% elimination of aerosol formation, but that some water soluble nickel is emitted from splashing, agitation and polishing operations. Engelhard

believes that soluble nickel poses a lower threat than other forms of nickel.

RESPONSE:

See the response to Comment B2.

4) **COMMENT:**

Engelhard urges that before proceeding with regulation of nickel, to consider the following points:

1. Accurate, reasonable, and current statistics on nickel emissions.

2. Clinical evidence that the soluble nickel emissions used in electroplating are carcinogenic when inhaled.

3. A finding from the DHS that air pollution from nickel plating does cause an increase in mortality, serious illness, or does pose a present hazard to human health.

RESPONSE:

The findings of our report reflect the most current emissions inventory and health effects studies. If Engelhard Corporation has new information in these areas we would appreciate the opportunity to review it.

J) Gene's Plating Works.(GPW). August 7,1990.

1) **COMMENT:**

GPW would like a stronger distinction between the carcinogenic effects of "soluble " and "insoluble" nickel made.

RESPONSE:

See the response to Comment B2.

2) **COMMENT:**

GPW would like to see a reference to support the SCAQMD study which cites that 1.4 tons per year of nickel emissions are from electroplating sources.

RESPONSE:

See the response to Comment A1.

3) **COMMENT:**

GPW questions the use of only nine samples to represent the wide range of insoluble nickel in the air. They request the justification for the use of 90% when the range was 55% to 90%.

RESPONSE:

See the response to Comment D3.

4) **COMMENT:**

Indoor exposure to nickel from wood burning or cigarette smoke is not completely presented.

RESPONSE:

See the response to Comment D4.

5) **COMMENT:**

CTP feels that all available monitoring data (two years) should have been utilized to estimate long term nickel exposure.

RESPONSE :

See the response to Comment D5.

6) **COMMENT:**

Nickel oxides are not quantified from various metal melting, production, and recovery operations and could be in the insoluble form.

RESPONSE:

See the response to Comment D6.

7) **COMMENT:**

The range of 10.5 to 345 tons per year for nickel emissions from residual fuel oil seems too broad to use to prioritize the importance of this source.

RESPONSE:

See the response to Comment D7.

8) **COMMENT:**

GPW questions the statement on page A2, which states that "total nickel emissions from stationary sources are estimated to be 18-353 tons per year."

RESPONSE:

See the response to Comment D7.

K) Modern Plating Company,(MPC), August 9, 1990.

1) **COMMENT:**

MPC believes that a greater distinction needs to be made between "soluble" and "insoluble" nickel because there is not enough evidence to support the consideration of soluble nickel as a carcinogen.

RESPONSE:

See the response to Comment B2.

2) **COMMENT:**

MPC would like more detailed information regarding the SCAQMD study, which indicates 1.4 tons per year of nickel emissions from the electroplating industry.

RESPONSE:

See the response to Comment D2.

3) **COMMENT:**

Only nine samples were used to represent a wide range of insoluble nickel in ambient air. MPC questions the justification for using only the 90% if the range was 55% to 90%.

RESPONSE:

See the response to Comment D3.

4) **COMMENT:**

Indoor exposure is not properly or completely presented for nickel emissions from wood burning or cigarette smoke.

RESPONSE:

See the response to Comment D4.

5) **COMMENT:**

Nickel oxides are not quantified from various metal finishing, production, and recovery operations.

RESPONSE:

See the response to Comment D6.

6) **COMMENT:**

The range of 10.5 to 345 tons per year for nickel emissions from residual fuel oil seems too broad to to use to prioritize the importance of this source.

RESPONSE:

See the response to Comment D7.

7) **COMMENT:**

MPC believes that the statement on page A2 that "total nickel emissions from stationary sources are estimated to be 18 to 353 tons per year" is too broad.

RESPONSE:

See the response to Comment D7.

L) Department of Water and Power: The City of Los Angeles (LADWP), August 20, 1990.

1) **COMMENT:**

The LADWP questions the large (2.9 to 112 tons per year) nickel emissions from utility residual oil combustion. They believe staff should re-investigate the estimated fuel nickel concentrations used for emission calculations and use the concentration proposed by Southern California Edison and referred to in the draft report.

RESPONSE:

See the responses to Comment D7 and Comment E1.

2) **COMMENT:**

LADWP believes that the staff should re-evaluate the statement on page A44 regarding the projected future of residual fuel oil usage, which takes into consideration the restrictions adopted by the SCAQMD on residual fuel use.

RESPONSE:

More recent information from the California Energy Commission (CEC) shows that California utilities used approximately 134 million gallons of residual oil in 1987 and 526 million gallons in 1988 (about 3.9 fold increase) (CEC, 1988; and CEC 1989). These data indicate an increase in the use of residual oils by California utilities. In the absence of other information, the staff believes that the CEC has reasonably forecasted the use of residual oils by the utility industry. However, the information from SCAQMD indicates that residual fuel use will decrease in the South Coast in the near future due to natural gas and clean fuels usage. We have revised the report to indicate this.

M) Pacific Gas and Electric, (PG&E). August 22, 1990.

3) **COMMENT:**

PG&E believes that Table III-1 should subdivide the residual oil category into low and high sulfur categories, using 0.5% sulfur as the dividing point. Corresponding revisions should be made in Appendix V.

RESPONSE:

The estimates of nickel emissions from fuel oil combustion were derived by using residual oil sample analysis rather than source test results. The nickel content of residual oil samples from throughout the USA ranged from 3 ppm to 118 ppm according to the information obtained from the literature search. The reason for the broad range in nickel content in the residual oil has not been determined. If nickel is identified as a toxic air contamiant and it is considered for control, it would be appropriate to determine an average nickel content of residual oil and the emissions that result from its combustion.

According to the information provided by PG&E, nickel concentrations in oils tested by PG&E in 1984 ranged from 8.4 to 23.2 ppmw. Oils burned at three plants were again tested in 1990 and the results show a nickel concentration of 23 ppmw for low sulfur units and 28 ppmw for high sulfur units. These values are within the range of concentration data used by the staff (3 ppmw to 118 ppmw) to estimate a range of nickel emissions from residual oil combustion.

4) **COMMENT:**

PG&E believes that in Table III-1, the emission numbers from oil combustion should be those which are expected to be emitted as insoluble nickel oxides, not those which are emitted as soluble nickel sulfates or total nickel.

RESPONSE:

In the revised report, the staff footnoted Table III-1 to clarify that the nickel species column presents the most likely form of nickel expected to occur in the emission categories, i.e. for fuel combustion it is nickel sulfate (Radian, 1985).

5) **COMMENT:**

PG&E believes that Table II-5 should be revised to more clearly show that projected total body exposure from ingestion exceeds projected total body exposure from inhalation. This information should be included in Parts A and B and in the Executive Summary.

RESPONSE:

Table III-5 lists indoor air and ingestion exposures to nickel which contribute to the total exposure. No total indoor inhalation exposure can reasonably be calculated from the information available to enable a total inhalation exposure estimate to be made. Also, insufficient information is available to permit numerical comparison of indoor exposures to ambient exposures.

6) **COMMENT:**

PG&E believes that on Page A1, the claim that 55 to 90 percent of total nickel is insoluble should be restated as a preliminary test result and not conclusive for all of California.

RESPONSE:

These data are no longer included in the report. See the response to Comment B2.

N. INCO, August 22, 1990.

INCO RECOMMENDATIONS:

1. Try to identify the nickel species in ambient air.

RESPONSE:
In the revised report all forms of nickel are considered as carcinogenic substances. Therefore, speciation of nickel in ambient air is no longer necessary.

2. Analyze all the available data on ambient airborne nickel concentrations.

RESPONSE:
The ARB is continuously collecting and analyzing data. The ARB staff compared the 1986 data with the 1987 and 1988 data. The results showed

no statistically significant changes between the mean nickel concentrations for 1986 and those of 1987 and 1988.

3. Treat the nickel concentrations as being lognormally distributed as mentioned in the staff report.

RESPONSE:
Because of the characteristics of the overall nickel data we believe the data should be treated as being normally distributed. The staff report has been revised to clarify this and all the references to data being distributed lognormally have been removed from the report.

4. Identify any long-term trends in the nickel concentration data and take them into consideration.

RESPONSE:
Our analysis of data from the toxics air contaminant monitoring network indicates that nickel concentrations have increased at some locations and decreased at others. Therefore, no long-term statewide trend in the nickel concentrations have been identified.

5. Use a more realistic formulation of exposure.

RESPONSE:

We used the information available to us to estimate the emissions inventory of nickel sources in California and resulting ambient concentrations. The ambient concentrations were taken from our toxics ambient network described in the report, and which is the most comprehensive network in the country. We agree that the overall exposure assessment is an estimate. Should nickel be identified as a toxic air contaminant, further investigation will take place during the control phase. We have revised the report so that either "potential" or "estimated" was added whenever we used the term "population exposure."

6. Deal explicity with the uncertainties in estimated quantities and calculated risk.

RESPONSE:

We cannot deal explicity with the uncertainties without using unsubstantiable assumptions in the distributions of both ambient nickel concentrations and population.

INCO COMMENTS:

1) **COMMENT:**

Does Section 39655 of the Health and Safety Code or ARB policy rely on the level of estimated risk to determine whether a substance is a toxic air contaminant? Or does the Code require only a finding that a substance has produced an adverse health effect in animals or humans regardless of the dose or the route of administration?

RESPONSE:

Section 39655 defines a toxic air contaminant as "an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health." According to Section 39660 the evaluation should assess "the availability and quality of data on health effects, including potency, mode of action, and other relevant biological factors, of the substance."

2) **COMMENT:**

Emphasis needs to be made to reflect the fact that the report presents only estimates of potential exposure.

RESPONSE:

See response to recommendation N5.

3) **COMMENT:**

Why does Table II-1 indicate only 1392 samples, when 1454 samples were collected in the 1985-1987 period according the text.

RESPONSE:

Table III-1 (formerly II-1) reflects a correct total of 1392 samples. The value of 1454 samples in the text was a typographical error.

4) **COMMENT:**

ARB should indicate whether it used Gleit's method on the logarithms of the nickel concentrations or on the concentrations themselves.

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RESPONSE:

We used Gleit's method on the logarithms of the nickel concentrations and this has been clarified on page A21 of the report.

5) **COMMENT:**

Table II-1 shows that data for January and February 1987 were collected at only six and three of the 20 sampling locations. Why was a small set of monitoring data for January and February 1987 included in Figures II-2 through II-4?

RESPONSE:

Based upon re-evaluation of the monitoring data we have deleted the figures in question.

6) **COMMENT:**

Figure II-5 (and presumably Table II-4) were calculated "using logarithms and represent plus or minus two standard errors" but both the figure and table show arithmetic means. The means and upper and lower bounds shown in Table II-4 and Figures II-5, II-6 and II-7 are in error.

RESPONSE:

The data presented in Figure II-5 and Table II-4 were derived logarithmically. In revising the report we have excluded the use of upper and lower bounds estimates. As indicated in the revised report we are now conducting the analysis using upper and lower bound intervals. The revised calculations do not have significant effect on the statewide population-weighted exposure.

7) **COMMENT:**

The nickel concentration data should be summarized in terms of geometric, not arithmetic, parameters.

RESPONSE:

The nickel concentration data are not lognormally distributed. The geometric mean is a parameter for identifying a lognormal distribution and therefore was not used.

8) **COMMENT:**

Is it coincidence that the population-weighted "exposure" estimates in Table II-4 for the SCAB and SFBAAB are the arithmetic averages of the corresponding estimates for the individual sampling locations within the basin?

RESPONSE:

See the response to Comment 6.

9) **COMMENT:**

The 95 percent confidence limits discussed in the third paragraph on page A14 do not "represent the range of values that the mean exposure could assume."

RESPONSE:

The Commentor is correct. The statement has been deleted.

10) **COMMENT:**

How was the statewide population-weighted exposure in the Table II-4 calculated? The lower bound and mean should be 5.3 and 6.7 respectively, instead of 6.0 and 7.4 as shown.

RESPONSE:

The data were recalculated and the revised version of Table II-4 (now Table III-4) gives the mean estimate of 7.3 for the overall statewide population-weighted exposure.

11) **COMMENT:**

Why does Figure II-6 not represent the data shown on Table II-4?

RESPONSE:

Figure II-6 (now Figure III-6) has been re-plotted to reflect the data contained in Table III-4.

12) **COMMENT:**

"Potential" should be added to the title of Figure II-7 and it should refer to "cumulative frequency" or "cumulative probability." This kind of graph traditionally is presented as increasing from left to right.

RESPONSE:

Figure II-7 has been deleted from the revised report.

13) **COMMENT:**

The chapter "Indoor Exposure to Nickel" is an appropriate place to give at least a brief description of the ongoing studies about indoor concentrations of nickel. Are they experimental studies; how many of each kind of building will be sampled; when can results be expected; what will ARB do if it can't satisfy the requirement of the Code to provide a quantitative "relative contribution"; does the Code include occupational exposures and how are they evaluated?

RESPONSE:

The intention of Part A is to provide information on completed studies. However, the ARB and EPA are currently conducting a joint study of indoor, outdoor and personal concentrations of particulate pollutants in about 170 homes in Riverside, California. Although the samples will be analyzed for nickel, those analyses are not expected to be completed until early 1992. Second, when adequate data are not available to develop a reasonable indoor exposure estimate, we present our general (nonquantitative) assessment of the relative contribution. We are not required to calculate a quantitative relative contribution in order to fulfill the Code requirement, and the availability or lack of indoor exposure information does not determine whether a pollutant should be identified as a toxic air contaminant. Third, the ARB does not factor occupational exposures into exposure assessment. The ARB addresses general population exposures. Cal-OSHA has exclusive and pre-emptive authority over occupational exposures; however, the DHS works closely with Cal-OSHA in assessing risk related to occupational exposures.

14) **COMMENT:**

Solomons et al., showed that the absorption of nickel from milk, coffee, tea and orange juice after fasting was less than it was from water. Thus the extent of absorption depends significantly on temporal

patterns of eating and drinking as well as on the nickel content of the foods and beverages consumed.

RESPONSE:

Sunderman et al., (1989) confirmed the findings of Solomons et al., (1982) that "certain dietary constituents (e.g. ascorbic acid) and beverages (e.g. milk, coffee, tea, orange juice) reduced the bio-availability of orally administered nickel in humans...." and inferred that approximately one percent of nickel in food is absorbed from the human alimentary tract. However, as indicated in the ARB report, Christensen and Langesson (1981) showed that over a period of three days the cumulative absorption was three percent. (This information has been incorporated into the report). Our statement that "1 to 10 percent dietary nickel is absorbed" is reasonable because even INCO mentions much more than 10 percent can be absorbed under certain circumstances.

15) **COMMENT:**

As more data are accumulated on nickel in diet, the upper range limit seems to be decreasing markedly and the report should reflect these changes.

RESPONSE:

The six studies on dietary nickel referenced by Sunderman et al. (1989) were small studies containing eight to no more than 30 subjects each. These studies were done between 1972 and 1989 and show no trend in dietary intake of nickel. Consequently, we do not agree with INCO.

16) **COMMENT:**

Can the nickel content of California's surface waters be estimated more accurately than "less than 70 ug/l". The range of zero is not very useful.

RESPONSE:

The sentence has been removed from the text.

17) **COMMENT:**

Trying to estimate deposition exposure is either double-counting or irrelevant because the amount of nickel from deposition was included in the amount of nickel ingested in food and water.

RESPONSE:

This section of the report did not attempt to quantify dose from nickel deposition exposure, but rather just show the existence of the nickel ingestion pathway. At the present time exposure assessment modeling does tend to over-predict the dose from deposition of particulates. However, this conservative aspect of the model is offset by the uncertainty of the emissions estimates themselves and dose response.

18) **COMMENT:**

What is the ISCST model?

RESPONSE:

It is the mathematical model which estimates pollutant concentrations. The ISCST model is described in the Glossary of the report.

19) **COMMENT:**

In Table II-6 the title and footnotes should indicate the concentrations represent estimated potential exposures unless the people live outdoors. The table is confusing.

RESPONSE:

"Potential" was added to the text and the table (now Table III-6) has been simplified.

20) **COMMENT:**

The means estimated by dispersion modeling were very much higher than the means from the observations, can it be explained by the location of the sampler?

RESPONSE:

The ranges (not means) were chosen to demonstrate potential population exposure near emission sources.

21) **COMMENT:**

Is there a program for measuring actual concentrations at California's "hot spots"?

RESPONSE:

The results of the AB 2588 program will provide an indication of the location of potential hot spots of nickel in California.

22) **COMMENT:**

The language in the report leads the reader to question the modeling and to the suggestion that the modeling predictions should be compared with the observed data to provide some perspective.

RESPONSE:

The observed data from the toxics air contaminant network is used to calculate average ambient population weighted exposure. The purpose of the modeling exercise was to predict nickel concentrations that can result in hot spot exposures.

23) **COMMENT:**

Very little nickel is used in the pure form. Most of it is used in ferrous and non-ferrous alloys.

RESPONSE:

We agree with the commentor. This information is in the report.

24) **COMMENT:**

Figure III-1 shows 160,000 tons imported and 10,000 tons exported, which differs from the figures given in paragraph 2 page A34.

RESPONSE:

A correction has been made to Figure III-1 (now Figure II-1) to remove the discrepancy.

25) **COMMENT:**

Hanna's facilities in Oregon were reopened by Glenbrook Nickel in 1989. The smelter is currently processing ore that Hanna stockpiled before it closed the operation.

RESPONSE:

The staff has incorporated this information on page A3 of the revised text of the report.

26) **COMMENT:**

AMAX closed its Louisiana nickel operations in the last quarter of 1985. We understand that a small section of the refinery has been reopened in a joint venture with Shell Oil to recover metals from spent petroleum catalysts.

RESPONSE:

The staff appreciates the information and has incorporated it on page A2 of the text of the report.

27) **COMMENT:**

INCO does not believe the amount of nickel recovered from secondary aluminum smelting is significant.

RESPONSE:

The amount of nickel recovered from secondary aluminum smelting was presented in the text without any comment as to it significance. However, it is one of many secondary smelters that may produce nickel as a by-product. The purpose of presenting this information is to show that secondary aluminum smelters may be sources of nickel produced in California.

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28) **COMMENT:**

The forecast rate of nickel demand in the US is too high. However, INCO is not permitted to suggest an alternative.

RESPONSE:

We do not have any other data to support or deny the forecast rate of nickel demand in the US.

29) **COMMENT:**

"p.A40, para.1: This paragraph implies that stainless steel scrap will be a more important source of nickel for the US than will imported nickel. This is clearly not the case. While there are no primary nickel producers in California, Ni-Cal has been considering for years the possibility of treating laterite deposits at Gasquet Mountain in Del Norte county."

RESPONSE:

On page A6 of the revised report the staff has added the information regarding the Gasquet Mountain laterite deposits.

30) **COMMENT:**

Has ARB considered using the data on routine releases reported under the SARA III regulations as part of its estimate of nickel emissions?

RESPONSE:

The ARB has considered the data from SARA III, Section 313, however, the staff did not use it because the SARA inventory does not reflect mobile sources or activities that use nickel incidentally.

31) **COMMENT:**

Several of the indicated nickel species in emissions have been improperly identified. Combustion of fossil fuels also releases oxidic nickel, as would iron and steel foundries; metallic nickel is unlikely to be released from sewage sludge incineration.

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RESPONSE:

The staff appreciates the comments regarding nickel species from different emissions sources. We have changed Table II-1 to reflect that nickel oxides are predominantly released from municipal waste sludge incineration and iron & steel foundaries. It is important to note that this information is now less significant since DHS regards all nickel species as carcinogenic.

32) **COMMENT:**

The combustion of petroleum products seems to be the major anthropogenic source of ambient nickel in California, ARB should expend some effort to reduce the uncertainty in the estimated amount of nickel emitted by oil combustion. The range of "10.5 to 345 tons" is too broad.

RESPONSE:

See the response to Comment D7.

33) **COMMENT:**

Metallic nickel emissions from sewage sludge incenerators as indicated in table III-1 seem questionable.

RESPONSE:

The staff has contacted EPA regarding the tests performed at the two sewage sludge incinerators mentioned and we have incorporated the preliminary findings of these tests in Appendix V.

34) **COMMENT:**

Appendix V does not support the estimated 1.4 tons per year of nickel emission from platers in the SCAQMD.

RESPONSE:

See the response to Comment A1.

35) **COMMENT:**

What are the chemical reactions of fine airborne particles of nickel in the atmosphere if previously in the report it is mentioned on page A2

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that "Little information is available, at present, about the chemical transformations of nickel..."

RESPONSE:

We have clarified the report to indicate that no information is available regarding the atmospheric transformation of nickel.

36) **COMMENT:**

Does ARB think that nickel carbonyl exists in California air despite its short half-life?

RESPONSE:

We don't know. The sentence in the report on page A53 only indicates that nickel carbonyl is the most toxic form of nickel that can occur in the air. We also indicate that we do not have emissions estimates at this time.

37) **COMMENT:**

What reference supports the demonstration of the formation of nickel carbonyl during the combustion of fossil fuels?

RESPONSE:

The sentence on page A54 in the report was an assumption, based on the fact that nickel carbonyl is formed by the direct combination of metallic nickel and carbon monoxide, and the amount is inversely proportional to temperature. The sentence has been deleted from the revised report.

38) **COMMENT:**

What is the "process of pigmentation" and is it used in California?

RESPONSE:

Anticorrosive pigments are used to prevent the formation or spread of rust on iron when the metal is exposed by a break in the coating. Metallic pigments such as nickel are used very often. We do not have emissions inventory data for the pigmentation process used in California.

39) **COMMENT:**

The assumption that most of the atmospheric nickel (especially from combustion sources) is present as nickel oxides is questionable.

RESPONSE:

This assumption was made by Schroeder et al., 1987 cited in Chapter IV.

40) **COMMENT:**

What methods were tested for nickel and how well did the different laboratories agree?

RESPONSE:

For total nickel the ambient samples were taken on quartz filters and were analyzed by X-Ray Fluorescence (XRF) method at the ARB laboratory and by Atomic Absorption (AA) method at Air and Industrial Hygiene Laboratory in Berkeley using the INCO procedure. A linear correlation of XRF and AA methods: XRF(Ni) = 0.5 + 0.88 AA(Ni) in ng/m3. The r2 correlation coefficient is 0.998.

41) **COMMENT:**

Nickel in insoluble fly ash is not present as nickel oxide. It is present in complex oxides with other metals.

RESPONSE:

U.S. EPA 1986 indicates that the forms of nickel in order of predominance in fly ash are: soluble nickel sulfate, insoluble nickel oxide and complex nickel oxides.

42) **COMMENT:**

Alexander (1983) showed that, if nickel carbonyl existed in mainstream cigarette smoke, it must have been below 0.1 ppm detection limit.

RESPONSE:

Alexander et al., (1983) failed to show that nickel carbonyl is not formed during the combustion of tobacco, for as the author stated: "The initial formation of $Ni(CO)_4$ ...cannot be entirely discounted...

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A band centered at 2061.6 cm^{-1} was not due to $Ni(CO)_4$ and inhibited its detection at low concentrations."

43) **COMMENT:**

Is ARB undertaking the research outlined here with respect to the contamination of the indoor environment by cigarette smoke?

RESPONSE:

The ARB will obtain limited data on nickel levels in smoker's homes from the particle study in Riverside mentioned in response to Comment 13. The ARB does not have research funds available for in-depth study of nickel from cigarettes.

44) **COMMENT:**

Without a probability distribution of the total indoor concentration of nickel, it is not possible to put the indoor environment into perspective relative to the outdoor environment. ARB should concentrate on indoor air if it wants to make a significant reduction in total nickel exposure.

RESPONSE:

Health and Safety Code section 39660.5 requires ARB to assess indoor exposure when considering identification of a substance as a toxic air contaminant. ARB is to consult with the Department of Health Services regarding substances that are potential toxic air contaminants that may be found in indoor environments and methods for measuring exposure and to refer all data from such assessments to other state agencies with authority to regulate such exposures. ARB does not have the authority to regulate indoor air quality. ARB, in compliance with these requirements, has considered indoor nickel exposures, but there are simply not enough data available to permit any reasonable calculation of the population's indoor exposures to nickel. As our reports are completed and approved, they will be forwarded to the appropriate agencies. With regard to indoor nickel, especially that from cigarettes, the agency that could best make recommendations to address those exposures, the Department of Health Services, is closely involved in the development of the toxics reports and is fully aware of the data available.

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III.

Department of Health Services Staff Summary of Responses and Comments on the Preliminary Draft Part B

DEPARTMENT OF HEALTH SERVICES (DHS)
STAFF RESPONSES TO PUBLIC COMMENTS
ON PART B OF THE TECHNICAL SUPPORT DOCUMENT FOR THE
PROPOSED IDENTIFICATION OF NICKEL
AS A TOXIC AIR CONTAMINANT

Comments from the Nickel Producers Environmental Research Association, Inc. (NiPERA)

1. Comment: **The choice of studies for quantitative risk assessment is predicated on the assumption that no new cohort studies have been published since the U.S. Environmental Protection Agency (EPA) published its health assessment document on nickel and nickel compounds in 1986 (NiPERA submittal dated August 13, 1990 [NiPERA-1], page 1).**

Response: No new cohort studies suitable for quantitative risk assessment had been published at the time the DHS Health Risk Assessment Document was drafted. Since then the ICNCM undertook further follow-up for some of the existing cohort studies (see response to comment 2).

2. Comment: **It is unfortunate that the California Air Resources Board (ARB) was unaware that results from the International Committee on Nickel Carcinogenesis in Man (ICNCM) were published in a February, 1990, special issue of the Scandinavian Journal of Work, Environment, and Health (NiPERA-1, p. 1).**

Response: The ICNCM report appeared after the draft document was completed (see response to comment 3).

3. Comment: **The ARB should review the ICNCM information carefully, as it represents the most recent data on several cohorts of exposed humans. Of particular interest is the ICNCM's conclusion that the risk to the general population is minute, if indeed there is any risk at all (NiPERA-1, p. 2).**

Response: The ICNCM information has been reviewed for the purpose of revising the document. The ICNCM did not undertake a quantitative risk assessment (p. 74 "*..it left the development of quantitative dose-specific models of risk for future work*"). In the Concluding Remarks at the end of the report it was stated that ..." *it can be concluded that the risk to the general population from exposure to the extremely small concentrations (less than 1 ug Ni/m3) to which it is exposed in the ambient air is minute, if indeed there is any risk at all.*" When compared to the occupational risks experienced by nickel exposed smelter workers in the past, the risks to the general population are indeed very small. The draft Document estimates risks to the general population to be in a range of 0.5 to 85 per million with the best value being 2 based on a non-threshold model since is not possible to quantitatively determine a carcinogenic threshold. This risk is much smaller than that of the Ontario nickel smelter cohort used in the risk assessment which involve 495 workers with 37 of the 85 deaths being due to lung cancer, most of which are attributable to exposure to nickel. The DHS staff therefore believe that the risk estimates in the draft Document are consistent with the views of the ICNCM expressed in their Concluding Remarks in that they are very small scale relative to the occupational exposure.

4. Comment: **The problems noted regarding the precision and accuracy of relative risk estimates from the Huntington cohort should be weighed against the utility of this cohort for risk assessment purposes. This cohort is useful because the workers were exposed to concentrations that approximate environmental conditions. Before dismissing this cohort from risk assessment use, this issue should be reexamined using the new updated information within this study (NiPERA-1, p. 2-3).**

Response: The utility of a cohort study for quantitative risk assessment depends in large part on the accuracy and precision of the estimates from the study. As was presented on pages 101 and 102, the problem with estimates from the Huntington, West Virginia cohort study lies in precision of the estimates. This cohort had relatively low exposures to nickel (See Table 10 of the ICNCM report). The consequence was that lung cancer risks were only slightly elevated and the confidence limits on relative risk estimates are broad. As noted on p. 102 of the draft Document, *..the range of estimates which could come from this study are such that they would encompass any estimates based on much more heavily exposed cohorts.* It might further be noted that the only significant exposure appear to have been in the calcining department which was closed in 1947 and no exposure measurements are known for this department (p. 20 ICNCM report).

5. Comment: **The ARB should use the more recent data presented on the Copper Cliff cohort workers presented in 1984 and 1989 reports by Roberts *et al.* and in 1990 by ICNCM (NiPERA-1, p. 3).**

Response: With regard to exposure data, the ICNCM does not report any measures of exposure for the Ontario cohort other than those which have been used in the quantitative risk assessment. The ICNCM and Roberts *et al.* 1989 papers do present further follow-up of the cohort (see response to comments 6-8).

6. Comment: **The ARB's 25 percent adjustment for fraction lost to follow-up in the Copper Cliff cohort is unjustifiable. Because of a highly reliably death registry in Canada and statistics that show little emigration from that country, it is prudent to assume that those lost to follow-up are likely to be alive at the end of the follow-up period (NiPERA-1, p. 3).**

Response: The adjustment for the fraction lost to follow-up was incorporated in the spirit of avoiding the underestimation of cancer risks. We agree that identification of deaths would be more complete than the identification of those still alive. However some deaths probably occurred among those lost to follow-up and ignoring them would contribute to under-estimation of risks. In the absence of more information, it was therefore assumed that those lost to follow-up had the same mortality as those traced.

Roberts *et al.* 1989 investigated loss to follow-up by further follow-up of a subset of 1000 workers of unknown status. They estimated that there might have been under ascertainment of total deaths by about 5%. Assuming the same under ascertainment of deaths for the Chovil study, we have incorporated a revised adjustment for loss to follow-up. Rather than dividing by 0.75, which assumed that mortality was the same amongst those lost to follow-up as among those traced, we have divided by 0.95, which assumes only a 5% loss to follow-up. See section 7.2.5 for details.

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7. Comment: **The background lifetime lung cancer rate of 0.049 used in analyzing the Copper Cliff workers is inappropriate. The ARB notes that the estimation method used gives a certain lifetime risk of lung cancer mortality, when it actually gives the proportionate mortality ratio (PMR), which does not directly measure the lifetime risk of death from lung cancer. Considering the age distribution of the population affects estimation of this parameter. Calculations suggest that an estimate of 0.029 is more accurate than 0.049. Because the background rate is such an important component of the risk estimate, Canadian mortality statistics should be examined further (NiPERA-1, p. 3-4).**

Response: Under the assumptions given, the estimate used of the lifetime risk of dying from lung cancer is valid (Smith AH. Epidemiologic input to environmental risk assessment. Archives of Environmental Health 43:124-127, 1988). For a dynamic cohort (i.e with replacement) of fixed size and age structure and with constant age-specific mortality rates, the proportion of deaths from a particular cause is a direct estimate of the lifetime risk of dying from that cause.

There is no ideal method for calculation of lifetime risk of death from lung cancer. At any one point in time, age specific mortality rates come from different birth cohorts who may experience different mortality from the cause of interest and from competing risks. Thus a lifetable estimate of lifetime risks from a particular cause must make many assumptions about which age structure and which mortality rates are being used. Under the assumptions listed above, a lifetable estimation of the lifetime risks of death from lung cancer would yield the same answer as that obtained by the much simpler approach used.

The purpose of this calculation is to estimate the lifetime risks in the background Canadian population to be used in conjunction with the Ontario cohort data. The relevant information must come from the Canadian population at the time of ascertainment of lung cancer deaths for the cohort. The estimate derives from 1963-78. It does not involve only one year's data.

The figure of 0.029 suggested by NiPERA is much too low. For example, in 1978, there were 97,115 deaths among males in Canada. Lung cancer deaths totalled 6435, which was 6.6% of all deaths. Lung cancer rates increased from 1963 to 1978. Deaths in earlier years were lower and consequently the overall estimate is 0.049.

Data have now been obtained from the Province of Ontario. In the period 1963-78, there were 26,655 lung cancer deaths among males, and 521,376 deaths form all causes. Thus the fraction of deaths which were from lung cancer was 0.051. We have therefore used this as an estimate of the lifetime risk of males dying from lung cancer in Ontario at that time.

The revised report provides more detail on the approach used to derive this estimate in section 7.2.4.

8. Comment: **More appropriate (scientifically based) calculations suggest a 95% upper confidence limit unit risk of 96 lung cancer deaths per million and a "'best estimate" unit**

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risk of 73 per million (for a unit of 1 microgram per cubic meter). The estimated risk to residents of California from inhalation of atmospheric nickel is not likely to be higher than 0.08 to 2 lung cancer deaths per million. This is a minimal risk for exposures to nickel and its compounds (NiPERA-1, p. 4-6, 7).

Response: The quantitative risk estimates were based on a study by Chovil *et al.* on the Ontario cohort. (This study was omitted and not discussed in the ICNCM report). The ICNCM report involves follow-up for a further 6 years. The Chovil cohort was defined to include workers with 5 or more years service for the company including at least some at the sinter plant. There were 37 lung cancer deaths reported in this group. From Table 6 of the Chovil paper one can conclude that at least 3 of these individuals had less than 5 years exposure. In view of the weighting of the early exposure period, it is not possible to say how many more had less than 5 years of exposure.

In the ICNCM report, the cohort was defined differently to involve workers who had worked for the company in Ontario for 6 months or more (rather than 5 years or more as in the Chovil study). There were 63 lung cancer deaths with at least 15 years latency in the sinter plant workers. However, there were only 30 individuals with 5 years or more work in the sinter plant.

The question raised by NiPERA concerns the number of new cases of lung cancer ascertained in the further follow-up period. The ICNCM report does not identify the cases by year. However it is likely that the number of lung cancer deaths in the further follow-up period was considerable. Fig. 1 in Chovil *et al.* identifies 10 living lung cancer cases diagnosed in the period 1978-80 and other living cases diagnosed in earlier years. In view of the high fatality of lung cancer, this evidence does not support the claim that further follow-up involved no new deaths.

More directly, one can note that the two studies provide very similar estimates of lung cancer mortality. For 5 or more years work at the sinter plant starting prior to 1952 (as did most of the cohort), the ICNCM estimated an SMR of 8.55. The estimate from Chovil for at least 5 years service with the company, some of which was at the sinter plant, was 8.71. Some of these workers had less than 5 years at the sinter plant, so an adjusted estimate from Chovil would be higher. Nevertheless, the findings are remarkably close.

The Chovil *et al.* study has an important advantage compared to the NiPERA use of the ICNCM report. Cumulative exposure was estimated in the Chovil study by taking into account the measured levels of nickel in air. In contrast the NiPERA estimate involves a rough approximation for exposure since data were lacking to take into account person time of exposure prior to 1952. Furthermore, the fact that exposures were about twice as high before 1952 as after was appropriately taken into account in the Chovil *et al.* study.

With regard to NiPERA Table 2, the difference in slope is a relatively small contributor to the overall threefold difference in risk estimates. The main single source is the difference in background lifetime risk estimates for lung cancer as discussed in Comment 7.

9. Comment: The risk assessment in Part B differs from the EPA's average relative risk method only in that it uses more than one data point to estimate the slope of the dose-response line. Weighted least squares is used to this end, but this does not directly address

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the probability structure of the data. The maximum likelihood estimation approach is a more rigorous method (NiPERA-1, p. 6). Because the ARB could not replicate certain calculations, it chose an approach that was more simplistic and easy to replicate. This was not a scientific decision (NiPERA-1, p. 6).

Response: In preparing the Nickel document, the EPA risk assessment method was reviewed. In our analysis an error was found in the EPA method. The EPA used a MLE model. In contrast our document uses a relative risk model which has the greatest scientific rigor of those models currently used. Reasons were given on pages 105, 106 of the 1990 draft Document. In our opinion, it is inappropriate to use the EPA model since it is in error and is less scientifically rigorous.

10. Comment: Competing risks will undoubtedly factor into any risk assessment based on nickel exposures alone. The ARB should contact the EPA for clarification of the issue of competing risks and its relation to the difficult-to-replicate maximum likelihood estimation method. This method gives consistently lower risk estimates. Use of an average relative risk model may not be warranted and may result in overestimation of risks (NiPERA-1, p. 6-7).

Response: See response to comment 9. In addition, EPA staff were contacted and they were unable to replicate their method. The lower estimate in the MLE method appears to be due to a systematic error in the model or its application and the relative risk model has not been shown to "overestimate" risks.

11. Comment: The risk attributable to individual nickel species has not been taken into account. Exposure to different nickel compounds will likely yield different unit risk estimates. There is no evidence that metallic nickel is associated with increased lung or nasal cancer risks. The issue of speciation and associated risks deserves further attention by the ARB (NiPERA-1, p. 7).

Response: The risks attributable to individual nickel species was discussed in the report in Section 8 of the 1990 draft Document. As indicated in the most recent IARC report, metallic nickel is possibly carcinogenic to humans.

12. Comment: At the public consultation meeting in August, this commentator made the following comments and recommendations regarding the risk assessment: a) New information on the Copper Cliff Sinter Plant workers should be utilized; b) Adjustments for lack of follow-up should be eliminated based on the reliability of tracing methods used in updating this cohort; c) The use of the proportionate mortality ratio to estimate background lifetime risk is questionable; d) Maximum likelihood estimation (MLE) of the slope of the dose-response curve should be investigated; and e) The EPA should be contacted to ascertain the reasons for differences between certain MLE-based and average relative risk approach-based risk estimates (NiPERA submittal dated October 19, 1990 [NiPERA-2], page 1).

Response: Each of the comments listed has been answered in responses to comments 5-11 above.

C33511

13. Comment: The reason for the draft risk assessment's use of weighted least squares instead of the maximum likelihood estimation (MLE) approach is unclear. MLE estimation is more rigorous than weighted least squares in that it explicitly utilizes the assumed Poisson error structure of the data. This is particularly important in estimating the upper 95% confidence limit for the slope parameter that drives the risk assessment (NiPERA-2, p. 1).

Response: Weighted least squares estimates are appropriate for the model chosen. The EPA used a different model which it fitted by maximum likelihood estimation.

14. Comment: Although the draft (Part B of the) technical support document notes that *a priori* considerations "clearly favor a relative risk model" for the risk assessment (page 107), it seems to argue against this position in presenting the results of Magnus *et al.* (1982), which clearly suggest that the effects of nickel exposure and smoking are closer to additive than multiplicative (NiPERA-2, p. 4).

Response: This comment is not correct for reasons given in Section 7.2.3.2 and in the third paragraph of page 107 of the 1990 draft document.

15. Comment: One cannot estimate additive risks with either the Chovil *et al.* or ICNCM data because the person-years associated with the observed lung cancer deaths are unavailable. The draft document seems to imply that applying relative risk estimates to background rates for the period that the Copper Cliff cohort was followed provides reasonable estimates of additive risk. It is not clear that this is true. To properly perform the risk assessment, it would be desirable to obtain the raw data and apply the additive model (NiPERA-2, p. 4).

Response: The comment is incorrect. This was discussed in Section 7.2.3.2 of the 1990 draft Document.

Comments from the Southern California Edison Company (SCEC)

1. Comment: The draft DHS report recommends that "'insoluble nickel" be considered capable of causing cancer in humans, and that the potency of all insoluble nickel compounds be considered equal to that of nickel refinery dust. This conclusion is not supported by the current state of knowledge regarding nickel toxicity. Only nickel subsulfide, nickel refinery dust, and nickel carbonyl have shown evidence of carcinogenicity from environmental exposures. Only for nickel subsulfide and nickel refinery dust is there sufficient evidence to support listing as toxic air contaminants. No evidence exists to support the conclusion that other forms of nickel can cause cancer by inhalation or ingestion. The information used by the DHS to conclude that nickel oxide has the same potency as nickel subsulfide is from injection studies, which are not relevant for inhalation risk assessment. The relevant studies cited by the DHS are either negative or inconclusive regarding hazard identification for inhalation of nickel oxide; they do not give scientific support for the conclusion that nickel oxide can cause cancer in humans (SCEC submittal, pages 1-2).

Response: The reasons for assuming that nickel oxide was carcinogenic were given on p. 116 of the draft document. Nickel oxide and nickel subsulfide are carcinogenic when given by injection. Since inhalation studies involving nickel oxide are inadequate, the report noted that in the absence of good evidence to the contrary, it would seem prudent to consider that both nickel oxide and nickle subsulfide be carcinogenic. However, in a recent review of nickel compounds, IARC (Volume 49, 1990) concluded that based on the result of epidemiologic studies, carcinogenicity studies in experimental animals, and data supporting the underlying concept that nickel compounds can generate nickel ions at critical sites in target cells, all overall nickel compounds are carcinogenic to humans and the metallic nickel is possibly carcinogenic to humans. Also, IARC specifically referred to the existence of sufficient evidence in humans for the carcinogenicity for the water-soluble compound nickel sulfate. Consequently, DHS staff have concluded that all nickel compounds should be considered carcinogenic.

The ICNCM Report has also suggested that many forms of nickel are potentially carcinogenic. Additional information concerning the potential carcinogenicity of various nickel compounds has been added to the Genotoxicity and Mechanism Section as well as the Carcinogenic Effects in Animals subsection on Injection Administration.

As discussed in Section 6, genotoxic responses occurred from both soluble and insoluble forms of nickel. In Section 6.2, the document discusses that the nickel ion is the ultimate carcinogenic form of nickel and nickel compounds. Thus, the epidemiologic **evidence, the animal experiments and the genotoxic mechanism of nickel indicate that all** nickel compounds may be potentially carcinogenic, with the potency differences related to the varying degree of bioavailability (i.e. the ability to provide nickel ion in adequate concentrations at the critical site in the cell). Unfortunately, the available *in vivo* data is not adequate to quantitatively estimate differences in bioavailability. Consequently, the available scientific evidence indicates that all nickel compounds should be regarded as potential carcinogens, and not simply nickel subsulfide, refinery dust and nickel carbonyl. Also, the ICNCM Report suggests that soluble forms of nickel may be as potent (or possibly more potent) than insoluble forms.

2. Comment: The draft DHS report should be revised to accurately reflect the scientific data and the EPA's review of the data (SCEC, p. 2).

Response: We believe the report accurately reflects the scientific data. We also note that nickel refinery dust has nickel oxide and subsulfide as major constituents. Furthermore, the report contains an extensive discussion of the EPA review. The reasons for not following the EPA risk assessment approach are stated in responses to comment 9 of NiPERA.

Comments from Kathleen A. Hazer

1. Comment: The draft report mentions neither the existence of the ICNCM report nor its results. The carcinogenesis section should therefore be revised and should, as appropriate, include new unit risk factors for the different nickel species addressed by the ICNCM report (nickel oxide, nickel subsulfide, soluble nickel, metallic nickel, and total nickel) (KA Hazer, p. 1).

000513

Response: As previously noted, the ICNCM report was not available when the draft document was prepared. No new exposure measurements emerged in this document. Reasons are given in the response to the NiPERA comments and some modifications to the risk assessment calculations. The report is referenced in the revised nickel document.

2. Comment: **Although 35-50 *u*g/day and 120 *u*g/day are presented as levels of nickel possibly required in the human diet, breathing the air of California at the standard rate of 20 m3/day, which amounts to 0.022-0.472 *u*g/day, seemingly puts one at risk for cancer, according to the draft report. The issue of this contrast should be more thoroughly addressed, possibly in conjunction with a more detailed discussion of tissue distribution and route of exposure for soluble and insoluble nickel (KA Hazer, p. 1-2).**

Response: Section 4 clearly states that nickel has been established as an essential trace metal in a number of microorganisms, plants and experimental animals, however, the nutritional requirements of humans regarding nickel are not known.

Insoluble forms of inhaled nickel are not readily absorbed following inhalation and therefore would accumulate to much higher levels in the lung than soluble forms of nickel. The risk estimate for exposure to nickel in urban air is very low, and it was noted that it was presented in the absence of evidence for a threshold. There is no scientific reason for excluding the possibility that inhalation of nickel poses a lung cancer risk just because it may be required in the human diet. There was a discussion of apparent route specificity for the carcinogenic effect of nickel in Section 9 of the 1990 draft Document. The lung cancer endpoint is based on human studies, while the nutritional requirements of nickel are based on laboratory animal studies.

Comments from Falconbridge Limited

1. Comment: **The DHS states that there is no way to quantitatively determine a threshold for nickel carcinogenesis. The DHS nevertheless considers nickel carcinogenicity to be a nonthreshold process in the absence of compelling evidence for a threshold. This detracts from the draft report's credibility (Falconbridge submittal, page 1).**

Response: Since there is no evidence for a threshold, it is prudent to assume that there might not be one. This is the standard approach used in carcinogenic risk assessment by the state of California Department of Health Services and the U.S. Environmental Protection Agency.

2. Comment: **The International Agency for Research on Cancer has recently classified nickel compounds as Class 1 carcinogens and metallic nickel as 2B. The final report should reflect this change (Falconbridge, p. 1).**

Response: This information has been incorporated into the report, see the summary, Section 1.2.

C00514

3. Comment: **The paragraph on page 7 of the draft report on pharmacokinetics should be expanded to indicate that nickel absorption depends on the amount inhaled and breathing rate as well as chemical form (Falconbridge, p. 1).**

Response: A sentence stating that nickel absorption can also be affected by the amount inhaled and breathing rate was added to Section 3.1.1.2.

4. Comment: **The draft report notes that although nickel deficiency has not been described in humans, nickel has been established as essential for several microbe, plant, and animal species. This conflicts with the assumption that nickel carcinogenicity is a nonthreshold process (Falconbridge, p. 1).**

Response: It is possible for low level exposure to nickel via inhalation to increase cancer risks, even though ingestion may be required for some as yet unknown function of nickel. See response to comment 2 from KA Hazer.

5. Comment: **The draft report notes that lung reactions to nickel can vary among species, yet (on page 94) metabolic factors and absorption fractions are assumed to be the same for all species, including humans. The use of cross-species equality is considered to be a serious weakness of the draft report (Falconbridge, p. 2).**

Response: The cause(s) for different lung reactions to nickel is not known. The calculations and text on page 94 show that no adjustment for potential absorption differences was made because of a lack of experimental data. In the absence of data the absorption rate was assumed to be the same between humans and rats. EPA (1986) did estimate a human equivalent dose based on dose/body surface equivalence (BSE) (as was done in the draft report) and on dose/surface area of the lung (SAL). The second method, dose/SAL, took into account the available data regarding lung kinetics, etc. in the rat and human. The two methods, dose/BSE and dose/SAL, produced very similar human equivalent exposure values (46.1 vs 36.0 $\mu g/m^3$, respectively) and MLE's (3.1×10^{-3} vs 3.9×10^{-3}, respectively).

The best value for cancer potency in the nickel report are based on human data and no cross-species equality is assumed in these estimates.

6. Comment: **Use of a one hit model in the risk assessment is not appropriate, since carcinogenicity is a multi-stage event (see Grisham JW (1989) Current insights into the mechanisms of carcinogenesis, with implications for mesothelioma. CIIT Activities 9:1-9) (Falconbridge, p. 2).**

Response: When there is only one exposure dose, the multistage model cannot be used except in the form of a one-hit model. However, the human data risk estimation used in the nickel document does not assume a one-hit model.

7. Comment: **Use of the 1981 paper by Chovil *et al.* is suspect, since the study is not considered useful for determination of the magnitude of the increased risk. Too many cases were untraced and the untraced fraction was unacceptably assumed to have the same**

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cancer incidence as the rest of the cohort. Thirty-seven of the primary lung cancer cases were apparently determined using pathology or clinical reports rather than death certificate data alone; the corresponding Ontario vital statistics were based on death certificates only: comparing these is unacceptable epidemiology. The approach used to adjust for equivalent lifetime exposure could be improved: work periods were longer and vacation times shorter prior to 1950; more detailed information on work schedules could be useful (Falconbridge, p. 2).

Response: In the light of the Roberts *et al.* 1989 paper, we have revised the estimates so that they no longer assume that those untraced had the same mortality as those traced (See response 6 to NiPERA). The 37 lung cancer deaths used in the risk were identified by death certification, and not as stated in the comment.

8. Comment: Other shortcomings of the Chovil *et al.* (1981) study have been summarized by Wong O, D Foliart and RW Morgan in a 1983 report to NiPERA. These include the following: 1) the cohort was not a complete roll of the sinter plant workers; 2) the death records search could not have found deaths outside of Ontario in 1978; 3) it was not clear if incident cases who left Ontario after employment would have been identified; 4) the method of calculating the expected number of deaths was not the commonly accepted procedure; 5) multiplying the number of expected deaths by 1.5 to obtain the number of expected incident cases was a gross oversimplification; 6) available incidence rates could have been used for a more reasonable approximation; 7) it is not clear whether only those lung cancer deaths between 1963 and 1978 were included; 8) the method used in the dose-response analysis, which was essentially an analysis by duration of exposure, may not have been appropriate: for example, expected deaths were apparently not based on person-years in each duration subgroup as person-years were assigned to subgroups incorrectly; 9) exposure subgroups that did not fit the cohort definition were included; 10) it is difficult to justify the decision to give double weight to pre-1951 exposures; 11) high levels of PNA in the work environment reduce the validity of the dose-response relationship; and 12) that over 90% of the workers smoked cigarettes reduces the validity of the dose-response relationship (Falconbridge, p. 2 and Appendix 2).

Response: None of the problems raised exceed the advantages of using this cohort for the risk assessment. 1) would not necessarily introduce any bias. 2) could lead to a small underestimation of risks. 3) The risk assessment was not based on incident cases. 4) The method of calculating expected deaths was unusual but would not result in major bias. 5 and 6) We did not use the incident data calculated in this manner stated in the comment. 7) Only lung cancer deaths between 1963 and 1978 were included as stated in Sections 7.2.1.2 and 7.2.5. 8) The methods used were unusual, but there is no evidence they were inappropriate or overestimate risk. 9) this comment is unclear, however, it does not appear that any subgroups were misclassified in a way that overestimates the risk calculation. 10) The decision was reasonable based on the exposure measurements. 11) There is no evidence for this conclusion. 12) The 90% figure is quoted from anecdotal evidence. Since mortality from circulatory disease was less than expected, it is unlikely that these workers smoked significantly more than the general population.

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Comments from Regulatory Compliance Consultants, Inc. (RCC)

1. Comment: **It appears that only selected studies were used to arrive at the conclusion that "all insoluble nickel compounds should be considered potentially carcinogenic to humans by inhalation" and that other studies listed in the draft report were rejected if they did not conform to this conclusion. The literature raises more questions regarding this conclusion than it does to substantiate it. The studies listed in the draft report are not conclusive or even generally supportive of the recommended findings. The conclusions in the DHS report appear to be stretched to arrive at some preconceived concept (RCC, p. 1).**

Response: The document has been revised to be consistent with the new IARC findings that while metallic nickel is possibly carcinogenic to humans, all nickel compounds are carcinogenic to humans. See summary, Section 1.

2. Comment: **Before the conclusions of the draft report are adopted, further definitive studies should be conducted to address the issue of whether all nickel compounds are carcinogenic by inhalation (RCC, p. 1).**

Response: Further studies are always needed and when they are completed further studies will still be needed. Public health decisions cannot and should not wait for the final answers from science if they ever come. As discussed in response to Comment 1 of the Southern California Edison Company, DHS staff have concluded all nickel compounds are carcinogenic based on the association of cancer with exposure to humans of various forms of nickel, of positive animal studies using various forms of nickel and the data indicating that nickel ion appears to act as the ultimate carcinogen for nickel compounds.

Comments from Cal Bumper

1. Comment: **The draft document and supporting reports are flawed, inaccurate, and incomplete. The sample groups and their definitions are unclear. There should be a distinction made in emissions reporting between soluble and insoluble nickel. This commentator questions the use of the highest possible percentage of total nickel that is insoluble nickel (90%) by DHS staff (Cal Bumper, p. 1-2).**

Response: This comment appears to be directed at ARB's part. However, since all nickel compounds are considered carcinogenic to humans, the estimation of the insoluble nickel fraction is no longer pertinent to the risk estimate.

2. Comment: **The draft report creates more issues than it resolves with respect to cancer risk. There is reference to four studies but only one was used for the purposes of the document. What was wrong with the other reports (Cal Bumper, p. 2)?**

Response: The reasons for rejecting the other studies were stated in Section 7.2.2 of the 1990 draft Document.

3. Comment: A conclusion based on a concentration that is one million times higher than that found in California air is without validity. This commentator questions whether the draft report "represents plausible estimates" of contaminants, emissions, results or risks. This commentator also believes that the statistical reports are flawed to the point of error. To make any decisions based on the document would be a mistake (Cal Bumper, p. 2-3).

Response: Reasons for not assuming a threshold were provided in the 1990 draft document in Section 1. With this assumption, the document attempts to give plausible upper bounds of what the true cancer risk estimates could be. There are acknowledged uncertainties in this process.

Comments from California Technical Plating, Inc. (CTP), the Modern Plating Company (MPC) and GP Gene's Plating Works (GPGPW)

1. Comment: A greater distinction should be made between "soluble" and "insoluble" nickel. As well as we can determine, there are no data to support the inclusion of soluble nickel as a carcinogen (CTP, p. 1, MPC, p. 1, and GPGPW, p. 1).

Response: The recent report of the ICNCM concluded that there was human evidence that soluble nickel was carcinogenic. Discussion of this is included in the revised document. The recent IARC report also concluded that nickel compounds are carcinogenic to humans. In particular, the IARC report states that there is sufficient evidence in humans of the carcinogenicity of nickel sulfate.

See also response to comment 1 from Southern California Edison Company.

2. Comment: Nickel chloride and nickel sulfate are essentially the only nickel compounds used in the electroplating process. Are the risk estimates by DHS staff based on only insoluble nickel in California air? If the range of insoluble nickel was 55% to 90% what is the justification for using only 90% (CTP, p. 1, MPC, p. 2, and GPGPW, p. 1)?

Response: The specific potency value presented by DHS is based on total exposure. However, the document does address the question of nickel speciation and quantitative cancer risk (Section 8). Additional information regarding the toxicity of various nickel forms has been added to the Genotoxicity and Mechanism Section, the Carcinogenic Effects in Animals subsection Administration by Injection, and Section 8.

The risk estimates were derived using workers exposed predominantly to insoluble nickel compounds. However in the light of the IARC and ICNCM reports and the information we have on how the nickel ion causes cancer, it would seem appropriate to apply the risk estimates to all nickel compounds until further information becomes available. Consequently, the estimate of the insoluble fraction is no longer pertinent to the risk estimate.

3. Comment: The way in which cigarette smoking was handled in the four occupational refinery studies should be clarified (CTP, p. 2, MPC, p. 2, and GPGPW, p. 2).

Response: As noted in Section 7.2.2, the Norwegian cohort study was the only one which had smoking data. Furthermore, since an interaction between nickel and smoking has not been established the smoking risk is not incorporated into the risk assessments.

4. Comment: How can anyone possibly have confidence in the science that could make the kind of extrapolation made in the draft risk assessment? Nickel exposure concentrations in the cohort study used to estimate cancer risk were one million times higher than California air (CTP, p. 2, MPC, p. 2, and GPGPW, p. 2).

Response: See response to comment 3 from Cal Bumper.

5. Comment: It is disingenuous at best to state that the draft report presents "plausible" risk estimates, in light of the rather questionable or unsupported data used, data (such as the emission estimates) with ranges so broad as to have little meaning, and extrapolations that are more a leap of faith rather than science (CTP, p. 2, MPC, p. 2-3, and GPGPW, p. 2).

Response: The methods used are intended to arrive at plausible estimates (rather than extreme) of upper bounds of what the true risk estimates might be. There are acknowledged uncertainties in this process. However, nickel compounds are known human carcinogens. Thus, many of the uncertainties in risk assessment are not present in this analysis. Also see response to comment 3 from Cal Bumper.

Comments from the Western States Petroleum Association (WSPA)

1. Comment: Many references regarding several issues of pharmacokinetics and general toxicology were not included in the draft report. The report's section on genotoxicity could also be improved (WSPA, Summary of Main Issues [summary], p. 1).

Response: The Reference Listing in the Draft Document provided only the references actually cited within the document. Additional references were reviewed but, for various reasons, not cited within the document. The Draft Report was not intended to furnish a complete literature review. Also see response to comment 14.

The genotoxicity section has been rewritten to incorporate more of the available data. Other sources of information such as the EPA and IARC reports are cited in the report and provide additional information.

2. Comment: Recent literature and data from an in-press IARC (International Agency for Research on Cancer) document should be reviewed for the section on animal model carcinogenicity (WSPA, summary, p. 1).

Response: The recent IARC document has been reviewed and is now cited in the nickel document.

3. Comment: **The latest and most detailed human data were not included in the draft report; therefore the document does not reflect the current state of scientific knowledge (WSPA, summary, p. 1).**

Response: See response to comment 1, 2, and 3 from NiPERA.

4. Comment: **Consideration should be given to whether multiple risk assessments should be developed for nickel and its various compounds (WSPA, summary, p. 1).**

Response: Consideration was given to the other cohorts and the reasons for choosing the selected cohort are given in Section 7.2.2.

5. Comment: **New IARC classification of nickel and nickel compounds should be included in the document (WSPA, summary, p. 1).**

Response: It is now included in the document.

6. Comment: **It should be made clear that the people "tested" for potential allergy to nickel, as noted on page 1, paragraph 3, line 7 of the draft (Part B) report, were persons with skin sensitivity or problems (WSPA, p. 1).**

Response: The statement on page 1, para 3, line 7 is based on the statement on page 50, para 7, line 4-5. We have re-checked the reference (Leonard *et al.*, 1981) and the statement: "...Approximately 10% of the tested populations were found to be potentially allergic to nickel." is correct. The reference did not state or indicate in any way that the populations tested consisted of individuals with skin sensitivity or skin problems.

7. Comment: **The oral and inhalation doses described on p. 2, par. 2 should be put in a form to show that the lowest observed effect levels (LOELs) are comparable (WSPA, p. 1).**

Response: This has been done. The LOEL exposure of 3.6 mg Ni/m3 in rats assuming 100% absorption and continuous exposure, would correspond to a daily intake of 0.3 mg Ni/kg-day. This is comparable to 0.4 mg Ni/kg-day as an oral exposure LOEL.

8. Comment: **The statement on p. 2, par. 4, lines 5-8 should be reconsidered after reading a 1990 report by Doll *et al.* (the ICNCM report, Scand J Work Environ Health 16:1-84) (WSPA, p. 1).**

Response: The wording of this statement has been changed as suggested by the comment.

9. Comment: **It should be noted that there was only one dose level in the inhalation study mentioned on p. 2, par. 5 (WSPA, p. 1).**

Response: This has been mentioned as suggested by the comment.

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10. Comment: Several statements on p. 3 and 4 should be reconsidered in light of the ICNCM report and after preparing a new risk assessment (WSPA, p. 1).

Response: The ICNCM report is considered in the revised draft.

11. Comment: Three specific references (Sunderman and Selin, 1968; Mikehyer, 1971; and Tanaka et al. 1985) should be included in the pharmacokinetics section (Section 3) of the document (WSPA, p. 1).

Response: The suggested references have been reviewed and relevant information was incorporated in the document where appropriate. Note: one reference, Sunderman and Selin, 1968 had already been reviewed in this section.

12. Comment: Section 4.2 should be labeled so as to clearly indicate it refers to interactions in deficiency states rather than interactions at normal levels of metals (WSPA, p. 2).

Response: Section 4.2. has been relabeled as suggested in the comment.

13. Comment: Separate sections considering metal-nickel interactions at normal levels and in carcinogenesis should be included in the document (WSPA, p. 2).

Response: Studies reporting nickel interactions at normal levels were not found in the literature at the time the draft document was prepared. A discussion of nickels interaction with other chemicals has been added to the Genotoxicity and Mechanism Section. See Sections 6.2.1 and 6.31

14. Comment: Twenty-two specific references on acute, subchronic and chronic toxicity should be included in the document, in appropriate subsections (WSPA, p. 2-3).

Response: Note: several references were cited more than once by the commentor. Only twenty individual references were suggested. The Draft Report was not intended to provide a comprehensive literature review. As stated by the commentator the references suggested for addition have been reviewed elsewhere. The intent of Section 5 was to provide information directly relevant to determining (if possible) inhalation and oral NOAELs and LOAELs. Therefore, studies utilizing high doses (e.g. LD50 studies, cases of fatalities) would not have been cited in the draft document. However, DHS staff have reviewed the suggested references. Those references providing relevant information will be incorporated in the document where appropriate. (Dadrup et al., 1983; Adkins et al., 1979; Dunnick et al., 1987; Bingham et al., 1972; Weischer et al., 1980a and 1980b; Yelfimova et al., 1976 and 1977; Curstedt et al., 1983 and 1984; Itskova et al., 1978 and 1969; Kosova, 1979; Clory, 1975; Mastromatteo, 1986; Haro et al., 1968; Whanger, 1973; Dieter et al., 1987; O'Dell et al., 1970; and Mathur et al., 1970).

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15. Comment: On p. 31, par. 3, line 6, the word "acute" should be included in noting the nickel carbonyl is the only nickel compound recognized as a cause of (acute) human systemic toxicity (WSPA, p. 3).

Response: The wording of the sentence has been changed as suggested by the comments.

16. Comment: Seven specific references should be included in the reproductive effects section (Section 5.5) (WSPA, p. 3). (Berman and Rehnberg, 1983; Nadeenko et al., 1979; Phatak and Patwordham, 1950; Tsujii and Hoshishima, 1979; Costa and Mollenhauer, 1979; and Gilani and Marano, 1980; Weischer et al., 1980a).

Response: The intent of this section was to determine mammalian NOAEL/LOAEL reproductive health effect levels for inhalation and oral exposure (if possible). Many of the references suggested by the commentator have been reviewed elsewhere. However, DHS staff have reviewed the suggested references. Those references providing relevant information will be incorporated in the document where appropriate.

17. Comment: The original reference should be given for the values given on p. 69, Section 5.5.5, par. 2, lines 10-12. Whether these are official EPA values should also be noted (WSPA, p. 4).

Response: The original references have been added to the text. The EPA recommended values have been updated since the draft document was written. New estimated intake values have been calculated utilizing the updated EPA values. The EPA reference has also been provided.

18. Comment: On p. 70, par. 1, the year of the Ottolenghi *et al.* study should be noted, a reference to the derivation of the 122.8 *u*g/m3 value should be included, how the 60 *u*g/kg-day value was obtained should be stated, "the lowest reproductive effect level" and "the LOEL in the rat" should be stated and referenced, and what was measured by the ARB (for "the maximum level reported by ARB") should be stated (WSPA, p. 4).

Response: As suggested by the commentator, the following information will be added to page 70 para 1:

1) The Ottolenghi *et al.* study was deleted since it referred to cancer effects and not noncancer effects;

2) Thus the value 122.8 ug/m^3 is no longer noted;

3) The lowest reproductive effect level will be stated and the reader will be directed to Section 5.4 for the derivation of this value. The level reported by ARB will be cited only when health based conclusions are being made, otherwise Part A can be consulted.

4) Additional information regarding the LOEL values for non-cancer health effects will be added as requested by the commentator.

19. Comment: A summary table for the genotoxicity section would be helpful. A specific table, from a 1987 review by S. Fairhurst and H.P.A. Illing, should be adapted and improved for use in the DHS report (WSPA, p. 4).

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Response: A tabular genotoxicity summary has been incorporated into the draft. However, the table was designed to best reflect the available data and did not adapt the Fairhurst and Illing's table per se.

20. Comment: The date of the "review of the current literature" mentioned in Section 7.1, par. 1 should be noted. The status or findings of the studies projected for completion in 1988 or 1989 should be discussed (WSPA, p. 4).

Response: This section has been altered to address the commentators concerns.

21. Comment: It is unclear whether certain parts of Section 7.1.1.1 refer to Hueper (1958) (WSPA, p. 4).

Response: Paragraphs 2-5 refer to Hueper, 1958.

22. Comment: The findings of Fisher *et al.* (1986) should be described in Section 7.1.1.4 and it should be noted that this was an intratracheal experiment (WSPA, p. 4).

Response: Comment is believed to refer to page 82, Section 7.1.1.4. A discussion of the findings of the intratracheal study by Fisher *et al.* 1986 will be added to the text.

23. Comment: The first four paragraphs on p. 88 of the draft report are a repeat of material on page 85 and should be deleted (WSPA, p. 4).

Response: Section 7.1.2 has been revised as suggested.

24. Comment: The second sentence in Section 7.1.4 is incorrect (see, e.g., Kosova (1979) Toxicity of nickel sulfate. Gig Trud Prof Zabol 23:48-9) (WSPA, p. 4).

Response: The Kosova (1979) study examined inhalation exposure of rats to nickel sulfate. There were 24 animals per group exposed for 9 months. Although the study is a chronic study, little detail is provided on the analytical procedures used. In any case, the study should not be misconstrued as a bioassay for the carcinogenic effects of nickel sulfate. Consequently, the sentence in the nickel document is correct. Note: IARC and EPA do not consider the Kosova study a cancer bioassay.

25. Comment: Nasal cancer is apparently not mentioned after p. 94. Why this is should be explained (WSPA, p. 4).

Response: The revised draft discusses this point explicitly. Nasal cancer risks could be added to the current estimate based on lung cancer. However the numbers of nasal sinus cancer in the Chovil study (3) was small, and inadequate for dose-response estimation. In the light of the fact that they contribute little to the risk in this cohort (there were 37 lung cancer deaths), it was decided to omit them.

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26. Comment: Certain additional articles may prove helpful for the discussion in Section 7.2 (WSPA, p. 4-5).

Response: The discussion has been confined to studies considered for quantitative risk estimation and is not intended to be an exhaustive review of nickel literature.

27. Comment: The possible, but improbable, involvement of nickel with other types of cancer should be discussed, considering some specific references (WSPA, p. 5).

Response: From the most heavily exposed cohorts of refinery workers, it can be concluded that other sites are not involved.

28. Comment: It would be helpful to review certain studies of welding, in spite of the statement on p. 96, line 3-5, regarding cancer possibly attributable to chromium (WSPA, p. 5).

Response: The reasons for not considering studies of welding workers was given and their validity is not being questioned. Expanding the document in this manner would not add to the major conclusions of the document or risk assessment.

29. Comment: Why only refineries and welders are mentioned for possible worker exposures should be explained. It may be helpful, for example, to review 11 specific cohorts from other occupations, and to show that the resultant risks were negative, insignificant, or low. Certain studies from Germany, Czechoslovakia, Russia and Japan, should also be reviewed (WSPA, p. 5).

Response: There is no evidence that the studies listed, many of which involve mixed exposure to lung carcinogens, could be used for risk estimation.

30. Comment: Although the draft report states that there have been no new cohort studies published since the EPA risk assessment, three groups of studies have been published. Certain sponsors of one of the studies (the ICNCM report) should be noted. In addition, several specific reviews should be considered and included in the DHS report, and 5 more cohorts of refinery workers should at least be mentioned (WSPA, p. 5-6).

Response: The revised document makes reference to the ICNCM report. We know of no additional cohorts that should be considered for risk assessment. It was not the intention to present an exhaustive review of the literature.

31. Comment: Certain other data should be considered in regard to the West Virginia cohort discussed in Section 7.2.1.1 (WSPA, p. 6).

Response: The 1982 paper by Enterline and Marsh gives all the important information on the cohort. The ICNCM report is also referenced in the revised document.

32. Comment: Section 7.2.1.1 and Table 7.8 give incorrect data for the *West Virginia cohort* and the values calculated in this section for cumulative exposure are therefore invalid (WSPA, p. 6).

Response: Section 7.2.1.1. has been revised. The rest of this section discusses the total cohort and the exposure values represent the total cohort. The values listed in this discussion were not "calculated" but reported by the authors.

33. Comment: A particular table (Table 63) in the ICNCM report should be of interest, since standardized mortality ratios (SMRs) were calculated for lung cancer versus cumulative exposure for metallic nickel, oxidic nickel, sulfidic nickel, soluble nickel, and total nickel (WSPA, p. 6).

Response: The ICNCM report was considered in the revised document. This table (63) like many others in the report was not based on actual measures of exposure. No definitive conclusions can be drawn from it concerning the carcinogenicity of the different forms of nickel.

34. Comment: The choice of cohort or subcohort and exposure data should be discussed in detail in further drafts of the document (WSPA, p. 6).

Response: The choice of cohort and exposure data was discussed in detail. See section 7.2.2 and 7.2.1.2 of the nickel document.

35. Comment: The Ontario cohort considered on pages 96-98 is really three cohorts -- Copper Cliff, Coniston, and Port Colborne. The total size of this INCO (International Nickel Company) Canadian cohort is 54,746 workers, of whom 50,977 were classed as "non-sinter" workers and 3,769 as sinter workers (WSPA, p. 6-7).

Response: The revised report makes clear that a subcohort was used.

36. Comment: Certain additional data should be considered in detail in the discussion of the Ontario workers on pages 96-98 (WSPA, p. 6).

Response: The more recent Roberts paper and ICNCM report are discussed in the revised report.

37. Comment: The Chovil *et al.* (1981) study used in the risk assessment is now out of date for this purpose, since additional follow-up information is now available (WSPA, p. 7).

Response: The ICNCM update of the Chovil cohort study has been discussed in the revised report.

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38. Comment: In the Chovil *et al.* (1981) study, it was thought that 25% of the cohort was lost to follow-up, but in later studies the method of tracing ex-workers is such that it is highly unlikely that any of the untraced workers have died. This comment applies to Sections 7.2.1.2 and 7.2.5 (WSPA, p. 7)

Response: The correction for loss to follow-up has been revised.

39. Comment: Because so many new data are now available, much of Section 7 of the document, including the risk assessment, should be reconsidered, rewritten, and recomputed (WSPA, p. 7).

Response: The new data available in the ICNCM report have been considered. Revisions to the risk assessment have been made, although the revisions do not impact the major conclusions or substantially alter the risk assessment.

40. Comment: A detailed discussion of certain pages (5-6 and 69-75) of the ICNCM report should be included in the document (WSPA, p. 8).

Response: Discussion of the ICNCM report is given in the revised document.

41. Comment: The choice of cohort or subcohort and exposure data should be discussed in detail in further drafts of the document (WSPA, p. 8).

Response: This was discussed in detail in Section 7.2.2

42. Comment: With regard to the Welsh cohort discussed in Section 7.2.1.3, data from several specific other reports should be considered. Data from the ICNCM report should be considered in detail (WSPA, p. 8).

Response: As noted in the revised document, the ICNCM report contains no measurements of exposure for the Welsh cohort from the relevant exposure period.

43. Comment: The Welsh cohort's qualification period was 1902-1960, rather than beginning in 1910, as implied on p. 99, line 1; the follow-up period for the ICNCM report was 1907-1984 (WSPA, p. 8).

Response: The commentator is referring to the recent ICNCM update of the cohort and their description. Reference is made to the updated and cohort in the revised document.

44. Comment: The exposure estimates for the Welsh cohort given in the ICNCM report should be fair and accurate and supersede earlier estimates. The plant at Clydach is of interest because its history is known in a great deal of detail and the plant's current medical director succeeded his father and comes from a family that has had a keen interest in (and knowledge of) plant affairs. The medical director has contributed new

data to the ICNCM report; his earlier exposure estimates (Morgan (1985)) are cited in the draft Part B (WSPA, p. 8).

Response: As indicated above the exposure estimates provided in the ICNCM report are not actually measured values. Consequently, the measured exposure values previously reported for the Ontario cohort by Chovil *et al.* remain the strongest dose-response information available for human exposure to nickel compounds.

45. Comment: The problems discussed in the last paragraph on p. 99 and the top of page 100 no longer exist. See, e.g., Table 17 of the ICNCM report. It can no longer be stated that "the number[s] of workers in the cohort ... are too few." Table 7.8 of the draft DHS report is in error; the correct N for the Wales study is 1348, and the number of lung cancer deaths is 172 (WSPA, p. 8).

Response: The problem of adequacy of numbers with sufficient latency of follow-up remains. Table 7.8 is not in error. The numbers given by WSPA are for the ICNCM report. Reference is made to the updated cohort in the revised document.

46. Comment: The choice of cohort or subcohort and exposure data should be discussed in detail in further drafts of the document (WSPA, p. 8).

Response: The choice of cohort has been fully discussed as mentioned in comments #34 and 41, above.

47. Comment: Regarding the Norwegian cohort (Section 7.2.1.4), in addition to the reports considered by the DHS, data from specific other reports should be considered. The data from the ICNCM report are of particular interest: the cohort size and number of lung cancer deaths have grown. Exposure data are now available, so extrapolations from other plants should no longer be used. Comparisons with exposures in other plants are available in the ICNCM report (WSPA, p. 8-9).

Response: The exposure estimated provided in the ICNCM report were not actual measured values but reconstructed estimates. Consequently, the exposure measurements for the Ontario cohort remain the most reliable human dose-response information available.

48. Comment: The Falconbridge, Ontario cohort of 11,594 workers should be included, with the other cohorts discussed on pages 100-102 of the draft report, in any discussion of risk assessment cohort choices in future drafts of the document. Exposure estimates also exist for this cohort as well as for several sub-cohorts, one of which is a "sinter workers" group of 1602 persons with 24 lung cancer deaths. Section 7.2.2 cannot be adequate for comment until a new Table 7.8 is constructed and the DHS reevaluates the cohorts or subcohorts to be used for risk assessment (WSPA, p. 9).

Response: No measurements of exposure are available for this cohort before the early 1960s, so it is not suitable for quantitative risk assessment. The ICNCM update is discussed in the revised document.

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49. Comment: Nearly all the observations made about the four cohorts in Section 7.2.2 are no longer applicable following the publication of the ICNCM report and a 1989 report by Roberts *et al.* (WSPA, p. 9).

Response: Revisions have been made in the light of the ICNCM report. However, the ICNCM follow-up does not alter the range of exposure estimates provided in the original draft.

50. Comment: Because of the ICNCM report, Table 7.9 should be recalculated, as should the values listed on page 105, lines 8-10 (WSPA, p. 9).

Response: Table 7.9 was derived from the EPA report as noted in the title. The values given in lines 8-10 are also taken directly from the EPA report.

51. Comment: The change in background population cancer rates with time should be adequately addressed. This comment applies to p. 105, lines 8-10, and page 115, paragraph 4 (WSPA, p. 9).

Response: The background lifetime lung cancer mortality rates for males in Ontario ranged from 0.036 (i.e. 36 per thousand) in 1963 to 0.068 (i.e. 68 per thousand) in 1978. The estimate for the entire period was approximately 0.051 or 51 per thousand. See section 7.2.5 of revised draft.

52. Comment: Because of the ICNCM report, Section 7.2.3.3 is now only of historical interest (WSPA, p. 9).

Response: The ICNCM report is of no relevance to section 7.2.3.3.

53. Comment: Because of the ICNCM report, some of the discussion on p. 107 should not be relevant to an updated risk assessment for nickel (WSPA, p. 9).

Response: We cannot identify anything in this section which is no longer relevant.

54. Comment: New follow-up periods from the ICNCM report should be used on page 108, line 5 of Section 7.2.4 (WSPA, p. 10).

Response: The risk assessment remains based on this follow-up period since the ICNCM update cannot be readily linked to the exposure data.

55. Comment: The statement regarding smoking starting on line 5 of the last paragraph of p. 111 may not be true for non-U.S. cohorts, because smoking became increasingly popular in Europe and the U.K. during World War I. After 1918, blue collar workers, particularly ex-soldiers, were seldom without their cigarettes (WSPA, p. 10).

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Response: It is our understanding that smoking increased in Europe as well as in the U.S. in the 40s and 50s. However the statement is not necessary and it has been deleted from the revised report.

56. Comment: Sections 7.2.4.2 and 7.2.5 and Tables 7.11 and 7.12 should be made relevant to the cohorts used in an updated risk assessment (WSPA, p. 10).

Response: The revised report gives reasons for still using the Ontario sinter plant cohort for quantitative risk estimates. Table 7.11 therefore remains as is, but there are some modifications to Table 7.12.

57. Comment: Paragraphs 1 and 2, and sentence 1 of par. 3, of Section 8 should be updated to reflect the data contained in the ICNCM report, including its Table 63 (WSPA, p. 10).

Response: The revised report considers the ICNCM evidence that soluble forms of nickel may also be carcinogenic and has been revised accordingly.

58. Comment: Sentences 4 and 5 of Section 8, par. 3 are incorrect because the negative study was intratracheal, and not an inhalation study (WSPA, p. 10).

Response: The text has been corrected.

59. Comment: Sentences 6 and 7 of Section 8, par. 3 should be updated following a new risk assessment based on data from the ICNCM report (WSPA, p. 10).

Response: The numbers in this paragraph have been revised in the light of the new potency estimates.

60. Comment: Regarding paragraphs 3 and 4 of Section 8, it would be instructive to compare the doses used in the studies of Ottolenghi *et al.* (1974), Glaser *et al.* (1986), and Wehner *et al.* (1975 and 1984), and convert them to human equivalent doses (WSPA, p. 10).

Response: Although it may by instructive, the Department does not plan to do so in this report since the identification of carcinogenicity and risk estimates are based primarily on human data.

61. Comment: Paragraphs 5, 6, 7, and 8 of Section 8 should be re-thought after review of the ICNCM report, particularly pages 71-5 (WSPA, p. 10).

Response: The revised document takes into account information given in the ICNCM report concerning carcinogenicity of different forms of nickel.

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62. Comment: **Does comparing the carcinogenic potency of inorganic compounds of an element by comparing times of residency in the lung (see the last two sentences of Section 8, par. 7) represent official DHS policy (WSPA, p. 10)?**

Response: No it does not. DHS staff try to utilize all available scientific evidence when developing a risk assessment. These statements were merely provided to help shed some light on the mechanisms of nickel compound carcinogenicity.

63. Comment: **Although the conclusions of Section 9 are correct, "produce evidence" on line 4 should read "produce scientifically valid evidence...." Also note that the degree of absorption of nickel oxide and nickel subsulfide from the alimentary tract will not be zero, and that sentence 6 is not logical because increasing concentrations of inorganic compounds in body organs do not necessarily lead to cancer (WSPA, p. 10-11).**

Response: The document has been corrected to read "provide sufficient scientific evidence."

Comments from the Pacific Gas and Electric Company (PG&E)

1. Comment: **Only insoluble nickel compounds should be identified as toxic air contaminants at this time (PG&E, cover letter dated August 22, 1990, p. 1 and p. B-1.).**

Response: See response to comment 1 from the Southern California Edison Company.

2. Comment: **The unit risk derived from sinter plant subcohorts of the Ontario cohort should only be applied to nickel subsulfide and nickel refinery dust. A separate, non-sinter worker cohort should be used for estimating risks from insoluble nickel compounds other than nickel subsulfide. This is the preferred and recommended course of action. Alternatively, a unit risk derived from the 47,980 non-sinter worker Ontario cohort should be used for unspeciated insoluble nickel. Using the non-sinter worker cohort, rather than the sinter plant subcohort, would reduce the unit risk estimate by a factor of approximately 5.7. The exposures of the non-sinter workers are more representative of expected California exposures. Basing all California insoluble nickel risks on the sinter worker subcohort with the highest SMR is unjustifiably conservative. The largest possible cohort or combination of cohorts should be used to generate the best estimate of risks (PG&E, cover letter p. 1, B-1 and B-2).**

Response: The risk assessment of nickel compounds is based on the strongest epidemiologic data available. The use of the cohorts as suggested would reduce the precision of the information linking exposure with response. Only the sinter plant workers had measurements of exposure for relevant time periods to link to later increased lung cancer mortality rates. Non-sinter plant workers had lower potential for exposure so even if one could base a unit risk estimate on them, there is no reason to expect it to be lower than that derived from the sinter plant workers. Furthermore, the sinter plant workers were exposed to a mixture of nickel compounds not simply nickel subsulfide. These data do not reflect the most conservative estimate available. As indicated in Table 7.9 of the report range of risks calculated by the U.S. EPA based on 7 cohort analyses is 1.9 to 46 x 10^{-5} per ug/m^3 compared to the DHS best value of 23 x 10^{-5} per ug/m^3. Review

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of the human data for nickel sulfate exposure in the ICNCM report indicates that risks based on those studies could produce higher potency estimates as well. The reason for not choosing these studies is the absence of measured exposure data. The upper range of risks reported in the revised document is 10-fold higher than our suggested best value. It is unlikely that use of other human cohorts would substantially lower the risk estimates and doing so would weaken the scientific analysis. Estimates from some other studies are higher. In particular, estimates for nickel sulfate exposed workers would be higher.

3. Comment: **The unit risk should not be increased by a factor of 1.33 to account for workers whose vital status could not be established. A factor of 1.05 would be adequate. This change would reduce the estimated unit risk by a factor of 1.27. A factor of 1.05 would account for "normal life span" rather than "still living" status. This is recommended in part due to the excellent death registry in Canada and the likelihood that the investigators found most of the deaths (PG&E, cover letter p. 1 and B-2).**

Response: The estimates have been revised to take into account new information on follow-up of the cohort.

4. Comment: **Instead of increasing risks by a factor of 4.6 to account for non-occupational exposure time, the risk assessment should use a factor no greater than 2 (and this would reduce the unit risk by a factor of 2.3). The DHS assumes that a unit exposure to insoluble nickel will cause 4.6 times more risks in California's ambient air than it is presumed to have caused in the Ontario "historic worker" cohort. On average, Californians spend 13% of their time outdoors; the workers were assumed to spend 22% of their time at the workplace. The workers' exposure to nickel did not necessarily end when they left work. Nickel associated dusts may have been carried home on clothing, and dusts vented from the plant may have contributed to elevated concentrations in the vicinity. Only the finer particles tend to be captured by the lung, and these particles would be most readily vented from the plant by the roof fans. Modern indoor particulate exposure levels and historic "after work" exposures should be incorporated into the risk assessment (PG&E, cover letter p. 1, B-2 and B-3).**

Response: The adjustment of exposure from occupational to ambient are standard procedures used by the Department. The commentor is incorrect in concluding that DHS analysis assumes that a unit exposure causes more risks to Californians than the original cohorts. The risk to the original cohort in Ontario is much greater than that for Californians. Instead the DHS report assumes that Californians will be exposed to average ambient air concentrations of nickel that equal outdoor concentrations of nickel that equal outdoor concentrations. The indoor air comes from outdoors and there is no reason to assume that indoor air has less nickel. There is inadequate data to characterize indoor air. Indoor air levels of particulates generally match those of outdoor air levels. However, based on particulate comparisons and the likely contribution from cigarette smoke, one would expect higher indoor air exposure to nickel. Consequently, it is likely that the exposure estimates in the report underestimate California's exposure to nickel compounds in air. The commentor is likely to be correct that Ontario worker exposure to nickel continued after they went home. Specific data to quantify this are not available, but it is not likely that such exposures would add significantly to the exposure experienced at the workplace. Incorporating non-workplace exposure into the estimates would have a negligible effect since the environmental levels of exposure are so much

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lower than the workplace exposures experienced by the cohort. For example, if we assume that the workers spent 22% of their time at work, and the remaining 78% of their time at home with the unlikely scenario that at home they were exposed to nickel levels one tenth of those at the workplace due to dust they brought home, then the increased exposure estimate would be quite small (1 unit of estimated exposure would increase to 1.35 units (0.22 x 1 + 0.78 x 0.1)/(0.22 x 1)). With a more reasonable assumption that exposure levels at home were less than one hundredth of those at work, 1 unit of estimated exposure would increase to less than 1.035. If we assume that the workers were exposed at home to levels 1000 times higher than current California ambient air levels (i.e. 0.02 mg Ni/m^3) in contrast to workplace levels of 75 mg Ni/m^3, then the exposure estimate would increase by a factor of only 1.001 (0.22 x 75 + 0.78 x 0.02)/(0.22 x 75).

5. Comment: **The proposed unspeciated insoluble nickel unit risk factor should be reduced by a factor of 10 or more. This follows from the cohort changes and adjustments suggested in the comments above, or adjustments including an average age adjustment factor of 3.3. A non-sinter plant assessment for nickel oxide-dominated insoluble compound exposures might qualify for a similar age adjustment (PG&E, cover letter p. 2, B-3 and B-4).**

Response: The revised estimates include a change in the adjustment for loss to follow-up of the cohort. The potency estimates were based on the sinter-plant subcohort since pertinent measurements of exposure were available and the precisions of the standardized mortality ratios were satisfactory, and a clear dose-response relationship evident. The same cannot be said for the non sinter-plant workers. Thus there is no evidence to conclude that using the entire cohort would reduce the estimated unit risk by a factor of roughly 5.7 as claimed. The environmental versus occupational component has been discussed above in response to comment 4.

6. Comment: **Page 118 (Section 9) of the draft report should clearly state that nickel sulfate is not expected to be carcinogenic by ingestion, and that ingestion of insoluble nickel is expected to be far less carcinogenic than inhalation. Based on page 90 of the draft report, it is erroneous to suggest that the carcinogenic potential of nickel sulfate ingestion needs further study. Also, since the risk assessment focuses on insoluble nickel, the last two sentences of Section 9 should read "insoluble nickel" rather than "nickel". Since soluble nickel has no known carcinogenic effect, and is more likely than insoluble nickel to be absorbed when ingested, it would be reasonable to conclude that ingestion of nickel compounds would pose lower cancer risks than inhalation of a similar amount of insoluble nickel. Certain specific revisions should be incorporated in the conclusion of Section 9 (PG&E, cover letter p. 2, B-4 and B-5).**

Response: Since the preparation of the draft nickel document, the ICNCM and IARC reports have been issued. Both reports conclude that nickel sulfate and all nickel compounds are carcinogenic to humans as discussed in the Summary. Consequently, DHS staff will consider all nickel compounds to be carcinogenic. However, DHS will consider its conclusions restricted to the inhalation of nickel compounds as indicated in Section 8 due to the inadequacy of oral studies. Furthermore, it is still the opinion of DHS staff that more research is needed to determine if nickel compounds are carcinogenic by the oral route since adequate oral studies do not exist.

7. Comment: Although recognizing the importance of pulmonary pharmacokinetics in assessing the internal doses of nickel compounds, the draft report does not include pulmonary pharmacokinetics in its quantitative risk assessment. The State of California should consider the usefulness of pulmonary deposition data for nickel compounds (PG&E, p. 12-13).

Response: See response to comment 5 from Falconbridge Limited.

8. Comment: The draft report does not discuss data regarding the distribution of nickel compounds in biological fluids in humans (PG&E, p. 14).

Response: The draft report does discuss the distribution and concentrations of nickel in the blood (Section 3.2.1) and urine (Section 3.4.2.). A statement regarding additional information on nickel in biological fluids will be added and the reader will be referred to National Academy of Science (1975).

9. Comment: Although the NOELs and LOELs reported on p. 52 of the draft report are consistent with this commentor's review of the available data, additional data of Dunnick *et al.* are available for discussion (PG&E, p. 18).

Response: The Dunnick *et al.*1989 study referred to by the commentator was reviewed in the draft document (See Page 46 and Table 5.3).

10. Comment: The actual margin of safety with respect to potential reproductive effects for most Californians is likely to be substantially larger than that suggested by the draft report, because of the report's use of very conservative assumptions (PG&E, p. 20).

Response: A statement regarding the health-protection provided by the assumptions and the margin of safety has been added. (Section 5.5.5 of draft report).

11. Comment: Data suggest that the most sensitive target organs for effects due to inhalation of nickel are the lungs and the immune system, and not the reproductive system (PG&E, p. 21).

Response: The available data suggest that the lungs and immune system are the primary target organs for non-cancer health effects (see statement page 51 of draft report). However, reproductive studies utilizing inhalation as the route of administration are virtually nonexistent. Therefore, it would be misleading to state that the "Data suggest that the most sensitive target organs for effects due to inhalation of nickel are the lungs and the immune system, and not the reproductive system."

12. Comment: Although the draft report suggests that nickel subsulfide and nickel oxide "possess approximately equal potency" for causing cancer, there are variables which suggest otherwise. These include latency period, survival period, and metastasis of observed tumors. Nevertheless, it should be noted that the injection study at issue has no

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relevance to the carcinogenic potential of nickel compounds from ambient (e.g., inhalation, ingestion) exposure of humans (PG&E, p. 21).

Response: A statement of clarification has been added to last sentence on page 90 of the draft document.

13. Comment: Since combustion of fuels such as coal and oil is a key anthropogenic source of airborne nickel, assessment of the chronic toxicity of fly ash is of particular interest in evaluating the carcinogenic potential of nickel compounds (PG&E, p. 23).

Response: The importance of fly ash may be considered in the control phase of the Toxic Air Contaminant Program. However, the study by Wehner *et al.*(1981) utilizing nickel enriched fly ash was discussed in the 1990 draft document (see page 81).

14. Comment: This commentator found that no epidemiological studies have been reported in the literature that (1) demonstrate an association between ambient forms of nickel and increased cancer risk in the general population, or (2) would associate exposure to nickel as found in ambient air with increased cancer risk (PG&E, p. 24 (1) and 28 (2)).

Response: Such studies do not exist for nickel or possibly any other compound due to the technical difficulties in testing such a hypothesis.

15. Comment: The draft report incorrectly assumes that all insoluble nickel compounds should be considered potentially carcinogenic to humans, and that the carcinogenic potency estimated from the experience of a sinter plant "subcohort" is representative of the potency of the mixture of nickel species in respirable ambient air particles in California. The exact agents that cause the observed increases in lung and nasal cancer have not been determined. The proportion of total nickel in ambient air that is insoluble varies. Nickel sulfate and nickel oxide are likely to predominate in ambient air and have not been as clearly identified as human respiratory carcinogens as nickel subsulfide. The dose levels experienced by the workers are four to eight orders of magnitude greater than those present in ambient air in California (PG&E, p. 32-33).

Response: Please see response #44 to WSPA in addition to response to #1 Southern California Edison Company.

16. Comment: The draft report's risk assessment is based, without adequate explanation, on only a portion of the Ontario cohort. There is something unique about sinter plant workers that makes their risks unique relative to other workers exposed to nickel. This factor is likely to be exposure to a greater portion of nickel subsulfide. The subset of sinter workers used in the Part B risk assessment is a poor choice. This choice unjustifiably elevates risk by a factor of 2.18. The failure to include non-sinter workers improperly elevates risk by a factor of 2.61. Thus a combined "deflation factor" of 5.69 can be applied to the observed SMR (which is proportional to the unit cancer risk) (PG&E, p. 38-39, 42, 45 and 49).

Response: There is nothing unusual about the sinter plant workers. The risks calculated by the U.S. EPA (Table 7.9) range from 1.9 to 46 x 10^{-5} per ug/m^3 based on 7 cohort analyses. The best value calculated in our analysis, 23 x 10^{-5}, is within that range. The sinter plant worker exposure concentrations are linked to sinter plant worker lung cancer mortality. Unit risk estimates derived for the rest of the cohort would have to involve estimates of exposure for the rest of the cohort. Data to do this are not adequate, but there is no reason to believe that such risk estimates would be lower than those obtained from the sinter plant workers. Furthermore, as indicated above, risk assessments on other groups can produce greater estimates of risk. The choice of cohorts in the nickel document is based on the scientific strength of the data available for analysis. Finally, as discussed in the response to comment by Southern California Edison, all nickel compounds are considered carcinogenic and not just nickel subsulfide.

17. Comment: The draft report looks at loss to follow-up in a peculiar way which artificially inflated the risk coefficient by a factor of 1.33. It would be appropriate to assume that cohort members not found to be dead were alive, since it appears that few people migrated out of the country. In this case, it may be scientifically justified to raise the risk coefficient by a factor of up to 1.05; therefore the manner in which the risk assessment treats loss to follow-up inappropriately inflates the risk coefficient by a factor of 1.27 (PG&E, p. 39-40, 42 and 49).

Response: See response to comment 6 of NiPERA.

18. Comment: The draft report's risk assessment inflates the general population's exposure to nickel compounds. Intermittent exposure time periods and changing exposure durations and concentrations (e.g., vacations, residence changes, indoor versus outdoor activities, and changing microenvironmental concentrations and inhalation rates) should be considered. The adjustment factor for equivalent exposure should be 13% (the amount of time an "average" person in California spends outdoors) divided by 22% (the amount of a sinter plant worker's time spent indoors at work. This is 0.59, which rounds to 1.0 (PG&E, p. 40-41, and 42).

Response: See response to comment 4.

19. Comment: If no alternative cohort is used for estimating "lifetime added risk" associated with insoluble nickel in ambient air, the draft report's proposed unit risk should be reduced by an order of magnitude (from $2.4x10^{-4}$ to $2.4x10^{-5}$) to account for several factors (PG&E, p. 48-50).

Response: Lifetime risk estimates calculated by U.S. EPA are presented in the report in Table 7.9. As indicated in our response to comment 16, there is no reason to assume the best value is an unusually high estimate. Furthermore, the most recent evidence reported by IARC and ICNCM, as discussed in comment 1 to the Southern California Edison is that risks from nickel are not isolated to insoluble nickel compounds. Thus, adjustments for these reasons are not required.

20. Comment: California should use an alternative cohort, such as the non-sinter plant workers of the Ontario cohort, as the basis for respiratory cancer risk assessment of

ambient nickel exposure. The unit risk derived from the 495-person sinter plant subcohort from Ontario should only be applied to nickel subsulfide and nickel refinery dust. It would be preferable to speciate insoluble nickel and use a non-sinter worker cohort with relevant exposure profiles to estimate risks from inhalation exposures to nickel compounds that are associated with ambient air particles. Although the sinter workers were exposed to insoluble nickel that contained a relatively high proportion of nickel subsulfide, oil combustion is the largest known source of airborne insoluble nickel emissions in California and is not believed to produce any nickel subsulfide. Studies of non-sinter workers consistently show lower risks than sinter worker studies. Use of non-sinter cohort data would yield a unit risk more reflective of typical California exposures (PG&E, p. 47-48).

Response: The nickel subsulfide exposure to the sinter workers has not been quantified. However, it is known that they were subjected to substantial nickel oxide exposure as well.

21. Comment: The ICNCM report should be considered in the DHS report's risk assessment. (PG&E, p. 48).

Response: This information has been incorporated into the draft report.

22. Comment: The report should consider development of quantitative data regarding the concentrations of different nickel compounds in indoor environments versus ambient air so that the significance of ambient concentrations can be better understood. This may be possible as part of an ongoing study. The accuracy of the assumption that ambient concentrations can be used to estimate human exposure levels should be investigated by examining certain data, in part to assess the contribution of control measures to minimizing human exposure. Outdoor versus indoor exposure estimates would be necessary if a proposed control measure mainly affects outdoor concentrations (PG&E, p. 51-52).

Response: Such a study is beyond the scope of the current analysis and may be beyond the resources of the Department and ARB. As indicated by ARB in their responses to comments there is currently inadequate data to characterize the indoor air concentration of nickel. However, it may well be higher than outdoor levels. Control measures may be considered by ARB at a later stage and at that time more information may be available to answer some of the questions raised in this comment.

23. Comment: The information [that was to be] presented at the EUROMETEAUX conference, September 17-19, 1990, in Brussels, Belgium, should be considered (PG&E, p. 52).

Response: No proceedings exist from this conference. According to Dr. I. Harding-Barlow, who attended the conference, no new information in addition to the information reviewed by DHS was presented.

Comments from the City of Los Angeles Department of Water and Power (LADWP)

1. Comment: **The facts discussed in Part B of the draft report support the notion that different nickel compounds should be treated differently with respect to health impacts of exposure. However, the report opts for a simpler approach in developing numerical guidelines for exposure to nickel. It assumes that all nickel compounds are as potent as the most potent compound, with regard to both non-cancer effect levels and cancer risk. The report establishes a risk factor for all nickel compounds based on nickel carbonyl exposure, contrary to statements in the report that certain nickel compounds, particularly soluble ones, are less carcinogenic than others. When appropriate, separate unit risk factors should be established for each nickel compound (LADWP, p. 2-3).**

Response: Since the development of the draft nickel document, ICNCM and IARC reports have been issued which indicate that all nickel compounds should be considered carcinogenic. Consequently, the new nickel document presents a risk for all nickel compounds. Although the risk assessment document suggests a single study as the best, it is not based on nickel carbonyl. Furthermore other studies indicate both higher and lower risks from nickel exposures.

2. Comment: **For effects with threshold exposure levels, the report relies on studies that used atmospheric nickel levels greater than 50 ng/l, which is the one-hour California standard for particulate matter (PM_{10}) exposure. The report should address the possibility that the observed effects are due to exposure to high particulate levels as well as nickel compounds (LADWP, p. 3).**

Response: The importance of particulate matter concentrations on nickel's carcinogenic potency has not been investigated to our knowledge. Consequently, conclusions regarding the relationship have not been presupposed in the nickel document.

3. Comment: **One of the assumptions in the Ontario study upon which the risk assessment is based is that exposure to nickel compounds occurred only during the work shift. This is likely to be in error because the workers probably lived in the vicinity of the emitting facility, which did not have efficient emission controls. DHS staff should investigate how accounting for this would affect the risk assessment (LADWP, p. 3).**

Response: The DHS risk assessment can only be as accurate as the available scientific data. To our knowledge a study on worker exposure after work hours has not been conducted. However, it is unlikely to add substantially to their high occupational exposure.

4. Comment: **The DHS report should address the reasons why its unit risk estimates (maximum likelihood and upper bound) are approximately three times as large as the unit risk calculated by the EPA, when both agencies used the same data (LADWP, p. 3).**

Response: Differences between the estimates are discussed in the revised report.

Comments from San Diego Gas & Electric (SDG&E)

1. Comment: **In Part B of the draft report, exposure was assumed to be zero when a worker was not at the plant. This is unlikely, as one would expect the ambient level of nickel in the community to have been very high. Workers would therefore have experienced round the clock exposure (SDG&E, p. 1).**

Response: The commentor is likely to be correct. However, the after hour exposures to nickel workers is not known and has not been incorporated into the risk assessment. In any case, as discussed in response to comment #6 of PG&E, the exposure outside the plant would have had negligible contribution to the risk estimate. That is, less than 1%.

2. Comment: **Rather than drawing the conclusion reached in Section 8 of the draft Part B, it would seem more logical to conclude that the current data do not show that nickel oxide is a carcinogen. Certainly there is no reason to ascribe the same potency to nickel oxide and nickel subsulfide. Assuming that all nickel compounds are equally potent carcinogens seems analogous to classifying all carbon compounds as carcinogens because a few exhibit carcinogenic properties (SDG&E, p. 2).**

Response: Following the recent conclusion of the IARC report, DHS staff have concluded that all nickel compounds are carcinogenic to humans. DHS staff believe the risk estimate based on the Ontario cohort is based on the best available scientific evidence and that its value is a reasonable representative for nickel compounds.

Comments from the Engelhard Corporation

1. Comment: **Current emission statistics should be evaluated by the DHS before any further action to establish standards for the electroplating industry (Engelhard Corp., p. 2).**

Response: note that the ARB sets the standards. The comment is more appropriate for ARB to address since DHS does not establish air emission standards.

2. Comment: **The chemicals which are used in electroplating of nickel are water soluble; nickel plating is an aqueous-based technique. Much of the work reported in the draft Part B on aqueous compounds of nickel utilized routes of entry to the body that are not particularly pertinent to environmental exposure to air emissions (Engelhard Corp., p. 1-3).**

Response: See response to comment 1 from the Southern California Edison Company regarding soluble species of nickel.

3. Comment: **The conclusion drawn on page 88 of the draft Part B (in the last paragraph of Section 7.1.2) regarding the dietary rat study of nickel sulfate appears unusual in light of prior discussion in the document (Engelhard Corp., p. 3).**

Response: The conclusion on page 88 (para 5), Section 7.1.2 refers to the dietary studies conducted by Ambrose et al, 1976, not the Schroeder studies. A clarification was added to the report.

4. Comment: If we are to agree with the conclusion of the staff of DHS that "nickel is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness ..." (page 4), then insoluble nickel compounds should be used as the exposure index rather than total nickel. It would follow that any air emission standard would be established for specific insoluble nickel compounds (Engelhard Corp., p. 3).

Response: Although this was the intent of the initial draft document, new information from IARC and ICNCM indicate that all nickel compounds should be considered carcinogenic.

Comment from the Metal Finishing Association of Southern California Inc. (MFASC)

Comment: The extrapolation required to relate known risks from nickel to the measured ambient nickel levels is gigantic. More relevant and specific data should be on hand prior to identification of nickel as a toxic air contaminant (MFASC, p. 1).

Response: The most relevant and scientifically appropriate data available were used in the nickel document analysis.

Comments from the Foss Plating Company Inc. (FPC)

1. Comment: The weight of evidence indicates that soluble nickel does not pose a major threat to the environment and that reasonable thresholds should be considered. There is no evidence that soluble nickel is a carcinogen and it should not be considered a toxic air contaminant (FPC, p. 2). All current evidence should be taken into account in the risk assessment. The types of nickel in the ambient air should be considered. Soluble nickel should be segregated out in the risk assessment (FPC, p. 2).

Response: See response to comment 1 from the Southern California Edison Company regarding soluble species of nickel.

Comments from Inco Limited (Inco)

1. Comment: To improve the draft Part B report, staff should look for epidemiological and toxicological information on nickel-containing substances like those in ambient air (Inco submission ["Recommendations and comments on the Part B report of the technical support document titled Proposed Identification of Nickel as a Toxic Air Contaminant," dated September 5, 1990, page 1).

Response: The nickel document summarizes the data available on nickel compounds. In particular information on the forms of nickel that exist in Calif. ambient air are not available.

2. Comment: The DHS should rethink the definition of "threshold" and consider non-genotoxic mechanisms of carcinogenesis. Literature on nickel involves such mechanisms, which are particularly important when doses are being extrapolated over six or seven

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orders of magnitude. Cancer risk was confined to a few workplaces in the nickel-producing industry, and has not been detected in the nickel-consuming industry. DHS should examine this information in more detail to see where practical thresholds exist. (Inco, p. 1).

Response: The section on genotoxicity and mechanism of action have been rewritten. The proposed mechanism(s) of action include several non-genotoxic mechanisms. However, based on the data available, DHS staff do not consider nickel compounds as carcinogens with thresholds.

3. Comment: **The report should deal explicitly with the uncertainties in the unit risk estimate and in estimated risk, so that the risk manager can associate a probability with any value of the estimate, not just the upper 95% confidence limit. The uncertainty in the population exposure estimate should be incorporated into the risk assessment to provide an associated probability for the estimated cancer incidence (Inco, p. 2).**

Response: Although this may be useful, such a standardized procedure has not been developed and is beyond the scope of the report. Risk managers often discuss the risk assessment reports with DHS staff to gain a better understanding of the information presented.

4. Comment: **Part B should make use of more recent information. A number of specific papers (mentioned in the commentor's submittal) should be of use in this regard. In addition, the DHS should revisit the literature on nickel and its compounds. Many of the studies described in Part B are less than perfect; the DHS should take advantage of ongoing National Toxicology Program (NTP) bioassays of nickel sulfate, nickel subsulfide, and green nickel oxide. The DHS should obtain access to other information before it completes its final Part B report (Inco, p. 2-3).**

Response: We have been in contact with the investigators conducting the NTP studies. The study proper (i.e. exposures and necropsies) have been completed, however, the pathological results will not be available before the end of 1991. The investigators were unable to provide us with preliminary information. New information from the IARC and ICNCM reports has been incorporated.

5. Comment: **The various welders' symptoms listed on page 1, paragraph 2, of the draft Part B report have not been "attributed" to nickel exposure by authors other than DHS. In any event, the metals in welding fumes are almost always completely oxidized (Inco, p. 4).**

Response: Original reference (Davies 1986) states: "Three cases of occupational asthma are described, probably induced by exposure to nickel compounds in the manufacture of nickel catalyst." and "These cases of occupational asthma induced by exposure to nickel salts have been identified on clinical observation only but with strong circumstantial evidence to support the diagnosis."

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6. Comment: Regarding p. 3, par. 2, only 266 of the 1855 were classified as refinery workers (Inco, p. 4).

Response: The word "refinery" has been dropped from the sentence.

7. Comment: Regarding p. 3, par. 2, the average concentrations for the Ontario cohort ranged from about 30 to about 250 mg Ni/m3 (Inco, p. 4).

Response: Individual measurements ranged up to about 400 mg/m3. However the averages were lower. The statement has been revised to read:

The Ontario cohort involved 495 sinter plant workers. Average levels of exposure were in the early 1960s were approximately around 50-250 mg/m3.

8. Comment: The DHS should be multiplying its unit risk estimate by a lifetime exposure concentration, rather than the range of concentrations given on p. 4, par. 4 (Inco, p. 4).

Response: The range of concentrations represent the test values available for exposure. Concentrations likely to be present in the future cannot be estimated at this time.

9. Comment: Page 1, par. 5 seems to differ from p. 117, par. 4. Page 1 implies that the risk estimate will be based on total nickel, while p. 117 says it will be based on insoluble nickel (Inco, p. 4).

Response: Based on the new data available from IARC and ICNCM, the risk assessment will be based on all nickel compounds.

10. Comment: The draft Part B does not completely report on IARC's classification of nickel and nickel compounds (Inco, p. 4-5).

Response: The new information from IARC has been incorporated into the document.

11. Comment: Item II A 2 of the Risk Assessment Highlights (p. 5) should be rephrased so as to not imply that more than one study's data were consistent with a linear relationship. Also, "linear relationship" should not be taken to mean linear extrapolation to ambient levels of nickel (Inco, p. 5).

Response: The wording was changed to: Human data are consistent with a linear dose response relationship.

12. Comment: Regarding item II E of the Risk Assessment Highlights, DHS should explain what kind of information it would accept as evidence of a threshold. Epidemiology reveals practical thresholds for carcinogenicity of nickel greatly in excess of ambient concentrations (Inco, p. 5).

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Response: A threshold for a compound could be determined based on a combination of data regarding mechanism of action, ambient bioassays and epidemiology. A "practical" threshold as referred to by the comment would not be considered a threshold primarily due to limitations in the study with regards to power and intra-individual sensitivity. The risk assessment indicates that the risk in ambient air is very small compared to that of the occupationally exposed.

13. Comment: Are the levels reported in item III A 1 of the Risk Assessment Highlights the range or the mean of observed concentrations (Inco, p. 5)?

Response: The range reflects the levels reported in Part A of the nickel document.

14. Comment: The first sentence of item IV C of the Risk Assessment Highlights (p. 6) is not clear. In any event, the DHS has no basis for comparing the forms of nickel involved in occupational and ambient exposures because the ARB has not identified the forms in ambient air (Inco, p. 5).

Response: The sentence has been deleted.

15. Comment: It is not appropriate to use ambient levels of nickel to estimate a human lung cancer risk; such a calculation should be based on a dose (Inco, p. 5).

Response: The risk estimate is based on dose. The dose is calculated by multiplying ambient levels times 70 years of exposure. Thus, the risks are reported in terms of lifetime exposure.

16. Comment: Regarding p. 7, par. 3, an absorption "rate" without a time dimension is meaningless (Inco, p. 5).

Response: The term "rate" will be deleted.

17. Comment: Regarding p. 8, line 8, the report should distinguish between insolubility in water and insolubility in biological fluids because the former is not always a good predictor of the latter (Inco, p. 6).

Response: The terms insoluble and soluble refer to water solubility.

18. Comment: Regarding p. 8, line 6, the cited study did not attempt to speciate the nickel present in the nasal mucosa. How can the DHS rule out the possibility that the nickel which was removed from the mucosa was originally present as soluble nickel (Inco, p. 6)?

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Response: This paragraph does not state that the investigators attempted to speciate the nickel present. The paragraph will be rewritten to read:

Torjussen and Anderson (1979) reported that nickel accumulation in the nasal mucosa of nickel workers was highest with inhalation of particulate subsulfide and oxide forms as compared to inhalation of nickel chloride/sulfate aerosols. This finding would be expected based on the relative water solubility of the respective compounds. Nasal mucosal nickel underwent very slow clearance having a half-life of about 3.5 years.

19. Comment: Regarding p. 8, par. 4, the DHS should note that the cancers associated with nickel exposure in certain refining operations were in the sinonasal cavity and the bronchial region, i.e., where coarser particles deposited. Deposition in rat lung does not seem relevant to the Department's concerns. The DHS should ask the ARB to provide information on the size distribution of nickel-containing particulate in ambient air to see where it is likely to deposit in the respiratory tract (Inco, p. 6).

Response: The importance of size distribution and nickel respiratory carcinogenicity has not been ascertained. For the purpose of this risk assessment it is assumed that any deposition in the respiratory tract has equivalent carcinogenic potential. The information on deposition of nickel particles in rats is presented since information cannot be ascertained from human studies. Both nasal and lung cancers are caused by exposure to nickel. Since the number of nasal cancers tend to be small compared to the excess numbers of lung cancers in most of the cohort studies, nasal cancers were not included in unit risk estimation. With regard to lung cancers, particle size would influence the location of deposition. However we have not seen any evidence to suggest that the location of lung cancers among nickel exposed workers differs from the location of lung cancers found in the general population. Most lung cancer are "bronchogenic". Even if there were such differences, there is no evidence to suggest that nickel compounds would be more or less potent according to the location of particle deposition in the lungs.

20. Comment: Regarding the last paragraph on page 8, workers (Menzel *et al.*, 1986) not cited in the draft report investigated the clearance of nickel chloride after inhalation (Inco, p. 6).

Response: The suggested reference and a more recent publication by the same investigators (Menzel *et al.*, 1987) have been reviewed by DHS and relevant information has been incorporated into the document where appropriate.

21. Comment: Regarding the mention of English *et al.* (1981) on p. 12: these workers tested a substance that is unlike most of the nickel oxides reported in the literature or that might have existed in the nickel refineries. Therefore this study is of little relevance for risk assessment (Inco, p. 6).

Response: A statement will be added to the text (page 16) and relevant table regarding the conditions under which "nickel oxide" was prepared for this study. Whenever this study is discussed in the subsequent text nickel oxide will be placed in quotations and the reader will be referred back to page 16. It is important to note that one can not dismiss this study simply because of the method utilized for generating nickel oxide since the conditions under which environmental nickel oxide is generated are not known.

000513

22. Comment: **Shouldn't some data for metallic forms of nickel be given in Table 3.1 (Inco, p. 6-7)?**

Response: Published data on metallic forms of nickel were not available when the reported was written. The commentator has suggested an unpublished manuscript (Muhle *et al.*), which he has provided. Generally DHS does not incorporate unpublished findings into the health assessment document unless the information is relatively new and could have impact on the conclusions of the document. The unpublished study was not incorporated into the document since the data presented would not alter the findings of the document or the risk assessments.

23. Comment: **The results of Benson *et al.* (1986) (p. 13) are not credible. No other work has suggested that Ni_3S_2 would be cleared more slowly than NiO (Inco, p. 7).**

Response: No comparison between NiO and Ni3S2 clearance was made in the text. The Inhalation study by Kadoma *et al.*, (unpublished) report supplied by commentor suggests a similar half-time.

24. Comment: **The unusual finding of English *et al.* (1981) mentioned on p. 16, par. 3, may have been due to the fact that different substances were tested under the rubric "nickel oxide." The DHS has made a mistake by assuming that nickel oxide (NiO) is a unique compound. The "NiO" produced by English *et al.* was least likely to resemble the kinds of nickel oxide found in nickel refineries. It contained some nickel hydroxide. This material should never be referred to as nickel oxide. "Nickel oxide" describes a family of substances in which subtle differences in composition and structure can make large differences in physio-chemical and biological properties (Inco, p. 7-8).**

Response: See response to comment 21. The importance of the temperature utilized in preparing nickel oxide(s) is noted in the revised Section 3 and 6.

25. Comment: **There are published follow-ups to the Kodama *et al.* (1985) paper mentioned on p. 16, par. 3. These papers, by I Tanaka and colleagues, are not cited in the draft Part B (Inco, p. 8).**

Response: The references suggested have been reviewed by DHS staff and additional relevant information provided by these references will be incorporated into the document where appropriate in Section 3.1.1.2.

26. Comment: **Regarding p. 16, par. 3, Y Kodama and co-workers have reported to NiPERA on further related work [a copy of their report is Appendix C to this commentor's submittal] (Inco, p. 8).**

Response: Since the current draft document does not contain information on lung kinetics and nickel subsulfide following inhalation exposure the report of Kodama and co-workers will be reviewed and relevant information will be added to the document. However, since

we were unable to locate a published version of the submitted report the citation in the document will be accompanied with the statement "...in a recent unpublished report ...".

27. Comment: Regarding p. 16, par. 4, work of H Muhle and co-workers is relevant, as is work by Benson *et al.* and JK Dunnick and co-workers describing lung burdens of nickel subsulfide after inhalation exposures. From this information, the DHS could probably estimate the clearance half-time by fitting a simple model (Inco, p. 8-9).

Response: Generally DHS does not incorporate unpublished findings into the health assessment document unless the information is likely to have some impact on the conclusions. The unpublished work of Muhle and co-workers (Appendix A of commentor's submission) while relevant would not add to the information already contained in the document nor would it affect the risk assessment. Benson *et al.* (1987) and Dunnick *et al.*(1988) reported lung nickel burdens following inhalation exposure. Neither study supplies adequate data to quantify clearance rates. Any attempt to estimate half-time would only produce a "guestimate" and would not alter the conclusions of the document or affect the risk assessment.

28. Comment: Regarding p. 16, par. 5, more complete data are available. These include data from reports by JK Dunnick and co-workers, MA Mendinsky and co-workers, and Benson *et al.* (1988) (Inco, p. 9).

Response: Relevant information regarding the clearance of nickel sulfate following inhalation exposure is currently lacking in the draft. Data supplied by Dunnick and co-workers and Benson *et al.*(1988) is inadequate to quantify clearance rates. Information from Medinsky and co-workers (1987) will be incorporated into the document.

29. Comment: Regarding p. 16, par. 6, a 1980 paper by AP Wehner and co-workers should be considered. The authors preferred the results of this study to the earlier study (Wehner *et al.* 1979) mentioned by the DHS (Inco, p. 9).

Response: The suggested reference will be reviewed and relevant information will be incorporated into the document in Section 3.1.1.2.

30. Comment: Regarding p. 17, par. 6, it would be useful, in light of the first sentence of Section 3.1.1.2, to know what form of nickel was used in the Kirchgessner *et al.* (1985) study (Inco, p. 9).

Response: Note: Section 3.1.1.2. addresses absorption following inhalation exposure. Section 3.1.2. on page 17 deals with absorption following oral administration.

The reference (Kirchgessner *et al.*, 1985) did not state what form of nickel was utilized. However, Kirchgessner *et al.*1984 (Z. Tierphysiol., Tierernahrg. u. Futtermittelkde 52 (in press) was cited as the reference source for the diet composition we have not been able to locate this reference in the published literature.

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31. Comment: A 1989 paper by FW Sunderman and colleagues should be reviewed for the section (3.1.2) on gastrointestinal absorption (Inco, p. 10).

Response: Information from Sunderman et al, 1989 will be added to section 3.1.2.

32. Comment: Regarding p. 18, par. 5, it is important to note there is a significant difference in skin permeation rate between two water soluble nickel compounds. This again raises the question of whether it is reasonable to attribute comparable biological behaviors to different forms of nickel simply because they have similar solubilities in water (Inco, p. 10).

Response: The draft report does not attribute comparable biological behaviors to different forms of nickel simply because they have similar water solubility. Wherever available we have reported the biological behavior of individual forms of nickel irrespective of their water solubility. The conclusions reached in this report depend most heavily on the biological behavior information not the solubility of the various forms of nickel.

33. Comment: Regarding p. 19, par. 5, nickel carbonyl is a poor model for the distribution of nickel inhaled as inorganic particulate: nickel carbonyl can pass through biological membranes without first being metabolized (Inco, p. 10).

Response: Nickel carbonyl is not presented as a model for the distribution of inhaled inorganic nickel particulate. Page 8 states that nickel carbonyl is a somewhat unique form of nickel in that it is lipid soluble. This statement will be restated in Section 3.6 for emphasis.

34. Comment: Regarding p. [20-]21, par. 1, The oxidic nickel tested by English *et al.* (1981) should not be referred to as nickel oxide (Inco, p. 10).

Response: See response to comment 21.

35. Comment: Why is nickel carbonyl classed with nickel chloride and nickel sulfate on p. 24, par. 6? It should be treated separately, if it is to be treated in the document at all (Inco, p. 10).

Response: The paragraph has been rewritten separating water soluble and lipid soluble nickel compounds.

36. Comment: Regarding p. 24, par. 7, nickel subsulfide and nickel oxide should not be grouped together because they have different lung removal half-times (Inco, p. 10).

Response: This paragraph has been rewritten with the additional information regarding lung kinetics of nickel subsulfide following inhalation exposure is incorporated into section 3.1.1.2.

37. Comment: Regarding p. 27, par. 7, could the higher "absorption" following instillation be due in part due to loss from coughing or mucociliary clearance (Inco, p. 10)?

Response: Yes. A statement to this effect will be incorporated into paragraph 7.

38. Comment: The reference to occupational asthma on p. 31, par. 2, is probably incorrect (Inco, p. 10).

Response: See response to comment 5.

39. Comment: Regarding p. 31, par. 3, a 1988 report by Sunderman *et al.*, on human ingestion of nickel-contaminated drinking water, should be considered (Inco, p. 10).

Response: The paragraph already states clearly that nickel states exhibit low acute toxicity. The draft report was not intended to be a comprehensive literature review document.

40. Comment: The discussion on p. 32, Section 5.1.1 of the paper by Akesson and Skerfving (1985) is inaccurate. The authors noted that the nickel aerosol "may" have been the cause of the symptoms. The draft document states that it "was thought to be" the cause (Inco, p. 10-11).

Response: The sentence: "Nickel aerosol was thought to be the cause of the reactions." will be changed to "The authors speculated that nickel aerosols were the cause of the reactions."

41. Comment: Why does Section 5.1.2.2 not report oral lethality? A paper is available (Inco, p. 11).

Response: See response to Comment 14 from Western States Petroleum Association.

42. Comment: Regarding p. 39, par. 3, the results of Spiegelberg *et al.* cannot be accepted without reservation because these workers are among a small group of researchers who have used a unusual, questionable, method of generating nickel oxide aerosol. In general, workers using this method have found adverse effects at much lower aerosol concentrations than have others who used more traditional methods of aerosol generation. At Spiegelberg's institute, appropriate control experiments were not done (Inco, p. 11-12).

Response: The method of nickel oxide generation will be noted in Section 5.2.1.1. It is important to note that one can not dismiss a study simply because of the method utilized for generating nickel oxide since the conditions under which environmental nickel oxide is generated are not known.

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43. Comment: Regarding p. 39, par. 5, this commentator can only assume that the effects attributed to nickel oxide at low doses were from studies using the questionable method of generating nickel oxide aerosol (low-temperature decomposition of nickel acetate) mentioned in the comment above. Here it would be interesting to note that JK Dunnick and co-workers have rated nickel oxide as less toxic than nickel subsulfide or nickel sulfate after certain inhalation exposures, using a better method of generating nickel oxide (Inco, p. 12).

Response: See response above. Also it is worth noting that Spiegelberg *et al.*utilized lower concentrations of nickel oxide than Dunnick, see Section 5.2.2.1 of draft report. All dose levels tested by Dunnick *et al.* exhibited effects, i.e. a NOEL was not determined.

44. Comment: In Tables 5.2 and 5.3, the entries for Spiegelberg *et al.* (1984) refer to an oxide produced by low-temperature decomposition of atomized nickel acetate (Inco, p. 12).

Response: See response to comment 42.

45. Comment: In Table 5.2, in order to provide perspective for the findings of Smialowicz *et al.*, it should be noted that Benson *et al.* were unable to find an effect of inhaled nickel sulfate on NK cell-mediated toxicity (Inco, p. 12).

Response: Benson *et al.*investigated the effects of nickel sulfate whereas Smialowicz *et al.* examined the effects of nickel chloride. The commentators suggestion is therefore inappropriate since the investigators evaluated two different forms of nickel. Note: while injection studies were summarized in Table 5.2 they were not included in determining LOEL or NOEL levels.

46. Comment: Why does the four-month exposure of Spiegelberg *et al.* (1984) that appears in Table 5.3 also appear in Table 5.2 (Inco, p. 12)?

Response: The comment is incorrect. Table 5.2 refers to shorter exposures at higher concentrations that appeared in the same publication.

47. Comment: Several of the results noted on p. 46 refer to an oxide produced by low-temperature decomposition of atomized nickel acetate (Inco, p. 12).

Response: The method of oxide production will be noted when available. It is important to note that one can not dismiss a study simply because of the method utilized for generating nickel oxide since the conditions under which environmental nickel oxide is generated are not known.

48. Comment: The results of the Takenaka *et al.* (1985) study listed in Table 5.4 refer to an oxide produced by low-temperature decomposition of atomized nickel acetate (Inco, p. 12).

Response: See response to comment 47.

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49. Comment: What was the mortality of the control group in the Sunderman *et al.* (1959) study listed in Table 5.4 (Inco, p. 12)?

Response: This information has been added to Table 5.4.

50. Comment: On p. 12, par. 3, the draft report gives too much credence to the relationship between nickel exposure and occupational asthma or chronic respiratory tract infections. The DHS should review a 1990 paper by KH Kilburn *et al.* and note the findings of Akesson and Skerfving (1985). The draft Part B inaccurately reports the findings of Davies (1986) here. In par. 4, the findings of Bencko *et al.* (1986) are reported in less absolute terms than used in the first sentence of par. 3 (Inco, p. 12-13).

Response: Relevant information from Kilburn *et al.*(1990) and Akesson and Skerfving (1985) will be incorporated into the document. The draft accurately reports the findings of Davies (1986) - see response to comment 5. Comment regarding Bencko *et al.* (1986) - the first sentence of paragraph 3 page 51 will be changed to "*Asthma and increased risk for chronic respiratory tract infections may also result from nickel exposure*".

51. Comment: In Section 5.4, the DHS should refer to the specific forms of nickel associated with a given health effect (Inco, p. 13).

Response: Section 5.4 is a summary of effects associated with nickel compounds in general. Specific information can be obtained from previous sections in the document.

52. Comment: Regarding p. 53, par. 3 and 4, what are the literature references for the effects cited here (Inco, p. 13)?

Response: The citations for the literature references will be added to the text in Section 5.5.1.

53. Comment: Why is the caveat regarding injection exposure given on p. 58, par. 4, not repeated in the other discussions of health effects produced by this route of administration (Inco, p. 13)?

Response: The caveat is mentioned in those cases where important conclusions could be drawn from the data that are presented. In this case the conclusion that could have been drawn was that of teratogenicity. The caveat was added because dose delivery is very important for estimation of this endpoint.

54. Comment: Par. 5 on p. 58 sounds like instructions to the consultant. Why is it in the document? If it is meant to be here, similar caveats should be inserted for every health effect (Inco, p. 13).

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Response: Current guidelines for evaluating developmental toxicity are not available. The information is provided to indicate the reasoning used in developing conclusions for this endpoint.

55. Comment: Section 6 (p. 70-71) contains too few citations to allow critical review by a reader (Inco, p. 13).

Response: This section has been revised and expanded as suggested.

56. Comment: Regarding Section 6.1, DHS should consider non-genotoxic mechanisms by which certain forms of nickel might cause cancer (Inco, p. 14).

Response: Non-genotoxic mechanisms are discussed in the revised Genotoxicity Section as suggested.

57. Comment: Regarding p. 72, par. 1, the list of nickel compounds alleged to have produced genotoxic effects must be examined closely for accuracy. The great variability in what is reported as "nickel oxide" (see above) should be considered. Few if any researchers are likely to have actually studied "nickelic oxide" or an oxide with an appreciable amount of trivalent nickel; none have studied "nickel carbonate." Simple-minded concepts of valence cannot be applied to nickel subsulfide. Whatever "valence" one would use to describe the nickel in nickel subsulfide must be the same for every nickel atom in the structure because the atoms are crystallographically equivalent and have the same local coordination polyhedra (Inco, p. 14).

Response: Section 6 has been rewritten.

58. Comment: Regarding p. 72, par. 2, the work at the University of Connecticut dealt with a wide variety of nickel oxides, and included determinations of solubility in biological fluids and the ability to produce erythropoiesis after intrarenal injection. This commentator believes that Sunderman would now agree that there is no unique nickel oxide. (Inco, p. 14).

Response: The paragraph simply summarizes work in the field that has been completed or is on-going. The current opinion of one scientist of another scientist's opinion is not pertinent.

59. Comment: The very poor survival of the controls should be noted along with the entries on p. 74-75 (Table 7.1) for the studies by Sunderman and colleagues (Inco, p. 14).

Response: The survival rates for all groups, including controls, are already stated in Table 7.1.

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60. Comment: Regarding p. 76, the Department should remember that the "nickel oxide" used in the Takenaka studies was produced by decomposing nickel acetate at relatively low temperatures and that the animals were exposed continuously (Inco, p. 16).

Response: The exposure regimen is described in the Table. See response to comment 47.

61. Comment: Regarding p. 78, why is an instillation study included in a table of inhalation exposures (Inco, p. 16)?

Response: Pulmonary instillation studies are generally included with inhalation studies.

62. Comment: Although the draft report suggests that hamsters may be non-responsive to nickel, in 1983, Sunderman concluded that, at least for nickel subsulfide, hamsters' lungs do respond (Inco, p. 16).

Response: The sentence referred to (page 79 paragraph 6 line 5) will be changed to "*The lungs of hamsters showed scarcely any chronic effects due to exposure, suggesting that this species may be non-responsive to this form of nickel*".

63. Comment: What is the Department's position with respect to non-positive results in hamsters by the inhalation and instillation routes? Although some risk assessors say that live hamsters are not good models for respiratory carcinogenesis, the same assessors are willing to accept positive results using various hamster cells *in vitro* (Inco, p. 16).

Response: The Department does not have a general position, but simply evaluates each study individually.

64. Comment: Regarding p. 79, the DHS should review a 1969 Master's thesis by MK Kim (Inco, p. 16).

Response: Generally, academic theses are not included in the DHS health effects document unless peer-review reports are published from the document or the thesis has information pertinent to the conclusions of the document or effect the risk assessment. Based on the information supplied by the commentor the thesis does not represent an adequately designed cancer bioassay and would not alter any of the conclusions of the report.

65. Comment: If any attention is to be paid to intratracheal instillation studies, two additional reports should be considered. These are a 1988 paper by H Muhle *et al.* and a 1987 paper by F Pott *et al.* (Inco, p. 16).

Response: The references will be reviewed and additional relevant information will be incorporated into the document where appropriate.

66. Comment: **If the studies of nickel carbonyl discussed in Section 7.1.1.2 had been completed today, they would be dismissed as inconclusive because of the very poor survival of exposed and control animals and the low incidence of tumors (Inco, p. 16-17).**

Response: Unfortunately cancer bioassays are very costly and difficult to produce. DHS staff must review the available data for the evaluation of nickel compounds.

67. Comment: **Regarding p. 81, par. 1, why does the draft report say that the carcinogenicity of nickel oxide has not been well studied in animals? The 102 animals cited there were exposed to such high concentrations of black nickel that massive pneumoconiosis developed (Inco, p. 17).**

Response: This is explained in the last paragraph of section 7.1.3 on page 82 of the 1990 draft report.

68. Comment: **Regarding p. 81, par. 4, while the form of nickel in the fly ash was not determined, it is a simple matter to calculate its concentration in the air (Inco, p. 17).**

Response: As indicated in the draft document the concentration and forms of nickel were not specified in the study.

69. Comment: **The "nickel oxide" used in the experiments discussed on p. 81, par. 5 was produced by decomposing nickel acetate at relatively low temperature and the animals were exposed continuously (Inco, p. 17).**

Response: The commentator is referring to studies by Tanaka and co-workers, see response to comment 60.

70. Comment: **Regarding p. 82, par. 3, the DHS should try to obtain information on the NTP bioassay of green nickel oxide. Even preliminary information should be very useful (Inco, p. 17).**

Response: See response to comment 4.

71. Comment: **Regarding p. 82, par. 3, the DHS should review the work of Y Kodama and colleagues presented in a 1989 report to NiPERA (Inco, p. 17).**

Response: Based on information provided by the commentator this study would not qualify as a cancer bioassay (the exposure period (6 mo) and observation period (1 yr) were insufficient to assess carcinogenic potential).

72. Comment: **Regarding p. 82, par. 3, I Tanaka and colleagues reported in 1988 on rats exposed to green nickel oxide (Inco, p. 17).**

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Response: The suggested study would not add to the document due to the limitation of exposure length and number of animals. Therefore it has not been incorporated into the document.

73. Comment: Regarding p. 82, if instillation is to be considered, a 1987 report by Pott *et al.* and a 1974 report by RL Farrel and GW Davis, should be reviewed (Inco, p. 18).

Response: See response to comment 65.

74. Comment: Regarding p. 82, par. 4, the Department should try to obtain at least preliminary results from the NTP inhalation bioassay of nickel subsulfide (Inco, p. 18).

Response: See response to comment 4.

75. Comment: Regarding p. 85, par. 1, the 1969 Master's thesis by Kim and the 1989 report to NiPERA by Kodama *et al.* are relevant (Inco, p. 18).

Response: See responses to comment 64 and comment 71.

76. Comment: Regarding p. 85, par. 1, is there to be no discussion of Fisher *et al.* (1986) after it was raised on p. 82 (Inco, p. 18)?

Response: A brief discussion has been included.

77. Comment: Regarding p. 85, par. 1, if instillation is to be considered, several additional papers (by Muhle *et al.*, Pott *et al.*, Kasprazak *et al.* and Sunderman) should be considered (Inco, p. 18-19).

Response: See response to comment 65. Note studies by Muhle *et al.*, Kasprazak *et al.*, and Sunderman were not adequately designed to assess carcinogenic potential.

78. Comment: Regarding p. 85, par. 1, the DHS should try to obtain information on the NTP bioassay of nickel sulfate hexahydrate. Even preliminary information should be very useful (Inco, p. 19).

Response: See response to comment 4.

79. Comment: Regarding Section 7.1.3, the DHS should not put much weight on results obtained by injection, which is an unrealistic route of exposure that produces tumors not relevant to respiratory cancer (Inco, p. 19).

Response: Little "weight" is placed on injection studies. However they are useful in helping to understand the carcinogenic nature of nickel compounds; IARC has used them.

The studies are not used for risk assessment, but are useful for comparing the carcinogenic activities of various forms of nickel.

80. Comment: The iron-nickel sulfur material mentioned on the last line of p. 88 was prepared by this commentator for Sunderman. It is not a single phase of composition Ni_4FeS_4; rather, it consists of at least two phases (Inco, p. 19).

Response: The last line of page 88 will be changed to "*...nickel ferrosulfide (referred to as Ni_4FeS_4 by the authors) induced....*"

81. Comment: Regarding p. 90, par. 1, not enough of the nickel oxide used in these tests was left to allow it to be properly characterized. Sunderman and co-workers have reported different results with other high-temperature nickel oxides (Inco, p. 19-20).

Response: The varying biological responses produced by different forms of nickel oxide have been noted in the revised Section 6.

82. Comment: Regarding p. 90, par. 5, Skaug noted in 1988 that he was not able to reproduce the high incidence of pleural tumors reported in Skaug *et al.* (1984) (Inco, p. 21-22).

Response: Reference to Skaug et al. (1984) has been deleted.

83. Comment: Regarding p. 90, par. 6, the DHS should remember that the NTP completed its chronic exposure of rats and mice to nickel sulfate hexahydrate this past spring. The [unpublished] reports of Kim and Kodama *et al.* (see above) should also be considered (Inco, p. 21).

Response: Although the animal exposures have ended, the study is by no means completed. The NTP protocol requires extensive reading of pathology slides and peer-review before findings are made available. Also see response to comment 64 and 71.

84. Comment: The draft report notes that "only" nickel sulfate has been adequately evaluated for oral carcinogenicity. Nickel sulfate is water soluble. Does the DHS think that an insoluble form of nickel is more likely to be carcinogenic by ingestion (Inco, p. 21)?

Response: DHS staff believe there isn't enough information to make a conclusion about ingestion of nickel compounds. Nickel sulfate has only been adequately studied in rats. Studies in other species would be necessary before a conclusion could be made about the compounds.

85. Comment: Regarding p. 91, par. 1, it is premature to draw conclusions about the relative carcinogenicity of nickel subsulfide and "nickel oxide" (Inco, p. 21).

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Response: The evaluation was made to see if data were available to treat them differently with regard to carcinogenic potency. The documents concluded the data were not available.

86. Comment: Regarding p. 91, par. 2, rather than regulating insoluble nickel compounds as a group, the ARB should try to identify the forms of nickel in ambient air and the DHS should see if they resemble any of the substances for which experimental data is available (Inco, p. 21).

Response: The suggestion is no longer pertinent since all nickel compounds are now considered carcinogenic.

87. Comment: Regarding Section 7.1.5.1, the DHS should use the best up-to-date risk assessment methodology, rather than adhering to the status quo of the early 1980s. What is the reasoning behind the assumption that weight per surface area per day is an equivalent dose between species? The only reasonable surface area to be used for this extrapolation is that of the respiratory tract (Inco, p. 21).

Response: See response to comment 5 from Falconbridge Limited.

88. Comment: Regarding p. 94, the variable i=I/W is confusing and completely unnecessary (Inco, p. 23).

Response: The calculations have been simplified and are more thoroughly explained in the revised document as requested by the commentor.

89. Comment: Regarding p. 94, the line dividing the numerators and denominators in the last two equations should not extend under and beyond the equals signs (Inco, p. 23).

Response: This will be corrected.

90. Comment: Regarding Section 7.1.5.2, the DHS can avoid one source of error by not relying on animal data value for its risk assessment. It can minimize the possibility of a second kind of error by avoiding the assumption that different forms of nickel have similar carcinogenic properties (Inco, p. 23 and Appendix E).

Response: DHS staff has not relied on animal data in choosing the best value for its risk assessment. The document reports risk estimates for the animal data to provide information on the range of carcinogenic responses reported. Cancer potency values cannot be determined for various nickel species at present See response to comment 32.

91. Comment: Regarding p. 96, par. 1, the DHS should review the ICNCM report carefully (Inco, p. 23).

Response: The report has been reviewed and incorporated into the nickel document.

92. Comment: Regarding p. 96, par. 2, the vital status of this cohort is updated in the ICNCM report and the DHS should note the estimated breakdown of nickel by species in Table 10 of that report (Inco, p. 24).

Response: The revised document incorporates data from the ICNCM report concerning this cohort.

93. Comment: Regarding p. 96, par. 3, the Copper Cliff sinter plant (CCSP) cohort should be referred to as something other than the "Ontario cohort." "Ontario cohort" should be reserved for the cohort of 54,509 men who worked in this commentor's Ontario Division that has been the subject of an epidemiological study. The CCSP cohort is part of the "Ontario cohort." There is some misunderstanding of the service requirement for entry into the Chovil cohort: it consisted of men who had five or more years of total service, including some sinter plant service. Roberts *et al.* included men with any recorded CCSP service (Inco, p. 24).

Response: The revised document makes clear that the sinter plant workers were a subcohort of a larger group of refinery workers.

94. Comment: Regarding p. 96, par. 4, Roberts *et al.* conducted follow-up to the end of 1984 and observed more lung cancer deaths and a lower SMR than did Chovil *et al.* (Inco, p. 24).

Response: The Roberts *et al.*update was not available when the document was first drafted. It has been discussed in the revised document.

95. Comment: Regarding p. 96, par. 5, the EPA has expressed concern that Chovil *et al.* underestimated the lung cancer risks by assuming untraced workers were alive, but this commentator could not find where EPA voiced the concern stated here (Inco, p. 24).

Response: The reader will be referred to Section 8.1.2.1.4 of the EPA document.

96. Comment: Regarding p. 96, par. 5, Roberts *et al.* estimate that their ascertainment rate was 95%, so the 25% that Chovil *et al.* were unable to trace is no longer a problem (Inco, p. 24).

Response: Changes have been made in the document using the new Roberts data.

97. Comment: Regarding p. 98, par. 2, it is unreasonable to state that Chovil's mortality data constrain one to assume anything about exposures. The draft report claims to be trying to evaluate a dose-response relationship, yet cannot do that if it estimates exposures based on mortality data. There is no justification for a step function change in nickel concentrations between 1951 and 1952 (Inco, p. 24-25).

Response: see fig.1. Examination of the exposure data presented in Fig 1 page 97 shows that it is reasonable to assume that exposure levels before 1952 were twice those thereafter. The data in Chovil *et al.*are presented in a manner that incorporates this assumption. The wording in the revised document has been changed to:

The cancer mortality data presented by Chovil et al.(Chovil et al., 1981) involve the assumption that exposures before 1952 were twice the average of exposures after 1952. Based on the data in Figure 1, we have assumed and average level of 150 mg/m3 before 1952, and 75 mg/m3 from 1952 to 1962.

98. Comment: Regarding p. 98, par. 3, Warner (1984) was trying to make the case that the use of nickel concentrations measured at the roof monitors would probably give conservative estimates of the environment at the working level. Warner was not advocating the use of still higher concentrations. The measurement of dust taken at floor level is in reasonable agreement with the monitor data (Inco, p. 25).

Response: DHS believes that the paragraph agrees with this comment.

99. Comment: Regarding p. 98, par. 3, the DHS should be concerned about dust that is coarser than respirable dust because the lung cancers in the sinter plant workers were in the bronchial region, not the pulmonary region (Inco, p. 25).

Response: We have not seen any evidence to suggest that the lung cancers occurring in the sinter plant cohort were any different in location from lung cancers occurring in the general population.

100. Comment: Regarding Section 7.2.1.3, the vital status of the Clydach cohort has been updated in the ICNCM report (Inco, p. 25).

Response: The ICNCM report information is discussed in the revised document.

101. Comment: Regarding p. 99, par. 5, exposures were also estimated for the ICNCM report (Inco, p. 25).

Response: The ICNCM report gives estimates but no further measurements in a pertinent period.

102. Comment: Regarding p. 99, par. 6, this commentator has included with its submittal some exposure estimates for the Clydach plant based on measured data (Inco, p. 25 and Appendix F).

Response: We appreciate the further data and estimates. However as the reviewer notes, these estimates are not relevant to the lung cancer risks demonstrated in this study.

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103. Comment: Regarding p. 100, par. 2, a better, comprehensive set of exposure estimates for the Kristiansand refinery is included in the ICNCM report (Inco, p. 25).

Response: Reference is made to the ICNCM estimates in the revised document.

104. Comment: Regarding p. 100, par. 5, the nickel concentrations in the air of the West Virginia plant were closer to ambient levels than were those in other plants. Also, the mix of nickel species in the West Virginia plant was probably closer to the mix in ambient air than was the mix in the other plants (Inco, p. 26-26).

Response: That may be the case, however the West Virginia cohort study was rejected from the quantitative risk estimate due the imprecision of its relative risk estimate as described on page 100 of the 1990 draft report.

105. Comment: This commentator does not recognize any "problems in precision of low exposure estimates." Rather, the important parameter is their accuracy (not their precision). The estimates for the West Virginia plant are more likely to be accurate than are the estimates for the other plants. The estimates for the West Virginia plant are based at least on some measured data and on chemical speciation whereas the estimates for most of the other plants are simply educated guesses (Inco, p. 26).

Response: As described on page 100, the imprecision refers to the size of the confidence limits around the SMRs.

106. Comment: Regarding p. 102, par. 2, there are now estimates of exposure for the Norwegian cohort. However, mixed exposures were the norm, so interpretation of the data will not be easy (Inco, p. 26).

Response: While there are estimates, we know of no measurements for a pertinent period. The wording has been changed to:

> However, there were no nickel exposure measurements available for this cohort.

107. Comment: The ICNCM report might provide enough data to satisfy the desire for precision voiced on p. 102, par. 3 (Inco, p. 26).

Response: Actual pertinent measurements are not available. As the commentator noted, the ICNCM exposure estimates were very broad.

108. Comment: Even though they were based on measurements, the data on exposures in the Copper Cliff sinter plant mentioned on p. 102, par. 4, should be referred to as estimates, not "measures" (Inco, p. 26).

Response: The exposure information used for the risk assessment was based directly on the measurements. This contrasts with exposure information for other cohorts which was estimated by ICNCM without measurements.

109. Comment: Has the DHS given any thought to the validity of assuming that either additive risk or relative risk should be related to cumulative exposure? Data reported in 1989 by I Anderson and KB Svenes on the nickel contents of the lungs of autopsied refinery workers indicate that lung cancer may not be predicted from cumulative dose of insoluble compounds. The workers who died of lung cancer had the same concentration of nickel in their lungs as the men who died of other causes. In addition, information on the effects of particle overload suggests that relatively short periods of high exposure my initiate irreversible processes whereas the same dose spread over a longer period of time may not (Inco, p. 26).

Response: In view of the latency of cancer causation, the quantity of nickel present at autopsy may have little relationship to the dose received in the causal period. The dose response relationship presented by Chovil et al.demonstrate a strong relationship between lung cancer risk and cumulative exposure estimates.

110. Comment: The DHS should consider whether the argument presented on p. 103, par. 3 of the draft report could be expressed more clearly (Inco, p. 26-27).

Response: The recommended wording change does, in our view, improve the sentence so it has been changed accordingly:

Thus if the background cancer risk and the risk for a particular cause both rise as the fifth power of age, the relative risk will remain constant.

111. Comment: The report could provide a service to its readers by explaining the derivation of the simple model presented on p. 103, par. 5 (Inco, p. 27).

Response: For the simpler model, the EPA document is referenced and should be used for further explanation of their approach.

112. Comment: If the discrepancies discussed in Section 7.2.3.3 have persisted, the DHS should consult with Steven Bayard of the EPA's Carcinogen Assessment Group. This commentator expects the matter could be resolved with him (Inco, p. 27).

Response: EPA was consulted on this point.

113. Comment: Regarding p. 107, par. 3, why is it not best to use a model that is compatible with the actual biological situation when trying to quantify the risk (Inco, p. 27)?

Response: The relative risk model is compatible with the actual biological situation. It would fit well if the agent of interest had a multiplicative synergistic effect with the background causes, and also as we have shown if it has an independent effect but with similar age dependence of incidence as for the background causes.

114. Comment: Regarding p. 107, par. 4, the DHS may wish to consider performing a risk assessment with the additive model as well as the relative risk model if it is given access to certain more complete data on the Copper Cliff sinter plant cohort (Inco, p. 27).

Response: The relative risk model was deemed to be the best for quantitative risk estimation concerning nickel, not just on the basis of availability of data.

115. Comment: The wording of par. 2 on p. 108 may lead some readers to think that cases and deaths are being indiscriminately mixed (Inco, p. 27).

Response: The wording has been changed from lung cancer cases to lung cancer deaths.

116. Comment: Regarding p. 108, par. 2, Ontario rates, not Canadian rates, should be used as background because they are what Chovil *et al.* used to estimate expected deaths (Inco, p. 27).

Response: The revised document uses mortality rates for Ontario as suggested.

117. Comment: Regarding p. 109, par. 2, it should be pointed out that Rivedal and Sanner concluded that benzo(a)pyrene probably acted as the initiator of cell transformation while nickel sulfate probably acted as a promoter (Inco, p. 27).

Response: The revised Genotoxicity section discusses this study in detail. A statement has been added to page 109, paragraph 2 referring the reader to the appropriate page containing this discussion.

118. Comment: Regarding p. 109, par. 2, several other reports should be considered for this section (Inco, p. 27-28).

Response: The revised Genotoxicity section does include a discussion of studies specifically designed to evaluate the synergism between nickel compounds and known carcinogens. The suggested references will be reviewed and relevant additional information will be added to this section where appropriate.

119. Comment: Regarding p. 109, par. 4, why doesn't the draft report discuss the Kreyburg (1978) study (Inco, p. 28)?

Response: The Magnus study involves the same cohort and gives more information.

120. Comment: Regarding p. 111, par. 4, the extent of smoking among the workforce at Falconbridge impressed visitors to the refinery, who noted the propensity of workers to roll their own cigarettes with nickel covered fingers in the presence of nickel-containing airborne dusts (Inco, p. 28).

Response: If this is so, it provides added support for the conclusion of this paragraph.

121. Comment: Regarding p. 112, par. 1, the Department seems to be satisfied that the risk of lung cancer from nickel exposure is independent of the risk of lung cancer from background causes, principally cigarette smoking. If so, doesn't this suggest the use of an excess risk model to evaluate the risk from nickel exposure alone? Why does the draft report then use a relative risk model to ascertain the risk for the Copper Cliff sinter plant cohort? Since the DHS has rejected biological synergism as justification for using the relative risk model, the report should provide some evidence for its other justification for using the relative risk model, i.e., that the age dependence of nickel-related lung cancer is the same as the age dependence of smoking-related lung cancer. Can this be done? Doesn't Kreyburg (1978) address this question (Inco, p. 28)?

Response: The relative risk model as employed in deriving the unit risk estimate does not assume a synergistic effect between nickel and background causes of disease (see Section 7.2.3.2). P. 112 para 1 of the draft document refers to the fact that the evidence does not suggest interactive effect between nickel and smoking in causing lung cancer (i.e. the evidence does not suggest there are either synergistic nor antagonistic effects). This does not mean that one cannot use a relative risk model to evaluate the risk from nickel exposure alone. The reasons for this are given in Section 7.2.3.2. The report uses a relative risk model with the Copper Cliff sinter plant cohort for the reasons given in Section 7.2.3.4. The choice between a relative risk model and an excess risk model was in part based on the straightforward mathematics involved. The relative risk model leads to us of simple linear regression which is more robust than fitting a more complex mathematical model which would be required for excess risk. To actually test for age-dependence as suggested would involve more data than are available from the sinter cohort study. Kreyberg reported similar age at diagnosis for two series but the data are insufficient to test for age dependence which may be confounded by latency and level of exposure.

122. Comment: Regarding the risk assessment of Section 7.2.5, the report should explain how, given that absorption, retention and excretion, and carcinogenic effects vary with the form of nickel, the risk of lung cancer from exposure to ambient nickel can be estimated from the experience of an occupational cohort exposed to quite different forms of nickel. It is amazing that toxicologists will take great pains to discriminate between individual organic compounds but will group all the forms of a metallic compound under one heading (Inco, p. 28).

Response: Decisions on how to protect the public health must be made before all desired data are available. There is no indication that nickel compounds vary greatly in carcinogenic potency.

123. Comment: Even if the DHS can justify using the Copper Cliff sinter plant cohort for ambient risk assessment, it should not use the Chovil *et al.* study because the Roberts *et al.* study is superior in every respect. In addition to using more up-to-date epidemiological data, the DHS should use better exposure estimates than did Chovil *et al.* [The commentator submitted more information on the sinter plant exposures, including several figures and tables, and suggested a method for estimating mean nickel concentration based on year.] It should be noted, however, that all Copper Cliff sinter

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plant workers were issued respirators but their wearing was not enforced and not uniformly practiced (Inco, p. 28-32 and figures and tables following p. 40).

Response: Information concerning follow-up given by Roberts *et al.*has been incorporated in the revised risk assessment. The exposure estimates used have been based on measurements at the plant given in the Roberts.1984 paper, and not on estimates given by Chovil *et al.* Their are uncertainties in the exposure estimates used. These uncertainties are largely a property of the limited number of measurements made. More refined statistical treatment of the exposure data will not reduce the underlying uncertainties.

124. Comment: The report could provide more equations to help the reader follow what is going on in the risk assessment. Why not show how each of the terms in the model are calculated (Inco, p. 32)?

Response: Table 7.12 has been expanded to give more details of the calculations.

125. Comment: The discrepancy between the EPA's results with two different forms of the relative risk model is not a justification for not applying the maximum likelihood approach to the Copper Cliff sinter plant cohort. The data available for this cohort do not meet the EPA's criteria for using the average relative risk model (Inco, p. 32).

Response: The discrepancy in EPAs results was not the reason for using a relative risk model. The reasons are given in section 7.2.3.4.

126. Comment: The DHS will presumably revise the draft report in light of the estimated nickel concentrations for the Copper Cliff sinter plant given in the ICNCM report. This commentator has certain reservations about those values (Inco, p. 33-34).

Response: The risk assessment is based on actual measurements of exposure. The ICNCM report did not present any additional measurements.

127. Comment: The draft risk assessment's analysis assumes either that the composition of the sinter plant dust remained constant over the life of the plant or that the airborne carcinogens all had equal potencies. Neither of these assumptions is true. The proportion of nickel subsulfide in the airborne dust decreased in later years as productivity increased. The potential for airborne polycyclic aromatic hydrocarbons (PAHs) (from coke breeze) also declined in later years. Other sources of air contamination were readily apparent at various stages of the plant's life (Inco, p. 34).

Response: Uncertainties surrounding nickel speciation and carcinogenic potency are discussed in the report and have been revised given the information in th ICNCM report. See Section 8.

128. Comment: Regarding p. 112, par. 3, using expected values as weights cannot eliminate possible errors due to inadequate latency periods. Since those exposed least were most likely to be exposed in later years, it is possible that insufficient time has elapsed to

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permit lung cancers to develop in their exposure groups. Thus the passage of time is likely to reduce the dose-response slope. With an update of the cohort, it might be possible to ensure that the various exposure groups are constructed of men with comparable latency periods (Inco, p. 34).

Response: Insufficient latency would lead to underestimation of risks, and hence of the dose-response relationship.

129. Comment: Regarding p. 115, par. 1, the DHS has no idea how the untraced workers were distributed across the exposure groups. It is inappropriate to assume that the assumed lung cancer deaths among these workers occurred across the exposure groups in the same proportions as they occurred in the traced workers. It is possible that untraced lung cancer deaths would have resulted in a smaller dose-response slope, rather than a larger one. Using the Roberts *et al.* data or the results of a planned update could eliminate the concern about lack of ascertainment (Inco, p. 34).

Response: The Robert *et al.* data was incorporated into the analysis.

130. Comment: Regarding p. 115, par. 4, the calculation of the background lung cancer mortality (Po) should be based on the same rates that were used to calculate the SMRs for the Copper Cliff sinter plant workers. Line 3 of this paragraph should specify lung cancer deaths. Several questions remain regarding the proper method of calculating Po. The draft report's approach could produce only a rough estimate of Po at best; it apparently neglects the "fine structure" of the population in age distribution and death rates. The DHS report should explain what Po should be and demonstrate that its approach yields the correct number. Po is too important a factor in the risk assessment to tolerate unnecessary uncertainty (Inco, p. 35-37).

Response: The background lung cancer mortality estimate has been based on Ontario mortality rates in the revised document. Line 3 of this paragraph has been corrected. The revised report also gives further information concerning the derivation of the background lung cancer mortality rate.

131. Comment: Regarding p. 116, par. 3, recent work has found that the process at the Copper Cliff sinter plant did not involve "various sulfur-containing forms of nickel," as stated here. Rather it involved only nickel subsulfide, to produce mainly nickel oxide and nickel-copper oxide. The subsulfide was contaminated with one to two percent by weight of a metallic fraction that was about 75 to 90% Ni. This contaminant was unlikely to become airborne, however. Data strongly suggest that the nickel sulfate found long after the sinter plant closed was formed by weathering reactions after the dusts were deposited. Prolonged heating of nickel subsulfide in air would have sulfated no more than 5% of the nickel subsulfide. In addition, there is no reason to expect that the sulfate so formed could have become airborne. Some "other" material (e.g., other metal oxides) would have been present in the plant's dusts. On the two days for which assays are available, about 60% of the nickel in airborne dust was present in NiO, about 35% in nickel subsulfide, and no more than 5% was in NiSO4 6H2O, if the sulfate existed at all. The airborne nickel oxide contained some copper oxide, amounting to from 5 to 10% of the weight of nickel-copper oxide. Nickel-copper oxide has been reported to be a potent experimental

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carcinogen. It should also be noted that the Clydach refinery treated a nickel-copper oxide as did the Kristiansand refinery. This commentator does not expect to find either a nickel-copper oxide or nearly-pure NiO in California air. Just because the Copper Cliff sinter plant was a nickel refinery doesn't mean that some form(s) of nickel was (were) the only possible explanation for the cancer hazard. PAHs were probably also present, and combined with the very high concentrations of airborne particulates, they could have played a significant role (Inco, p. 37-38).

Response: The results of the Copper Cliff study have helped to form the conclusion that nickel compounds are carcinogenic. Other studies described in the ICNCM and IARC reports indicate that nickel sulfate is also carcinogenic. Consequently, to conclude that a single or non-nickel compound is responsible for the effects at the Copper Cliff facility appears inappropriate.

132. Comment: **Regarding p. 116, par. 4, although most human studies have had to contend with exposures to mixed nickel compounds, the studies conducted at the Oak Ridge Gaseous Diffusion Plant clearly indicate that there was no risk of lung cancer associated with exposure to fine, pure metallic nickel powder (Inco, p. 39).**

Response: The conclusions on nickel's carcinogenicity is based on the large range of data available in humans, animals and other experimental studies. As indicated in the comment there is inadequate evidence of human carcinogenicity of metallic nickel. Consequently, metallic nickel is considered a possible human carcinogen as discussed in the IARC report.

133. Comment: **Regarding p. 116, par. 5, it seems premature rather than prudent to equate the carcinogenic potencies of nickel subsulfide and nickel oxide. Nickel oxide has not been a consistent experimental carcinogen. When nickel oxide known to be produced at high temperatures was tested it did not produce tumors by injection. The NTP is close to completing the best inhalation studies that will ever be done on these two compounds (Inco, p. 39).**

Response: See response to comment 4. Based on data presented in the nickel document, the ICNCM report and IARC report, nickel oxide is considered a human carcinogen.

134. Comment: **Regarding p. 117, par. 4, neither the DHS or the ARB has provided any evidence that the nickel found in ambient air is similar to the combination of nickel species found in the Copper Cliff sinter plant. There is no reason to expect to find nickel subsulfide, nickel oxide, or nickel-copper oxide in ambient air. Although the draft report refers to these compounds as "insoluble nickel" compounds, the risk assessment is based on circumstances not relevant to California ambient air. There is great diversity in biological behavior of nickel compounds with similar water solubilities. Aqueous solubility is not an adequate criterion for grouping nickel compounds according to carcinogenic potential. The fact that some water-insoluble forms of nickel can reasonably be associated with an increased risk of respiratory cancer in an occupational setting or in animal experiments does not constitute even weak proof that their carcinogenic potentials are the same. The DHS and the ARB have not shown that the substance for which they have prepared their technical support document is present in California ambient air, yet an ARB official has**

stated that this must be shown for a substance to be found to be a toxic air contaminant. Would the ARB propose to regulate as a group all organic species that had similar solubilities in a particular solvent (Inco, p. 39-40)?

Response: The report no longer separates insoluble and soluble nickel compounds with regard to their carcinogenic potential.

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Department of Health Services Staff Responses to Public Comments
on Part B of the Technical Support Document for the Proposed Identification
of Nickel as a Toxic Air Contaminant

ERRATA

DEPARTMENT OF HEALTH SERVICES (DHS)
STAFF RESPONSES TO PUBLIC COMMENTS
ON PART B OF THE TECHNICAL SUPPORT DOCUMENT FOR THE
PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT

Comments from the Western States Petroleum Association (WSPA)

29. Comment: Why only refineries and welders are mentioned for possible worker exposures should be explained. It may be helpful, for example, to review 11 specific cohorts from other occupations, and to show that the resultant risks were negative, insignificant, or low. Certain studies from Germany, Czechoslovakia, Russia and Japan, should also be reviewed (WSPA, p.5).

Response: There is no evidence that the studies listed, many of which involve mixed exposure to lung carcinogens, could be used for risk estimation. The IARC and ICNCM Reports cited in the document do review cohorts from various countries. DHS staff and the EPA report examined the most relevant cohort studies available. From these studies DHS staff chose the best cohort available for quantitative risk assessment.

Comments from the Pacific Gas and Electric Company (PG&E)

2. Comment: The unit risk derived from sinter plant subcohorts of the Ontario cohort should only be applied to nickel subsulfide and nickel refinery dust. A separate, non-sinter worker cohort should be used for estimating risks from insoluble nickel compounds other than nickel subsulfide. This is the preferred and recommended course of action. Alternatively, a unit risk derived from the 47,980 non-sinter worker Ontario cohort should be used for unspeciated insoluble nickel. Using the non-sinter worker cohort, rather than the sinter plant subcohort, would reduce the unit risk estimate by a factor of approximately 5.7. The exposures of the non-sinter workers are more representative of expected California exposures. Basing all California insoluble nickel risks on the sinter worker subcohort with the highest SMR is unjustifiably conservative. The largest possible cohort or combination of cohorts should be used to generate the best estimate of risks (PG&E, cover letter p. 1, B-1 and B-2).

Response: The risk assessment of nickel compounds is based on the strongest epidemiologic data available. The use of the cohorts as suggested would reduce the precision of the information linking exposure with response. Only the sinter plant workers had measurements of exposure for relevant time periods to link to later increased lung cancer mortality rates. Non-sinter plant workers had lower potential for exposure so even if one could base a unit risk estimate on them, there is no reason to expect it to be lower than that derived from the sinter plant workers. Furthermore, the sinter plant workers were exposed to a mixture of nickel compounds not simply nickel subsulfide. These data do not reflect the most conservative estimate available. As indicated in Table 7.9 of the report, the range of risks

calculated by the U.S. EPA based on 7 cohort analyses is 1.9 to 46 x 10^{-5} per $\mu g/m^3$ compared to the DHS best value of 23 x 10^{-5} per $\mu g/m^3$. Review of the human data for nickel sulfate exposure in the ICNCM report indicates that risks based on those studies could produce higher potency estimates as well. The reason for not choosing these studies is the absence of measured exposure data. The upper range of risks reported in the revised document is 10-fold higher than our suggested best value. It is unlikely that use of other human cohorts would substantially lower the risk estimates and doing so would weaken the scientific analysis. Estimates from some other studies are higher. In particular, estimates for nickel sulfate exposed workers would be higher. Consequently, the choice of the Ontario subcohort does not affect the ultimate risk number chosen, however, the purpose for choosing the Ontario cohort, as stated in the document is that the Ontario subcohort had the best exposure information available. That is, only for the Ontario cohort were actual measured levels of nickel exposure available.

4. Comment: Instead of increasing risks by a factor of 4.6 to account for non-occupational exposure time, the risk assessment should use a factor no greater than 2 (and this would reduce the unit risk by a factor of 2.3). The DHS assumes that a unit exposure to insoluble nickel will cause 4.6 times more risks in California's ambient air than it is presumed to have caused in the Ontario "historic worker" cohort. On average, Californians spend 13% of their time outdoors; the workers were assumed to spend 22% of their time at the workplace. The workers' exposure to nickel did not necessarily end when they left work. Nickel associated dusts may have been carried home on clothing, and dusts vented from the plant may have contributed to elevated concentrations in the vicinity. Only the finer particles tend to be captured by the lung, and these particles would be most readily vented from the plant by the roof fans. Modern indoor particulate exposure levels and historic "after work" exposures should be incorporated into the risk assessment (PG&E, cover letter p. 1, B-2 and B-3).

Response: The adjustment of exposure from occupational to ambient air are standard procedures used by the Department as described in the Departments' cancer guidelines. The commentor is incorrect in concluding that DHS analysis assumes that a unit exposure causes more risks to Californians than the original cohorts. The risk to the original cohort in Ontario is much greater than that for Californians. Instead the DHS report assumes that Californians will be exposed to average ambient air concentrations of nickel that equal outdoor concentrations of nickel. The indoor air comes from outdoors and there is no reason to assume that indoor air has less nickel. There is inadequate data to characterize indoor air. Indoor air levels of particulates generally match those of outdoor air levels. However, based on particulate comparisons and the likely contribution from cigarette smoke, one would expect higher indoor air exposure to nickel. Consequently, it is likely that the exposure estimates in the report underestimate California's exposure to nickel compounds in air. The commentor is likely to be correct that Ontario worker exposure to nickel continued after they went home. Specific data to quantify this are not available, but it is not likely that such exposures would add significantly to the exposure experienced at the workplace. Incorporating non-workplace exposure into the estimates would have a negligible effect since the environmental levels of exposure are so much lower than the workplace exposures experienced by the cohort. For example, if we assume that the workers spent 22% of their time at work, and the remaining 78% of their time

at home with the unlikely scenario that at home they were exposed to nickel levels one tenth of those at the workplace due to dust they brought home, then the increased exposure estimate would be quite small (1 unit of estimated exposure would increase to 1.35 units (0.22 x 1 + 0.78 x 0.1)/(0.22 x 1)). With a more reasonable assumption that exposure levels at home were less than one hundredth of those at work, 1 unit is estimated exposure would increase to less than 1.035. If we assume that the workers were exposed at home to levels 1000 times higher than current California ambient air levels (i.e. 0.02 mg Ni/m^3) in contrast to workplace levels of 75 mg Ni/m^3, then the exposure estimate would increase by a factor of only 1.001 (0.22 x 75 + 0.78 x 0.02)/(0.22 x 75).

15. Comment: The draft report incorrectly assumes that all insoluble nickel compounds should be considered potentially carcinogenic to humans, and that the carcinogenic potency estimated from the experience of a sinter plant "subcohort" is representative of the potency of the mixture of nickel species in respirable ambient air particles in California. The exact agents that cause the observed increases in lung and nasal cancer have not been determined. The proportion of total nickel in ambient air that is insoluble varies. Nickel sulfate and nickel oxide are likely to predominate in ambient air and have not been as clearly identified as human respiratory carcinogens as nickel subsulfide. The dose levels experienced by the workers are four to eight orders of magnitude greater than those present in ambient air in California (PG&E, p. 32-33).

Response: Please see response to #1 Southern California Edison Company.

20. Comment: California should use an alternative cohort, such as the non-sinter plant workers of the Ontario cohort, as the basis for respiratory cancer risk assessment of ambient nickel exposure. The unit risk derived from the 495-person sinter plant subcohort from Ontario should only be applied to nickel subsulfide and nickel refinery dust. It would be preferable to speciate insoluble nickel and use a non-sinter worker cohort with relevant exposure profiles to estimate risks from inhalation exposures to nickel compounds that are associated with ambient air particles. Although the sinter workers were exposed to insoluble nickel that contained a relatively high proportion of nickel subsulfide, oil combustion is the largest known source of airborne insoluble nickel emissions in California and is not believed to produce any nickel subsulfide. Studies of non-sinter workers consistently show lower risks than sinter worker studies. Use of non-sinter cohort data would yield a unit risk more reflective of typical California exposures (PG&E, p. 47-48).

Response: The nickel subsulfide exposure to the sinter workers has not been quantified. However, it is known that they were subjected to substantial nickel oxide exposure as well. The subcohort was exposed to both nickel subsulfide and nickel oxide, neither of which was quantified. They were also exposed to other forms of nickel as well. Consequently, assigning the risk of those workers to nickel subsulfide only, is inappropriate.

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Comments from Inco Limited (Inco)

41. Comment: Why does Section 5.1.2.2 not report oral lethality? A paper is available (Inco, p.11).

Response: The report submitted the Department did not contain information on oral LOELs or NOELs. Oral lethality information was not considered relevant to this report since the oral route is not being considered and there is ample information on inhalation lethality.

63. Comment: What is the Department's position with respect to non-positive results in hamsters by the inhalation and instillation routes? Although some risk assessors say that live hamsters are not good models for respiratory carcinogenesis, the same assessors are willing to accept positive results using various hamster cells in vitro (Inco, p. 16).

Response: The Department does not have a general position, but simply evaluates each study individually. The hamster studies are discussed in the cancer section in the document. Since nickel compounds are known human carcinogens, the negative results in hamsters appear to reflect a false negative response with regards to human carcinogenicity.

PART C ADDENDUM

PUBLIC COMMENTS AND RESPONSES TO THE DRAFT NICKEL REPORT

Prepared by the Staffs of the Air Resources Board
and the Department of Health Services

June 1991

Part C Addendum contains the comments received from the public during the April 22, 1991 to May 6, 1991 public review period for the Draft report on Nickel. The responses of the Air Resources Board and the Department of Health Services to those comments are also contained in this Addendum.

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I.

Comment Letters Received from the Public on the Draft Nickel Report

C00574

GENE'S
PLATING WORKS
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Nickel-Chrome Plating:
on Steel
on Aluminum
on Brass
on Die-cast

April 26, 1991

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant
Identification Branch
California Air Resources Board
Attn: Nickel
P.O. Box 2815
Sacramento, CA 95812

Subject: Final Draft Report to the Scientific Review Panel on Nickel

Dear Ms. Shiroma:

I am writing to request at least a 30 day extension on the comment period for subject report on Nickel. It seems rather unfair for you to take more than eight months to issue the revised report and then to give the regulated community less than two weeks to respond. I recognize that the primary consideration is to be able to have the Scientific Revue Panel discuss the report at its May 15 meeting; however, I would think that you would also want the most constructive response possible from those of [redacted] who are effected - and I do not believe two weeks is adequate.

I made this request by phone earlier this week and talked to two CARB people. The response from one was that "fairness" was not a consideration; the calendar had already been set. The second person acknowledged the shortness of time but pointed out that there weren't that many changes to review. That is really a disturbing adminssion for two reasons: One, regardless of how many or how few modifications to the original document were made, we still have to search the entire 5 inches of material to find them. Second, and much more important, if it is true that only "a few" changes were made, then it indicates that CARB and DOHS staff must not have paid any attention to the data submitted at the August, 1990 hearing. Ignoring the question of how the data is to be interpreted, it seems to us that there was enough presented to bring into question the very validity of the data in your original study.

Thank you for your consideration.

Yours very truly,

Harry Levy

Harry W. Levy
President

DRAFT

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May 3, 1991

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant Indentification Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Subject: Comments in Response to Final Draft Report to the Scientific Review Panel on Nickel

Dear Ms. Shiroma:

As I mentioned in my earlier letter, I feel quite strongly the lack of adequate time to prepare these comments. I am not a technical person and have only been able to review the report as a lay person. There was not enough time provided for me to get more technically competent people involved on our behalf. With that disclaimer my comments, questions, and observations are as follows:

Reference: Staff Report/Executive Summary:
Pg. 2, Paragraph 1 states that "DHS staff found that all nickel compounds should be considered potentially carcinogenic to humans by inhalation."

I disagree strongly with this conclusion. I do not believe that any data in this report justifies including soluble forms of nickel in general, or those used by the metal finishing industry in particular (most specifically nickel chloride and nickel sulfate). Further, your own statements in Part B would seem to reinforce my point of view:

B, Pg. 115, Par. 7.1.4. "Inhalation exposure cancer bioassays to date have only examined insoluble forms of nickel for their carcinogenic potential."

B, Pa. 115, Par. 7.1.4. "Water soluble nickel compounds have limited carcinogenic activity in whole animal cancer bioassay studies."

B, Pg. 113, Par. 7.1.3. "To date, injection administration is the only route of exposure for which data are available for direct comparison of carcinogenic potential of various nickel compounds."

B, Pg. 143, Par. 8. Next to last paragraph includes the statement "even if soluble nickel salts were carcinogenic by inhalation." Doesn't this imply that the researcher believes they are probably not?

B, Pg. 144, Par. 9. "The potency estimate presented relates to inhalation of nickel compounds. The following reasons suggest that inhalation is the only route of human exposure which needs to be considered when calculating cancer risks."

The above may be a rather simplistic approach, and has obviously been quite selective in the statements quoted, but I believe valid none the less. The sum and substance of it tells me that inhalation is the only route of concern; that there is no inhalation data on soluble nickel; that the report writers themselves question the carcinogenicity of soluble nickel salts - ergo soluble nickel should not be considered until and unless more data is presented.

By the way, if I am guilty of excerpting from the study only that which supports my .nterests, I am certainly no more guilty than the CARB and DOHS researchers who have .one exactly the same thing to support their predetermined bias, but they have done :o in a much more "scientific" fashion. I understand there is a great deal more data, .ot nearly so favarable to this study's conclusion in the later IARC data, that has .ot found its way into this report.)

:t may be appropriate to reiterate at this time that the National Toxicology Program NTP) has completed its comprehensive study of nickel and is in the process of preparing .ts report. It is hoped that this comprehensive and definitive study will be available .ate this year. Logic would suggest that all consideration of Nickel as a toxic air :ontaminant should be delayed until the NTP study is available.

.nother statement from the Staff Report/Executive Summary includes "electroplating" .s one of the anthropogenic sources of nickel emissions". Their estimated emissions rom this source is 1.4 tons per year as derived from an industry survey compiled by CAQMD in 1985 (Page A 11.). This data was solicited from and voluntarily submitted y a number of metal plating companies who used no scientific methods at all - but erely estimates of materials purchased, materials plated, materials discharged, and aterials emitted into the area. I suggest that this data has no validity whatsoever; nd further that CARB and DOHS have no other valid data to indicate any emissions of ol[redacted]e nickel by the electroplating industry into ambient air. The study itself states Pg[redacted] 11) that "there is insufficient data to estimate statewide nickel emissions from lectroplating operations".

n page A-42 (par. 3), the report suggests that besides nickel carbonyl other forms <u>may</u> ind their way to the atmosphere. Can we continue to regulate on "maybe's" and "what f's"? Aren't there enough real problems to address without conjuring up imagined ones?

n Appendix VI, attachment I, of Part A, nickel emissions from electroplating sources re again mentioned, and although they are categorized as "minor", I still question their nclusion.

n response N-6 to INCO (pg. C-18 of Part C), DOHS states they cannot respond without sing "unsubstantiable assumptions". I submit that whenever and wherever it suits their urposes, that is exactly what this document does. The comment above regarding emissions rom electroplating sources is <u>a</u> case in point, but not the only one.

final observation; CARB's response to questions from several commentors as to why and n what grounds were they including <u>soluble</u> forms of nickel; was that DOHS staff, based n all available data, concluded that "<u>all</u> nickel compounds should be considered poten- ally carcinogenic to humans by inhalation". I have discussed my perspective on this ssue earlier. I believe that the rationale for CARB's conclusion is rather obvious and ansparent. By so concluding, it is no longer necessary to do any real research to etermine that which needs to be regulated and that which does not. Thus many very gitimate questions as to sources, routes, concentrations, speciation, etc. can nveniently be ignored.

I hope that my comments in my earlier letter as to more time being needed, and in this letter as regards the NTP study, are given real consideration. I hope you will agree that "good" data is better than "fast" data; and that we will all be better served by working together to produce the regulations that both protect human health and human endeavor.

Yours very truly,

Harry W. Levy
President

HWL:jl

COPIED

Pacific Gas and Electric Company

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John F. McKenzie
Director
Environmental Planning

May 3, 1991

Ms. Genevieve Shiroma, Chief
Toxic Air Contaminant
Identification Branch
California Air Resources Board
Attn: Nickel
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma:

Comments on April 1991 Nickel Risk Assessment

As you know, Pacific Gas and Electric Company (PG&E) previously commented on the June 1990 draft "Proposed Identification of Nickel as a Toxic Air Contaminant". We appreciate this opportunity to further comment on the April 1991 revisions, and to reiterate those previous comments of greatest concern for this stage of the process, which the Department of Health Services has not incorporated into its revised Part B.

1. THE DHS PROPOSAL TO PROVIDE A SINGLE UNIT RISK ESTIMATE FOR ALL NICKEL COMPOUNDS IS NOT HEALTH PROTECTIVE. SEPARATE UNIT RISKS SHOULD BE PROVIDED FOR EITHER NICKEL SUBSULFIDE OR NICKEL REFINERY DUSTS VERSUS OTHER NICKEL.

While it may be health protective to assume that all nickel compounds pose some risk, it is not health protective to assume that all nickel compounds pose the same risks. The available evidence clearly suggests that inhalation of nickel subsulfide poses far greater risks than inhalation of the same quantity of nickel oxides or sulfates. Assuming that all nickel compounds pose the same risk will underestimate the nickel subsulfide risks if, as in this case, the epidemiological data includes exposures to other nickel compounds.

DHS should separately estimate nickel subsulfide (sulfidic nickel) and other nickel compound risks. This should be done using separate cohorts with different sulfidic nickel to total nickel compound ratios. For the one with the higher nickel subsulfide ratio, it should be initially assumed that all the risk comes from nickel subsulfide. For the one with the lower nickel subsulfide ratio, the range of "best" risk estimates for "other nickel" should include that calculated by first subtracting the estimated sulfidic nickel risk, as well as that calculated by assuming that all nickel compounds are

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equally carcinogenic. However, it would be illogical, given the evidence to the contrary, to include in the "other nickel" risk range, the assumption that sulfidic nickel is less carcinogenic or non-carcinogenic.

2. THE COPPER CLIFFS SINTER PLANT SUBCOHORT SHOULD ONLY BE USED TO EVALUATE SUBSULFIDE RISKS. A MORE REPRESENTATIVE COHORT SHOULD BE SELECTED TO EVALUATE OTHER NICKEL OR TOTAL NICKEL EXPOSURE RISKS.

In the April 1991 Part A report, Table II-1 page A7, it is estimated that 97% of known nickel emissions in California come from oil combustion (approximately 60% nickel sulfate, 40% nickel oxide, 0% nickel subsulfide per limited EPA reported testing). Exposures in the sinter plant subcohort were estimated on page 51 of the February 1990 "Report of the International Committee on Nickel Carcinogenesis in Man" (referred to henceforth as the "Doll report") as being 15-58% sulfidic, with the remainder primarily oxidic.

On Page 127 of the April 1991 Part B report, it is noted that the Lung Cancer Standard Mortality Ratios (SMRs) for four different studies (originally selected by EPA for the purpose of calculating subsulfide risks only) differed by a factor of 7.8 (from 1.12 to 8.71). DHS is basing its total nickel risk estimate on a study of the one subcohort yielding the highest SMR, without seriously evaluating how different nickel species ratios might have contributed to those differences.

We disagree with the DHS Part C response that the sinter plant subcohort was the "best" available. A larger number of people, exposed to levels closer to the expected ambient levels, and to a mixture of compounds more representative of the expected mixture in the ambient air, that is the entire cohort, would be better. Furthermore, in the Doll Report there is an extensive discussion of the role of different nickel compounds. While that report concludes on page 74 that "discussion focused mainly on the identification of nickel species hazardous to human health", and it "left the development of quantitative dose-specific models for future work", it provides numerous examples of cohorts with significant variations in SMRs relatable to variations in the type of nickel compound exposure involved:

Cohort	Lung Cancer SMR	Lung Cancer O/E	Nasal Cancer SMR	Nasal Cancer O/E
Table 48, INCO Sinter	261	2.6	5,073	51
Table 49, INCO Non-Sinter	110	1.1	142	1
Tables 32&36, Wales Metallic	249	2.5	---	62
Tables 32&37, Wales Soluble	133	1.3	---	120
Tables 32&36, Wales Oxidic	363	3.6	---	120
Tables 32&38, Wales Sulfidic	589	6.6	---	345
Table 63, Hunt Soluble <5 yrs	99	1.0	---	---
Table 63, Hunt Oxidic ≥ 5 yrs	71	0.7	---	---
Table 63, Hunt Sulfidic ≥5yrs	173	1.7	---	---

We do not understand why DHS does not utilize the Doll report either as a basis for picking separate and more representative cohorts for sulfidic nickel, oxidic nickel and soluble nickel unit risk assessment calculation purposes; or at least as a justification for adjusting the unit risks estimate attained from the INCO Sinter Cohort to the different proportions of nickel compounds expected to be found in California. (Note the comment from Dr. Harding-Barlow, Part C page 416, that the accuracy and size of Wales cohorts was enhanced in the Doll Report.)

3. THE ARB/DHS SHOULD NOT PROCEED WITH THE SCIENCE PANEL REVIEW OF SOLUBLE NICKEL UNTIL THE PUBLIC IS GIVEN AT LEAST A 30 DAY COMMENT PERIOD ON THE SOLUBLE NICKEL RISK ASSESSMENT.

Under the current procedure, the public is given 30 days to comment on new risk assessments, but only ten days to comment on minor revisions. We have previously noted that these comment periods are inadequate, particularly relative to the amount of time the agencies take to create the documents and to respond to comments upon them. However, in this particular case, given the major change, the addition of a whole new class of compounds (soluble nickel), this "revision" should have been treated as a new risk assessment subject to the 30 day comment period. We request that the ARB/DHS only proceed with its originally issued "insoluble nickel" risk assessment, at least until such time as the public is advised that it has 30 subsequent days to prepare comprehensive comments on the "soluble nickel" addition.

Granting an additional 20 days from the original release would not be equivalent to granting the 30 days we need, at a

minimum, to even begin a serious review of an entire risk assessment.

4. THE EXECUTIVE SUMMARY SHOULD NOTE THAT THE RISK NOT ONLY INCREASES WITH HIGHER OCCUPATIONAL EXPOSURES, BUT ALSO SIGNIFICANTLY VARIES WITH THE TYPE OF EXPOSURE, AND IS RELATIVELY INCONCLUSIVE AT EXPOSURES WELL ABOVE THOSE EXPECTED TO OCCUR IN CALIFORNIA.

At the top of page 2, the following should be added at the end of the first paragraph:

> "However, lower levels of historical occupational exposures (which were still well above currently expected ambient air exposures in California) did not consistently produce increased risk. In any event, existing data cannot establish whether exposures at ambient concentrations cause any risk. Also, the available data strongly suggests that sulfidic nickel may pose substantially higher risks than oxidic or soluble nickel."

5. THE ARB SHOULD NOT PROCEED WITH THE IDENTIFICATION OF NICKEL COMPOUNDS OTHER THAN NICKEL SUBSULFIDE, NICKEL CARBONYL, OR NICKEL REFINERY DUST AS TOXIC AIR CONTAMINANTS UNTIL IT OBTAINS AND UTILIZES THE RESULTS OF THE ONGOING NATIONAL TOXICOLOGICAL PROGRAM (NTP) BIOASSAYS ON NICKEL SULFATE AND GREEN NICKEL OXIDE.

PG&E supports INCO previous comments that the DHS/ARB should:

a. Rethink the definition of a threshold, given the data showing little or no risk at the lower observed levels of exposures, and hence little or no risk at current California exposures (Part C page 204).

b. Obtain access to the ongoing NTP bioassays of nickel sulfate, green nickel oxide, and nickel subsulfide before it completes its review of the Part B report (Part C pages 205-206). We understand that the NTP report should be available by this fall.

c. Recognize that "nickel oxide" (or oxidic nickel) describes a family of compounds in which subtle differences in composition and structure can make large differences in physico-chemical and biological properties (Part C, Page 210). Chemically and biologically, black nickel oxides produced by low temperature reactions (<550° C), are much more active than the high temperature

"green nickel oxides" (>850° C)[Part C, Page 278 and pages 284-288]. In evaluating nickel oxide data, and applying that to expected nickel oxide emissions from oil combustion, it will be important to correlate between the temperature of the epidemiological data source and the temperature of the sources most significantly contributing to California ambient nickel levels.

d. Recognize that large discrepancies between observed and predicted incidence of lung tumors (in individuals exposed to coal fly ash) are totally inconsistent with the assumption that nickel oxide and nickel-containing coal fly ash possess the same carcinogenic potency as does nickel subsulfide, after adjusting only for relative nickel content [Part C, pages 391-393, plus page 397].

6. COHORT DATA SHOULD NOT BE USED TO THE EXCLUSION OF EXERCISING SOUND JUDGEMENT.

PG&E supports NIPERIA's October 19, 1990 comments that:

a. Due to the uncertainty in estimates of the types and levels of nickel that workers were exposed to in the past, if models are to be used, they should not be used to the exclusion of exercising sound judgement on the basis of the qualitative and semi-quantitative information";

b. The cohorts that provide the most reliable information are the Huntington and Ontario cohorts. This is due to the fact that actual exposure estimates, albeit limited, are available for these workers. In regard to the Huntington cohort, the problems noted by the CARB regarding the precision and accuracy of the relative risk estimates... must be weighed against... the value of this cohort... (which) provides useful dose-response information at low doses (Part C, pages 423-424).

With our previous comments, we included a report from RiskFocus, which summarized available laboratory data consistently showing that nickel oxides and nickel sulfates are less hazardous than nickel subsulfides. When that data is added to the Welsh and Huntington cohort data consistently showing lower human epidemiological risks from high soluble or high oxidic, as compared to high sulfidic exposures, it should be clear that using the Copper Clifts sinter plant cohort for subsulfides, and either the non-sinter plant cohort, or the total cohort, for all other nickel compounds, would be far more realistic that the current DHS assumption that all nickel

is equally hazardous.

Please call me at 972-6901, or Ted Holcombe of my staff at 972-6910, if you have any questions.

Sincerely,

B. B. Wroblewski for/
L. F. McKenzie

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May 6, 1991

Ms. Genevieve Shiroma, Chief
TAC Identification Branch
California Air Resources Board
Attn: Nickel
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma:

KCAC owns and operates a short-fiber chrysotile asbestos mining operation in San Benito County and a milling facility near King City in Monterey County. The ore deposit is unique in the world in that the fiber content of the ore is over 90% and it retains moisture at about 20%, which minimizes airborne emissions. There are no blasting, grinding or other operations at the mine which could create excessive airborne emissions. The mill, over 60 miles from the mine, uses hydraulic beneficiation to produce products which are essentially all pelletized. Airborne emissions are also therefore kept to minimum at the mill.

Although we have no technical comments on the Final Draft Report to the Scientific Review Panel on Nickel as a toxic air contaminant, we do have some general comments on Part A.

In the Introduction on page -A1- it is stated that asbestos mining and milling is a "major source" of ambient nickel emissions. In a single sheet marked Attachment I, toward the rear of Part A, it is stated that asbestos mining and milling is a "minor source" of nickel emissions. We feel that this contradiction should be resolved in favor of listing asbestos mining and milling only as a minor source, or not listing it as a source at all. Using ARB calculations, on page 7 of Appendix IV, the total nickel emissions from asbestos mining and milling are estimated to be 0.004 tons/yr. Another minor source listed in Attachment I, coal combustion, has estimated emissions of 0.49 tons/yr, over 100 times higher than from asbestos mining and milling.

We further question the use, on page 8 of Appendix IV, of 4500 lbs. as the estimated asbestos emissions from mining. In 1987 there was another asbestos mining operation in California which may have been a major contributor to the 4500 lbs/yr estimate (this facility discontinued operations in December 1987). Our mine is operated only every 3 or 4 years and is conducted in a manner which minimizes airborne emissions. If we were emitting 4500 lbs/yr, the entire area downwind of the operation would probably be white and heavily contaminated. Based on our estimates, our mining and milling operation would produce a

combined total of less than one pound, 0.0005 tons, of nickel emissions per year.

We urge you to delete asbestos mining and milling as a "major source" of nickel emissions and to re-calculate the estimated emissions from mining. This should prompt you to also delete asbestos mining and milling as even a "minor source" of nickel emissions.

Thank you for the opportunity to present these comments. Please contact me if you have any questions or require additional information.

Very truly yours,

John L. Myers

John L. Myers
President

/mbl

J. Stuart Warner
Vice-President
Occupational & Environmental Health

(416) 361-7866

May 3, 1991

Ms Genevieve Shiroma, Chief
Toxic Air Contaminant Identification Branch
California Air Resources Board
Att'n: Nickel
P.O. Box 2815
Sacramento, CA 95812

Dear Ms Shiroma:

On August 15, 1990, I submitted on behalf of Inco Limited, Recommendations and Comments on the Part A Report of the Technical Support Document dealing with the Proposed Identification of Nickel as a Toxic Air Contaminant. It was followed on September 5, 1990 by Recommendations and Comments on the Part B Report.

On April 22, 1991, I received copies of the revised Part A and B Reports and the new Part C Report. I believe the TSD has been improved as a result of the public comment and ARB/DHS's response to those comments. Nevertheless, I think the TSD fails to satisfy the intent of the California legislators that the identification of toxic air contaminants "should utilize the best available scientific evidence" (Health and Safety Code, Section 39650(d)).

In a recent letter to Mr. Harry Levy, you cited Section 39655 of the Health and Safety Code as requiring nickel and nickel compounds to be identified as toxic air contaminants because they have been identified as hazardous air pollutants under the revised federal Clean Air Act. You quote the section correctly but its requirement does not negate the requirement to utilize the best available scientific evidence. When Section 39655 was enacted, the Clean Air Act provided that substances would be designated as hazardous air pollutants only after a thorough scientific review by EPA. Although EPA has thoroughly investigated nickel and its compounds, it has not identified any form of nickel as a hazardous air pollutant. Instead, nickel was simply designated as such by the Congress along with almost 200 other chemicals and groups of chemicals.

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Specifically, EPA concluded that nickel subsulfide is a known human carcinogen and that nickel carbonyl is a probable human carcinogen. However, it declined to list either of them as hazardous air pollutants because "...to the extent that they occur, [they] do not pose a significant risk to public health for contracting cancer or non-cancer health effects" (Federal Register, Vol. 51, No. 186, Sept. 25, 1986, pp. 34135-34139). Furthermore, EPA did not find sufficient evidence of carcinogenicity for any other nickel compound (or for metallic nickel) to justify identifying any of them as a hazardous air pollutant.

The ARB/DHS response to many first-round recommendations and comments, the limited scope and severely limited time allowed for commenting on the revised drafts and your reference to Section 39655 suggest that ARB has made up its mind about identifying nickel as a toxic air contaminant. Consequently the usefulness of commenting further on the scientific issues is questionable. Nevertheless, I have revisited a few important issues in the attachment to this letter because I would not want to see the TSD accepted uncritically as a reference during the control phase. When nickel proceeds to the control phase, I intend to raise still more of the issues previously identified by me and by other public commenters.

Sincerely,

J Stuart Warner

atts.

COMMENTS ON THE REVISED TECHNICAL SUPPORT DOCUMENT

titled

PROPOSED IDENTIFICATION OF NICKEL AS A TOXIC AIR CONTAMINANT

1. *ARB HAS ARRIVED AT A REASONABLE ESTIMATE OF THE POPULATION-WEIGHTED CONCENTRATION OF TOTAL NICKEL IN CALIFORNIA AMBIENT AIR BUT MAY HAVE DONE SO FORTUITOUSLY*

ARB has made some unfortunate policy decisions and appears to have made some mistakes in the processing and presentation of the nickel data collected from the Toxic Air Contaminants Network. These include: failure to use all of the available data; failure to recognize statistically significant temporal trends at seven of the sampling locations; mixing normal and lognormal statistics in the treatment of the data; making arithmetic errors in the calculations leading to Table III-2, notably in the standard deviations for the San Francisco Bay and San Joaquin Valley air basins; incorrectly plotting (and perhaps incorrectly calculating as well) the values displayed in Figure III-2; losing information by averaging monthly means instead of averaging the raw data; using an unexplained and apparently unnecessary statistical procedure (i.e. "bootstrapping"); etc.

Table III-4 is a good example of the confusion rampant in this section of Part A. It presents estimates of the annual mean nickel concentrations for the individual air basins. Table III-2 first presented these quantities but only four of the six values in Table III-4 are the same as those in Table III-2. It is not clear where the other two values came from? They don't seem to have come from Table III-3 but, if they did, one wonders why the values of a variable keep changing. Regardless of the origin of the basin means in Table III-4, the population-weighted mean calculated from these data should be 7.1, not 7.3 ng Ni/m^3 as shown. If the calculation is repeated using all the basin means from Table III-2, the population-weighted mean is 6.7, not 7.3 ng Ni/m^3.

The foregoing notwithstanding, I do not find a very different answer for the statewide population-weighted geometric mean nickel concentration when I carry out the procedures that I recommended in my submission of August 15, 1990. Attachment A summarizes the data in a form that I believe to be much more informative than ARB's Figure III-3. The statewide population-weighted geometric mean concentration appears to be about 5.2 ng Ni/m^3. The difference between this number and ARB's number (whether it be 7.3, 7.1 or 6.7 ng Ni/m^3) may not be material to ARB's recommendation but my figure was arrived at by using all of the then-available data in a rigorous manner. I do not believe the same can be said for the ARB figure(s). Because of its failure to recognize temporal trends at different sampling locations, the ARB data treatment should not be used in the control phase.

2. *ARB/DHS HAS DEVELOPED A RISK FACTOR FOR LUNG CANCER THAT IS INAPPROPRIATE FOR THE FORMS OF NICKEL IN CALIFORNIA AMBIENT AIR*

DHS derived a risk factor from the human data for the Copper Cliff Sinter Plant. In Part B, p.142, para.4, DHS observed that: "Thus the risk estimates and their extrapolation apply to whatever combination of nickel species the refinery workers were exposed." Inexplicably, ARB has not conducted any physical research to ascertain the principal forms of nickel in California ambient air. When commenters pointed out this failure, ARB replied that it wasn't necessary to speciate nickel in ambient air because it now considers all forms of nickel to be carcinogenic. ARB's reply makes sense only if ARB believes that all forms of nickel have the same carcinogenic potential.

However, in Part B (p.116, para. 5), DHS concludes: "Until the in vivo bioavailability and its relation to the carcinogenicity of nickel is better understood, there is insufficient data to quantitatively predict the relative carcinogenic potency of specific nickel compounds." How then can DHS justify its prediction that the carcinogenic potencies of all nickel compounds are the same? In fact, the available data (e.g. Part B, p. 113) indicate considerable variation in potency, including zero potency.

ARB's approach to metals and their compounds stands in stark contrast to its approach to the organic "substances" associated with the Toxic Air Contaminant program. The great majority of the organics in the program are unique chemical substances ranging from acetaldehyde to vinyl chloride. To be sure, a few of the organics are grouped and others are dealt with as complex mixtures but the groups are defined (e.g. 15 species of chlorinated dioxins and dibenzofurans) and the mixtures are specified by their origin (e.g. diesel exhaust or coke oven emissions). Thus ARB is very precise with respect to the organics. If it treated them the way it treats nickel and its compounds, it would analyze sampled gases and particulates only for their carbon content or for some functional group and would then look for some organic species containing carbon or that functional group for which a dose-response relationship is available. Reductio ad absurdum!

The only other possible justification for using the risk factor based on the sinter plant is for ARB to show that the forms of nickel in California ambient air are indeed the same as those in the sinter plant. Even ARB does not believe this to be the case.

The sinter plant workers were exposed mainly to nearly pure nickel oxide (the product), followed by somewhat lower concentrations of nickel subsulfide (the feed), still smaller concentrations of nickel-copper oxide (a minor product) and possibly to small concentrations of nickel sulfate (an unwanted but possible process intermediate).

The same forms of nickel are not prevalent in California ambient air. ARB believes (and we concur) that nickel subsulfide is unlikely to be emitted in California (p.A7) and DHS states (Part B, p.143, para.3) that "environmental nickel exposure involves low proportions of nickel subsulfide".

ARB indicates (p.A7) that most of the nickel emitted to California ambient air is in the form of sulfate and oxidic nickel or complex oxides of nickel. These last two descriptors should not be confused with the term "nickel oxide", which ARB and DHS use incorrectly from time to time.

"Oxidic nickel" embraces all oxidized forms of nickel including nickel oxide, NiO, "Complex oxides of nickel" involve oxidic forms of nickel and other metals, often in the form of spinels. The metallic oxides have a significant affinity for each other and react readily at high temperatures. Nickel oxide can form solid solutions with oxides of metals such as magnesium, titanium, cobalt, iron and copper. It can form compounds with metals such as iron, aluminum and vanadium and can substitute for other metals in compounds such as $ZnFe_2O_4$ and $MnFe_2O_4$. In actual practice, the entities mentioned above (and more like them) can interact to form very complex molecules.

Unless an operation is conducted in an oxidizing atmosphere at high temperatures and nickel is the dominant metal present, one would not expect to find relatively pure nickel oxide produced. For example, research on dusts from electric arc steelmaking furnaces led to the conclusion that: "Nickel is not present as NiO to any extent but is probably in ferrite-type compounds" (U.S. NTIS PB82-182593). If one looks through the Final Appendix V-G of the PM10 Source Profile Library for the South Coast Air Basin, there are a number of dusts with non-zero concentrations of nickel. However, the nickel is accompanied by many other metals and is usually dominated by them. Where it is not dominated by them, analyses for sulfur or sulfate ion suggest that a good part of the nickel would be present as sulfate and that there would be more than enough other metals to combine with the residual (i.e. oxidic) nickel. Thus airborne nickel in California ambient air is likely to be present as the sulfate and in complex oxides with other metals.

3. *ARB/DHS SHOULD USE A SMALLER RISK FACTOR THAN THAT DERIVED FROM THE COPPER CLIFF SINTER PLANT COHORT*

DHS contemplated (Part B, p.143) how to apply the unit risk derived from the sinter plant data to exposures to mixed nickel compounds containing nickel subsulfide, nickel oxide and soluble salts. It concluded that nickel oxide is unlikely to be more potent than nickel subsulfide and that soluble compounds are likely to be less potent than insoluble compounds. Thus ARB/DHS should apply a risk factor smaller than that derived for the sinter plant workers to exposures involving nickel oxide and/or soluble nickel compounds.

It is very likely that oxidic nickel tied up in a complex oxide would be considerably less active toxicologically than pure nickel oxide. Since the oxidic nickel in typical California ambient air is present as complex oxides instead of pure nickel oxide, the risk factor used by ARB should be reduced still further.

4. ARB CONFUSES THE PRESENCE OF NICKEL IN AMBIENT AIR WITH EXPOSURE TO NICKEL

ARB acknowledges that Californians on average spend only about 13% of the time out of doors. However, ARB/DHS (Executive Summary, p.2) is presently unable to estimate the contribution of the indoor environment to the total exposure to nickel. Until ARB/DHS completes its study of indoor concentrations of nickel and of the nickel species in indoor air, it cannot make a reliable estimate of the excess risk of lung cancer for a lifetime in California.

If the concentration of indoor nickel is small compared with that encountered in the outdoors and/or the species of nickel found indoors have smaller carcinogenic potencies than do the species found out of doors, the population excess lung cancer risk will be substantially lower than the value estimated by ARB/DHS.

If the opposite is true, ARB/DHS should know this before it considers initiating a control phase for nickel. If indoor exposures dominate the risk of lung cancer attributed to nickel, they should be addressed before exterior emission sources are addressed. It would seem to be a great deal more effective for Californians to reduce their exposure to nickel from cigarette smoking and woodburning fireplaces, than to try to reduce emissions to ambient air from oil combustion, soil, etc.

5. DHS HAS IGNORED EVIDENCE OF A PRACTICAL THRESHOLD FOR LUNG CANCER

DHS is being too restrictive in looking for evidence of a threshold for respiratory cancer. Why hasn't DHS discussed mechanisms based on cytotoxicity and mitogenesis? Why must the evidence be mechanistic? Why not consider practical thresholds?

The ICNCM reported a practical threshold of 1 mg Ni/m^3 for soluble forms of nickel and 10 mg Ni/m^3 for insoluble forms of nickel. DHS estimates an excess relative risk of 4.61 for exposures of 1 mg Ni/m^3 in the Copper Cliff Sinter Plant. This concentration is the PEL and TLV for insoluble forms of nickel. Many workers have been exposed to nickel at levels close to this in both the nickel-producing and -using industries. These groups have been subjected to numerous epidemiological studies but no significant risk of lung cancer has been observed, let alon a relative risk of 4.6. There are at least two possible reasons why DHS's

risk assessment does not predict this outcome. First, the forms of nickel to which the workers were exposed may not be the same as the forms of nickel in the Copper Cliff Sinter Plant. (However, the forms of nickel in the producing industry are far more likely to be similar to those in the sinter plant than are the forms in California ambient air.) Second, there may be a threshold. (If no lung cancer risk was observed in these workers, there should be little concern about lung cancer in a California population exposed to nickel concentrations four and five orders of magnitude lower.)

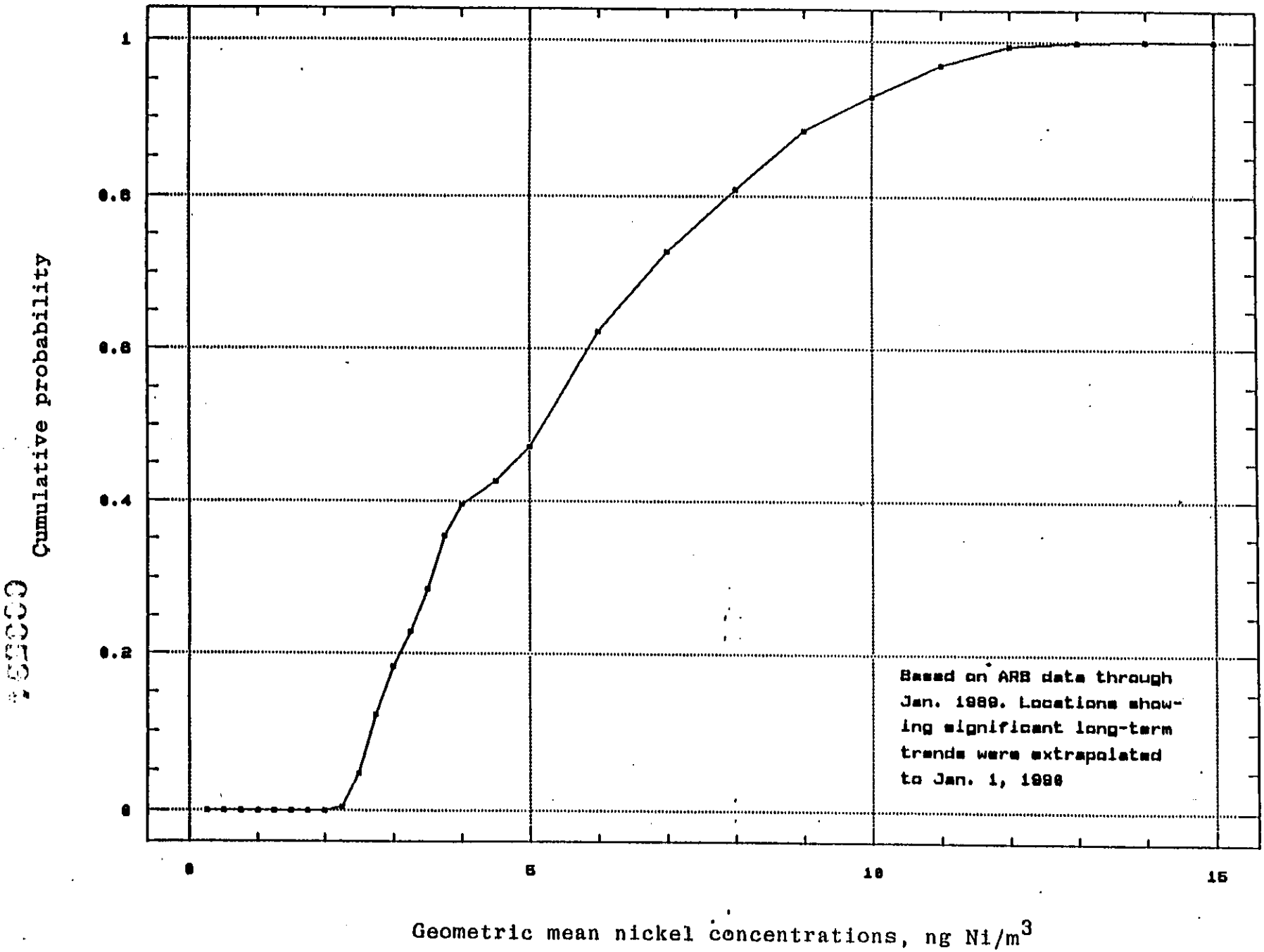
Another possible suggestion of a threshold effect may yet be found within the Copper Cliff Sinter Plant itself by comparing the early hires and late hires (ICNCM, p.52). Although more follow-up is required to resolve this question, the dramatic decrease in lung cancers among late hires (first noticed by Chovil et al.) is very encouraging (OBS=5, (EXP=4.25, 95% C.I. of SMR=38-274), particularly since the concentration of total nickel was still more than six orders of magnitude greater than the population-weighted mean annual concentration in California.

6. *DHS SHOULD AWAIT THE COMPLETION OF THE NTP CARCINOGEN BIOASSAYS BEFORE CONCLUDING THAT ALL FORMS OF NICKEL ARE CARCINOGENIC WHEN INHALED*

DHS has refused to develop risk factors for a number of cohorts described in the ICNCM report because the concentrations of nickel were largely estimated. DHS should be equally skeptical about the conclusions dealing with the carcinogenicity of individual species because the nature of the airborne species was not determined experimentally. The airborne species were simply assumed to be the same as, and generally in the same proportion as, the bulk species handled in the workplace.

The only thing the members of the ICNCM could be sure of was that there was an increased risk of respiratory cancer in certain obsolete nickel refining operations. Every conclusion beyond that involved varying degrees of conjecture because exposures were mixed within individual workplaces and because employees changed work assignments. It would have been difficult enough to divine the truth from the noise even if good data had been available on the relative concentrations of airborne species. (ICNCM, pp.69-72) Instead, the estimates of species and exposures were often made on different bases at different locations. Thus the validity of the semi-quantitative comparisons are questionable.

For this reason, DHS should closely monitor the NTP activity on nickel subsulfide, high temperature nickel oxide and nickel sulfate. These experiments may represent the best opportunity for evaluating the carcinogenicity of these three substances. In turn, this information might make it possible to extract more useful information from the epidemiological data.


Cumulative probability
1
0.8
0.6
0.4
0.2
0
0
5
10
15
Based on ARB data through Jan. 1989. Locations showing significant long-term trends were extrapolated to Jan. 1, 1990
Geometric mean nickel concentrations, ng Ni/m3

NiPERA INC.
Nickel Producers Environmental Research Association

May 3, 1991

Ms. Genevieve Shiroma
Chief, Toxic Air Contaminant
Identification Branch
California Air Resources Board
P. O. Box 2815
Sacramento, CA 95812

Dear Ms. Shiroma:

When NiPERA made its October, 1990, submission to CARB, I trusted that both your Agency and the Department of Health Services (DHS) would carefully consider NiPERA's comments so that CARB's decisions relating to the possible identification and regulation of nickel as a toxic air contaminant would, as required by Section 39650 of the Health and Safety Code, be based on "the best available scientific evidence gathered from the public, private industry, the scientific community and ... [governmental] agencies." Having reviewed both DHS's response to our comments and, as aptly stated by CARB, the "minor changes" that were made to the report in response to the extensive comments sent to CARB/DHS by others, I wonder whether my "trust," and that of others, was misplaced.

The effort put forth by CARB and DHS to consider the comments submitted to the two Agencies appears to be neither serious, nor rigorous. This is unfortunate as many of the comments were thoughtful, insightful and constructive in providing suggestions for improving the Air Toxics Report. The fact that so little time has been provided to respond to Section C of the report and to review the other sections, bespeaks reluctance of the two Agencies to enter into any meaningful scientific dialogue with those outside the State government.

In the brief time allotted for public response, NiPERA has prepared the enclosed submission which I hope will be considered by the Scientific Review Panel (SRP) more carefully than our earlier comments appear to have been considered by CARB/DHS. Of course, I hope that CARB/DHS will review these comments carefully (and reconsider our earlier comments) as well.

Sincerely,

Donna J. Sivulka

Donna J. Sivulka
Executive Director

DJS/cl

Enclosure

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I. INTRODUCTION

NiPERA has provided two sets of comments concerning the California Air Resources Board's (CARB) Proposed Identification of Nickel as a Toxic Air Contaminant. The first submission was made in August, 1990. The second set of comments, which incorporated revisions to the first set, was submitted in October, 1990. In its response to NiPERA's submissions, it appears that CARB misunderstood the revisions that were made in the second set of comments. The following discussion attempts first to clarify these points and then to elaborate upon concerns that NiPERA still has with respect to CARB's risk assessment.

II. POINTS OF CLARIFICATION

1. Estimates of Background Rates

In its August submission, NiPERA incorrectly stated that the lifetime risk of lung cancer for Canadian white males during the period 1965-1979 was 0.029. In our October submission, we rectified this error as evidenced in the table on page 7 of our comments which gives the 75-year lifetime risk for the period 1965-1984 (P_0) as 0.041. A more complete set of estimates for 1965-1979 and 1965-1984 is given below:

Lung Cancer Mortality Risk
Canadian White Males

Age Classification	1965-1979	1965-1984
Up to 75 years of age	3.863×10^{-2}	4.085×10^{-2}
100+ years of age	5.213×10^{-2}	5.671×10^{-2}

These estimates were based on 5-year age- and date-specific lung cancer and all cause mortality rates averaged over the periods of interest. For example, there were 16 age intervals for each of three 5-year time periods between 1965 and 1979. Lung and all cause rates for each of the 16 age classes were averaged across the three time intervals. A conditional hazard function (life-table) approach was used to estimate lifetime risk, based on the rates from the 16 age

intervals. The 1965-1979 100+ year lifetime estimate (0.052) is consistent with the proportionate mortality ratio estimate in Ontario males given by CARB (0.051). In calculations that follow, the age-interval rates used to derive the 75-year (expected lifetime) and 100+ year risks are utilized.

2. Maximum Likelihood Estimation

In its October comments, NiPERA advocated (and continues to advocate) the use of maximum likelihood estimation (MLE), as opposed to weighted least squares. CARB did not use maximum likelihood estimation since it could not resolve the discrepancy between EPA risk estimates derived from maximum likelihood estimation and those obtained from the average relative risk approach. NiPERA determined the reason for this disparity. As indicated on page 2 of our October submission, the reason for the difference was EPA's error in representing the conditional hazards model that the Agency employed, not in calculating the maximum likelihood estimate. The EPA-derived maximum likelihood estimate for the slope of the dose-response curve was correct and, indeed, consistent with that obtained from the average relative risk approach (4.19×10^{-5} vs. 4.89×10^{-5} in the units used by EPA). As these results are easily reproduced, we do not understand why CARB has been unable to do so. In our response, we proceeded to identify the error that was made by EPA in estimating unit risk. As indicated on page 2 of our October submission, the corrected risk estimate based upon maximum likelihood estimation and a conditional hazards model was 1.1×10^{-4}. This estimate is quite consistent with the 8.9×10^{-5} produced by the average relative risk approach.

While there are uncertainties associated with any risk estimation approach, we disagree with CARB's statement "that it is inappropriate to use the EPA model since it is in error and is less scientifically rigorous." This is simply not true. To start, MLE is not a model, nor is it something that EPA developed; it is an estimation technique that appropriately reflects the assumed (Poisson) error structure of the mortality observations. In this way, it is more statistically rigorous than a weighted least squares regression which assumes normality of the regression errors. In addition, the model in question is that of conditional hazards. It is frequently used by risk assessors because of its ability to account for competing mortality risks from other causes. In this way, it is more realistic and rigorous than a simple approach that applies excess relative risk to background mortality rates. Again, this is not EPA's model. To indict the use of this standard model as a result of EPA's misrepresentation of it is not defensible.

III. ISSUES OF CONCERN

1. Chovil et al. vs. ICNCM Data

In its August and October comments, NiPERA indicated that the risks estimated in the Chovil et al. study of the Copper Cliff sinter plant workers were higher than those presented in a more recent report of this cohort that included five additional years of follow-up [International Committee on Nickel Carcinogenesis in Man (ICNCM)]. CARB claims that the risks estimated in the two studies are consistent and, therefore, feels justified in continuing to use the Chovil data. CARB's claim rests in the following argument: "For 5 or more years work at the sinter plant starting prior to 1952 (as did most of the cohort), the ICNCM estimated an SMR of 8.55. The estimate from Chovil for at least 5 years service with the company, some of which was at the sinter plant, was 8.71." Because the two SMRs are of similar magnitude, CARB contends that the estimated risks from the two studies are "consistent."

This comparison is inappropriate since a large proportion of the men that were included in the Chovil analysis were hired after 1951 (216/495= 44 percent). A more appropriate comparison can be obtained by using Chovil's Table 5, in which the SMR for men hired before 1952 is given as 11.36 (O=36, E=3.17). This SMR reflects risks that are over 30 percent larger than those estimated by the ICNCM for men hired during the same period but with 5 years of sinter plant experience (SMR=8.55, O=30, E=3.51). This difference is even more striking given that all of the men in the ICNCM study worked in the sinter plant, while those in the Chovil study may have worked in other (less hazardous) areas of the Copper Cliff Refinery.

CARB correctly indicates that the Chovil study provided a better categorization of men by exposure level than did the ICNCM study. However, the fact that exposure information from the Chovil study is superior to that in the ICNCM does not eliminate CARB's responsibility to consider the ICNCM data, especially in light of a potential 30 percent bias in the risk estimates that drive its risk assessment. This is the reason for our recommendation to obtain the updated raw data on the Copper Cliff sinter plant workers to perform the risk assessment. In its October comments, NiPERA estimated exposure levels for the ICNCM results in order to demonstrate the effect that using the two different cohorts has on the estimation of risks.

2. Lifetime Exposure and Lifetime Risk

In its October comments, NiPERA presented lung cancer risk estimates for a 75-year lifetime (assuming exposure to nickel at 1 $\mu g/m^3$ for the same period). The choice of 75 years was not arbitrary; this was the expected life span for U.S.

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citizens born in 1987. By using this life span, we felt that we were providing a reasonable (indeed, conservative) characterization of risk for the "average" California resident. In its characterization of risk, CARB mixes 70-year ("lifetime") exposure with risks associated with lifetimes in excess of 70 years (all lung cancer deaths/all deaths, irrespective of age). Thus, the excess risks that are estimated by CARB are unconditional, reflecting not only those risks for an expected life span but also for individuals that have exceeded the expected life span. We feel that if 70 years constitutes a "lifetime" exposure, then it follows that 70 years should be used as the "lifetime" for which risk is estimated. If, on the other hand, CARB's intention was to lag the effect of exposures on individuals of more then 70 years of age, then this lag should be consistently incorporated in the risk estimation procedure. At the very least, the difference in lifetime exposure and lifetime risk should be made clear, since the reader of the document is likely to assume that the risks are estimated for a 70-year lifetime.

IV. IMPACT OF ISSUES ON RISK ESTIMATES

The following table compares risk estimates derived under varying assumptions and approaches. Specifically, the difference in estimates based on the Chovil et al. and ICNCM data are provided. The approach to exposure estimation for the ICNCM data is given in our October comments. Admittedly, this approach approximates the exposures, but estimates based on these exposure estimates give a sense of the difference in risks estimated using the two sets of data.

Risk estimates are given for both 75-year and 100+ year lifetimes. Unless otherwise stated, a 70-year exposure was assumed (consistent with CARB approach). Risk estimates are based on both the "best" estimate of the dose response parameter and its upper 95 percent confidence limit. Risks are estimated using maximum likelihood estimates (MLE), with and without conditional hazard (CH) function adjustment. When the conditional hazard function was not used, risk estimates were applied to the P_0s presented in section II.1. Risk estimates also reflect an inflation factor of 1.052 to be consistent with the 5 percent loss-to-follow-up adjustment used by CARB.

Excess Lung Cancer Risks (per 10,000) Associated with
Exposure to 1 $\mu g/m^3$ Exposure for 70 Years

75-year Lifetime

Risk Estimate	Without CH Adjustment			With CH Adjustment		
	Chovil (WLS)	Chovil (MLE)	ICNCM (MLE)	Chovil (WLS)	Chovil (MLE)	ICNCM (MLE)
"Best" Estimate	1.60	1.58	1.02	1.40	1.39	0.90
Upper 95 Percent C.L.	1.94	2.15	1.36	1.71	1.89	1.20

100+ year Lifetime

Risk Estimate	Without CH Adjustment			With CH Adjustment		
	Chovil (WLS)	Chovil (MLE)	ICNCM (MLE)	Chovil (WLS)	Chovil (MLE)	ICNCM (MLE)
"Best" Estimate	2.10	2.09	1.41	1.91	1.90	1.26
Upper 95 percent C.L.	2.57	2.85	1.89	2.33	2.58	1.68

These results indicate the following:

- When unit risks are estimated using identical approaches, the ICNCM-based estimates are 25-35 percent lower than those based on the Chovil et al. results. Although the ICNCM results are based on less precise exposure characterization, the difference is not likely to be due solely to this factor. As indicated above, the difference is likely due to improvement in the estimates of risks in sinter plant workers because of increased follow-up.

- The 100+ year lifetime estimates of increased lung cancer risks are approximately 25-35 percent higher than those of individuals with the expected (75-year) lifetime. Thus, the expected lifetime risk of lung cancer is appreciably lower than that estimated by CARB.

- Maximum likelihood estimation gives similar "best estimates" to those obtained using weighted least squares. MLE variance estimates for the Chovil data are higher than those obtained from weighted least squares. This is due to a more appropriate (Poisson) modeling of the error structure. It is in this way more rigorous than weighted least squares regression.

- Conditional hazards adjustment results in risk estimates that are about 10 percent lower than those resulting from a simple application of excess risk to background mortality rates. The conditional hazard approach is more rigorous in that it reflects the competing mortality risks.

V. UPPER LIMIT FOR THE UNIT RISK ESTIMATE

CARB gives the upper limit of the range of estimated lung cancer risks as 37×10^{-4}. This is based on the Ottolenghi study in which rats were exposed via inhalation to Ni_3S_2. CARB notes that since Ni_3S_2 does "not predominate in environmental exposures" (in fact, CARB never lists Ni_3S_2 as a nickel species likely to be present in the ambient air from any source), "the potency estimate for Ni_3S_2 derived from animal studies would not seem particularly relevant." NiPERA agrees with this statement. Furthermore, we would note that risk estimates obtained on these data are far more uncertain than those obtained from human data as they are derived from many unverified assumptions. In particular, species differences in uptake, metabolism, deposition and retention of Ni_3S_2, or any other nickel compound for that matter, are unknown. In addition, as EPA itself notes, "the concept of equivalent doses for humans compared to animals on a mg/surface area basis is virtually without experimental verification regarding carcinogenic response." Hence, risk extrapolations from rat to man using human equivalent exposures are highly uncertain.

Given the questionable accuracy of risk estimates from animal data and CARB's own admission that the estimate based upon the Ottolenghi study is not "particularly relevant," the repetitive presentation of the estimate as an indication of the "upper range" of cancer risks is inappropriate. The limitations noted above are only briefly mentioned once in the document. Thereafter, they are ignored and the "upper range" is presented without explanation. By the time the estimate is reported in the Executive Summary (the document that is most likely to be widely distributed and read), there is no indication that the estimate is even based upon animal data and represents a 95 percent upper confidence bound. NiPERA feels that presentation of this number is misleading and unduly alarming to the general populace. Discussion of it is purely academic and should be confined to Section 7.1.5. of the report.

VI. CONCLUSION

Based on epidemiologic data, CARB has estimated excess lifetime lung cancer risks associated with 70 years of continuous 1 $\mu g/m^3$ Ni exposure to range from 2.10×10^{-4} to 2.57×10^{-4}. Using more complete epidemiologic data (30 percent more follow-up) and more rigorous statistical methodology (maximum likelihood

estimation/conditional hazard model approach), increased risks for a 100+ year lifetime are estimated to be in the range of 1.26×10^{-4} to 1.68×10^{-4}. Excess risks for an expected lifetime (75 years) are estimated to be in the range of 0.90×10^{-4} to 1.20×10^{-4}.

The demonstrated disparity in the risk estimates using the two different data sets warrants CARB's further attention. The message that CARB consistently conveys in this report is that its estimate is "good enough" because it is easy to calculate and based upon an available, albeit outdated, published study of sinter plant workers. We believe the more recently published information on this group of workers (with 30 percent more follow-up) potentially provides more accurate and reliable estimates of the workers' lung cancer risks. To be sure, the raw data would have to be obtained on these workers to get a more accurate assessment of their exposures. However, we do not think it unreasonable for CARB to take the extra initiative required to acquire this information particularly since, once the data are obtained, the unit risk number could be recalculated without great effort. Therefore, NiPERA continues to recommend acquisition of the updated data set for risk and exposure assessment. We also recommend more realistic characterization of "lifetime" risks and increased statistical rigor in the analysis.

C23603

D. WARNER NORTH
THIRTY SKYWOOD WAY
WOODSIDE, CALIFORNIA 94062

May 3, 1991

Genevieve Shiroma, Chief
Toxic Air Contaminant
Identification Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Attn: Nickel

Dear Ms. Shiroma/Members of the Scientific Review Panel:

The SRP should review very carefully the scientific issues in the proposed listing of nickel in all chemical forms as a toxic air contaminant. While IARC has recently chosen to classify nickel compounds as Group 1 and metallic nickel as 2B, both EPA and the Proposition 65 Scientific Advisory Panel have chosen to classify as carcinogens only selected nickel compounds.

I was a member of the Environmental Health Committee of the EPA Science Advisory Board at the time of their review of the draft version of *Health Assessment Document for Nickel and Nickel Compounds* (EPA/600/8-83/012F, September 1986). Subsequently, as a member of the California Governor's Scientific Advisory Panel (SAP) for Proposition 65 I had responsibility for recommending to my colleagues on the SAP whether SAP should recommend listing nickel compounds as known to the State of California to cause cancer. The applicable pages (197-219) from the transcript of the SAP meeting of August 28, 1987 are attached. (I have corrected some obvious transcript errors by hand). Based on the recommendations of the SAP, nickel refinery dust from the pyrometallurgical process, nickel carbonyl, and nickel subsulfide were added to the Governor's Proposition 65 List on October 1, 1987. Although in the transcript the SAP chairman discussed returning to nickel oxide to

consider its listing at a later date, I do not believe nickel oxide was subsequently discussed during the remainder of my term on the SAP.

At the August 28, 1987 meeting representatives of the California Department of Health Services recommended that all divalent nickel compounds be listed. I opposed this recommendation, on the grounds that SAP had adopted, as its criteria for listing, a determination of sufficient evidence in animals or in humans using the EPA *Guidelines for Carcinogen Risk Assessment*, and that this criteria should be applied on a substance-by-substance basis.

It is my impression from a cursory reading of the Technical Support Document (TSD), *Proposed Identification of Nickel as a Toxic Air Contaminant* (Scientific Review Panel Version, April 1991) that very little new scientific information on the carcinogenicity of nickel has emerged since the EPA *Health Assessment Document for Nickel and Nickel Compounds* and the SAP meeting of August 1987 (TSD, Part B, p. 90). The evidence that "points to ionic nickel (Ni^{+2}) as the ultimate toxic agent of the various nickel compounds" (TSD, Part B, P. 90) is essentially the same as was available to EPA and SAP. This nickel ion hypothesis is based mainly on in vitro studies plus animal studies indicating that many nickel compounds induce tumors at the site of injection. Inhalation studies have shown evidence of carcinogenicity only for nickel subsulfide and nickel carbonyl. Direct confirmation of the carcinogenicity of other nickel compounds through inhalation bioassays has not yet been obtained. Significant new information should become available soon from the inhalation bioassays that have been carried out by the National Toxicology Program on nickel oxide, nickel sulfate, and nickel subsulfide.

Occupational exposure in nickel refineries has caused respiratory cancer. The issue is what species of nickel compounds are responsible. The TSD cites (p. 142) a paper by J.S. Warner of Inco as the "main source of information" on the form of nickel present at the Copper Cliff sinter plant in the Ontario refinery. This same individual submitted extensive comments that are included in Part C of the TSD. The comments on his pages 37-38 (Part C p. 240-41) merit careful consideration. Nickel subsulfide appears to constitute at least 35% of the nickel refinery dust on the two days for which assays were available, and a significant amount of

nickel-copper oxide may have been present as well. These two substances are potent experimental carcinogens (Warner cites Sunderman for this characterization of nickel-copper oxide). Therefore, one or both of these substances could be the agents responsible for the observed respiratory cancer; organic agents could have contributed significantly as well.

The support for the conclusions on page 143 of Part B of the TSD seems quite weak. There is no basis for inferring from the epidemiological data that other nickel species, such as nickel oxide or nickel sulfate, are carcinogenic. The carcinogenicity of nickel oxide and soluble nickel salts at the same potency level as nickel subsulfide has been assumed based on "prudence" and some limited evidence from in vitro studies and injection bioassays. The use of total nickel as a surrogate for nickel subsulfide (and perhaps nickel-copper oxide) may not just "slightly overestimate cancer risks." (TSD, Part B, p. 142, line 24-25). According to the last sentence of TSD, Part A, p. A42, "It is generally assumed that most of the atmospheric nickel (especially from combustion sources) is present as nickel oxides." Nickel subsulfide may therefore not be present in California air, and the cancer risk estimates derived from the Ontario sintering plant cohort may therefore be gross overestimates of cancer risk in California. The cancer risk from nickel species in the California air could be zero, because the carcinogenic species that caused the occupational respiratory cancer are not present in ambient California air.

I urge the members of the SRP to consider carefully the basis for IARC's listing of nickel compounds and compare it to the criteria that SRP has used previously in recommending substances as toxic air contaminants. Then consider whether you should endorse the recommendation of the Department of Health Services and the Air Resources Board to designate nickel and all nickel compounds as toxic air contaminants, or whether at this time only nickel subsulfide, nickel carbonyl, and nickel refinery dust from the pyrometallurgical process should be so designated. The forthcoming results from the National Toxicology Program's bioassays will provide a much better basis for a determination on nickel oxides and soluble nickel compounds than the information and assumptions set forth in the TSD.

I am submitting these comments as an individual. My affiliations are listed below as a matter of information only.

Sincerely,

D. Warner North

D. Warner North
Principal, Decision Focus Incorporated, Los Altos, California
Consulting Professor, School of Engineering, Stanford University
Member, Committee on Risk Assessment Methodology, National Research Council, National Academy of Sciences
President-elect, Society for Risk Analysis
Member, Environmental Health Committee, Science Advisory Board, U.S. Environmental Protection Agency, 1982-1990, currently a consultant to this committee
Member, Governor's Scientific Advisory Panel for the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), March 1987-June 1989
Presidentially appointed Member, Nuclear Waste Technical Review Board, 1989-1994

Okay. The next compound is nickel and nickel compounds.

PANEL MEMBER NORTH: That's again a hand-off to me. And, again, I would like to use the EPA health assessment documents as the basis for my recommendations.

I am going to be quoting from the final version, which is dated September 1986, which was reviewed by the Science Advisory Board, in which I participated. We actually reviewed an earlier version draft of this document. I have the letters from that review that I can make available to the State for the record.

But I would like to summarize the very complicated situation on nickel by reading from the summary of the Health Assessment Document on page ~~210~~ 2-10 and page ~~211~~ 2-11, with respect to EPA's conclusions on the carcinogenic effects of nickel. This will address nickel compounds, as well.

> "There is evidence both in humans and in animals for the carcinogenicity of nickel, at least in some forms. But the human evidence of a cancer risk is strongest via inhalation in the sulfide nickel matte refining industry.
>
> "This evidence includes consistency of findings against many different studies, several different countries; specificity of

tumor site, lung and nose; high relative risk, particularly for nasal cancer; and dose response relationship by length of exposure.

"There are also animal and in vitro studies on nickel compounds which support the concern that nickel, at least in some forms, should be considered carcinogenic.

"The animal studies have employed mainly injection as the route of exposure, some studies using inhalations as exposure route, while the majority of the compounds tested in the injection studies have caused tumors at the injection site only.

"Nickel acetates, when tested in Strain A mice, and nickel carbonyl at toxic levels, have also caused distal site primary tumors.

"The relevance of injection-site-only tumors in animals to human carcinogenic hazard, be it inhalation, ingestion or cutaneous exposure, is uncertain. Orally in animals, three low-dose drinking water studies and one diet study with soluble nickel compounds have not shown any increase

in tumors.

"Thus, nickel, at least in some forms, should be considered carcinogenic to humans via inhalation, though the evidence via ingestion is inadequate.

"Based on analysis of all the available data, there are only three compounds or mixtures of nickel compounds that can be currently as classified as either Group A, known human carcinogens, or B, probable human carcinogens, according to the Environmental Protection Agency's classification scheme for evaluating carcinogens.

"Nickel refinery dust from pyrometallurgical sulfide nickel macrefineries is classified as Group A. The fact that nickel subsulfide is a major nickel component of this refinery dust, along with the evidence of animal in vitro studies, is sufficient to conclude that nickel subsulfide is also in Group A.

"While there is inadequate evidence from epidemiological studies with regard to evaluating the carcinogenicity of nickel

carbonyl, there is sufficient evidence from animal studies to classify it as Group B2.

"The carcinogenic potential of other nickel compounds remains an important area for further investigation. Some biochemical in vitro toxicological studies seem to indicate that nickel ion is a potential carcinogenic form of nickel and nickel compounds. If this is true, all nickel compounds might be potentially carcinogenic with potency differences related to their ability to enter and make the carcinogenic form of nickel available at a susceptible cell.

"However, at the present time, neither the bio-availability nor carcinogenesis mechanism of nickel compounds is well understood."

So the understanding of the nickel ion hypothesis, as has been stated here -- this is a hypothesis for research. It does not qualify as the kind of evidence we want for known carcinogens.

So, in summary, then, we have the refinery dust and the nickel subsulfide as Group A, sufficient evidence in humans; and nickel carbonyl as Group B2, sufficient

evidence in animals.

Now, we went further earlier today with respect to injection sites. And I will try to summarize the information in this document from injection routes for nickel, where there is considerable evidence that I think we might deem sufficient for some nickel compounds; but not for others.

I will turn to page 8-209 of the document, with regard to nickel metal. Let's see. Okay. The summary appears on page 8-113 and that concludes -- or rather EPA's conclusion is: "For nickel metal, tests are presently inadequate to support any definitive conclusions with regard to its carcinogenicity."

Nickel oxide, there were -- it states at the bottom of the page:

> "Nickel oxide was tested to be carcinogenic in five intramuscular injection studies. Tumor incidence ranging from 5 to 93 percent, depending on the dose and species strain of animal used. Nickel oxide was also carcinogenic by intrapleural injections, with activity that approached that of nickel subsulfide."

So there, it would appear we have sufficient evidence.

We go to -- the next category is soluble and sparingly soluble nickel compounds. And the concluding summary is:

"Both soluble and sparingly soluble nickel compounds have the potential to produce tumors in animals, but these compounds have not been adequately tested to support a judgment of their carcinogenicity."

We do not have sufficient evidence there.

So the recommendation, therefore, on nickel is very complicated and substance-specific. I will take my previous quotations from EPA as the basis for the recommendation that the substances I have listed should be included as candidates for the list. So that would be the nickel oxide, the nickel carbonyl, the nickel subsulfide and the refinery dust.

CHAIRMAN KILGORE: Thank you.

I think we are going to have to take a ten-minute break here to give our stenographer a break. We will reconvene in ten minutes.

I hope to conclude nickel and nickel compounds and there are six nitroso compounds that we are going to take up; but these should not take a great deal of time. At 4:20, we will reconvene. Please get in here promptly.

(Recess taken.)

CHAIRMAN KILGORE: Can we reconvene, please. Time is up. Please be seated. Dr. Hooper.

Okay. We will continue our discussion on nickel and nickel compounds. I would like to ask the Panel if any Member has a question they would like to ask of Dr. North. No comments down there.

How about the Health Department? Do you have any comments to make?

Dr. Hooper.

DR. HOOPER: Yeah. I think that the Health Department has not reviewed this chemical or this set of chemicals in-detail, but our position at this -- tentative position is to favor more listing "nickel and nickel compounds," arguing that it's probably the divalent cation that is the causative agent and, in the sense of public health standpoint, err on the side of health protectiveness.

Our concern is that there have been several nickel compounds which are positive, and it's unlikely that all divalent nickel compounds will be tested. So that, by not listing certain chemicals because they haven't been tested and haven't been found to be positive, it gives a false sense of security that they are not carcinogenic.

As I stated, we haven't gone into this examination

in depth, but our initial position would be favor of being inclusive rather than exclusive. We are in favor of listing nickel and nickel compounds.

CHAIRMAN KILGORE: I notice that EPA has two nickel compounds listed, nickel refinery dust and nickel subsulfide.

No other comment.

Any comments from the floor?

You are Frank Scahller?

MR. SCHALLER: Still going by that name, sir, yes. I am Frank Schaller. I'm from Inco, Limited. Inco, Limited is the non-communist world's largest producer of primary nickel products and we are the world's largest supplier of nickel alloys.

The scientific literature and medical literature related to nickel and its compounds is quite extensive. The substance has been used for many years.

While no mention was made of skin administration, in our -- we are not aware of any experimental evidence that nickel causes skin cancer. And workers in our plant and the general public are exposed to nickel in coinage and stainless steel for many years. And if nickel did cause skin cancer, one would think it would have manifested itself. So our conclusion is that nickel does not cause skin cancer.

The United States Food and Drug Administration has listed nickel as generally recognized as safe, since they uncovered no evidence that oral administration of nickel caused carcinogenicity.

The National Institute of Occupational Safety and Health, in its 1977 criteria document on nickel, also concluded that nickel was not an oral carcinogen.

As Dr. North indicated, the U.S. EPA completed an extensive comprehensive review over a period of seven years of activity. It came before the Scientific Advisory Board.

And our company -- we disagree with some of the facts, some of the interpretations of the facts and some of the conclusions presented in the nickel health assessment document of EPA. But we do any think it is the best available summary of the potential health effects associated with the exposure to nickel and its compounds. It is markedly superior to the IARC evaluation of nickel in Supplement 4 and the section on nickel in the NTP's fourth annual report on carcinogens.

One of the conclusions that I would like to mention from that report is that the toxic -- this is the EPA health assessment document -- that toxicity of nickel should be assessed on a species-by-species basis, because the absorption, transport and distribution and excretion

of nickel depend on its chemical form. This was a detailed examination over three years; not, as Dr. Hooper indicated, a casual or less than thorough evaluation.

The relevance of injection site tumors -- this is another conclusion -- in animals to a carcinogenic hazard in humans is uncertain. As I pointed out in my remarks under cadmium, Dr. Thies, from the University of Texas, is pointing out that if you use injection site tumors which do not metastasize to other sites, it's equivalent to flipping a coin.

Therefore, I would disagree with Dr. North's recommendation that nickel oxide be listed by this Panel. There is a negative study, hamster inhalation study on nickel oxide. Why not use that as evidence that it is not carcinogenic?

The EPA also concluded that nickel is not an oral carcinogen. Nickel refinery dust and subsulfide -- we would support the Panel's listing of those as known human carcinogens.

CHAIRMAN KILGORE: That's nickel subsulfide and --

MR. SCHALLER: That's correct.

I just would clarify that not all nickel refineries -- there are none in the U.S. at this time. Not all nickel refineries use pyrometallurgical processes and not all of them treat sulfide ores.

The refinery out in Oregon that has just now closed treated oxidic ores. A study there did not uncover any excess respiratory cancer risks.

So it's a kind of a long thing to say nickel refinery dust from pyrometallurgical sulfide nickel, but that's, indeed, what it is. In fact, a massive epi study of our Ontario division covering a cohort of some 57,000 workers investigated a lot of processes, such as mining, milling of the ore, smelting and so on; and it was only in the calcining and centering of the nickel subsulfide-containing mets where we had elevated cancer risks. Only in that area.

We also would support your using EPA's conclusion -- that nickel carbonyl is a probable human carcinogen, and list that.

We would recommend to the Panel that you use EPA's conclusion, which was that the carcinogenic potential of other forms of nickel, including metallic nickel, nickel oxide, NIO, NI203, nickel sulfate, nickel chloride, nickel acetate and nickel sulfide -- that these remain important areas for further research. In fact, NTP is conducting inhalation studies at the present time on nickel oxide and nickel sulfate. As I mentioned, we do not support the listing of nickel oxide as a carcinogen.

With respect to the metal ion theory, those of you

that have looked in the NTP Fourth Annual Report, when they put out the draft document, there was no mention of nickel ion theory in that, and they called for public comments.

And then they issued the final document and had a paragraph under all of the metals that -- something to the effect that the ion may be the ultimate carcinogen and so and on and so on. So they don't follow the Administrative Procedures Act. But if they did, that certainly would be a violation of that rather shabby way of handling a potentially regulatory listing.

But EPA in its Scientific Advisory Board, and EPA in its document, health assessment document on nickel, rejected the suggestion that all nickel compounds might be potentially carcinogenic simply because they contain the nickel ion. Neither the bio-availability nor the mechanism for carcinogenesis of various forms of nickel are presently understood well enough to confirm this hypothesis.

For example, nickel sulfide, NIS, in crystallographic form, forms injection site tumors. In the amorphous condition, it does not. How does the nickel ion theory explain that?

Metallic nickel forms injection -- these are intramuscular injections -- site tumors. Metallic nickel

forms intramuscular injection type tumors almost 100 percent. Iron 40 percent nickel does not. How does the nickel ion theory explain that?

There are also negative inhalation studies on nickel powders, a couple of them; and one on hamsters on nickel oxide that I mentioned. How does the nickel ion theory explain that? It doesn't. It's just a hypothesis at this stage.

There may be other questions that come up that the Panel would like to address. Unfortunately, most of our experts are out of the country at this time because the Nickel Producers Environmental Research Association had a scheduled meeting which conflicted with this, so they are over in London.

Well, in conclusion, I just would support Dr. North's recommendation that nickel refinery dust -- that's the sulfide refinery dust -- and nickel carbonyl be listed. I would disagree that nickel oxide be listed as a carcinogen; and that the other substances not be listed.

Thank you very much.

CHAIRMAN KILGORE: Can you explain to me why you do not think nickel oxide should be considered a carcinogen.

MR. SCHALLER: Well, it's my understanding -- I may be wrong. Some of you may be more familiar with the experiments than I -- that nickel oxide tumors do not

metastasize. According to Dr. Theis' examination of the IARC monographs where they looked at substances which caused only injection site -- only tumors at the injection site, and were tested by some other route of administration, half of the time those were not -- the injection sites were not predictive of cancer. That's why --

CHAIRMAN KILGORE: They were benign tumors; is that what you are saying?

MR. SCHALLER: Pardon?

CHAIRMAN KILGORE: They were benign tumors?

MR. SCHALLER: No. The tumors were malignant at the injection site; but they were not predictive of carcinogenicity by oral or inhalation or dermal.

CHAIRMAN KILGORE: Were there a consistent number of these in all the experiments they ran?

MR. SCHALLER: Well, I think he looked at -- I would have to go back and look at the paper. I wasn't expecting to be before this committee today.

He looked at 25 or 30 substances, something like that. Again, this is the substances that caused injection site tumors which did not metastasize.

Those are my comments.

CHAIRMAN KILGORE: Dr. Ames.

PANEL MEMBER AMES: I wanted to ask Kim. Kim, wha

is the IARC policy on injection site tumors?

DR. HOOPER: There isn't -- I wouldn't say there is a policy. I thought -- this is inside information. I don't know what to say.

I had less confidence in injection site sarcomas than some of the other people did, who are probably more skilled at animal bioassays.

There is no specific policy. They don't specifically downgrade them. They do mention -- they do, in some sense, downgrade liver hepatocellular carcinomas. They make specific reference in the preamble to it. They Don't downgrade injection sarcomas.

I think the reason is that if you have twelve or fifteen animals and you inject the vehicle, it's zero of fifteen; but if you get twelve of of fifteen of the experimental, they feel that that's a sign of a carcinogenic event.

That's my interpretation.

CHAIRMAN KILGORE: Any other comments from the Panel or the audience?

MR. SCHALLER: I would just like to make one other comment. It was mentioned earlier about the experts being invited to IARC.

I think that anybody who knows anything about nickel toxicology would say that, in this country,

Professor Sunderman of the University of Connecticut knows more about nickel than anybody. His father, a pathologist before him, sort of handed down this and he became a pathologist also.

He was to be invited to that meeting, but then the meeting was held without him. So not always are the renowned experts invited to the meetings.

The other comment I would make is that we have been in nickel industry for some 50 years, and we have had no cases that we know of of injection site tumors in our work force. We do handle a lot of nickel.

MR. HOLZMAN: I am David Holzman, with the Health Department. I would have a few things I would like to add. I will do it as fast as I can.

First, I think that the Panel should be cautioned when it is advised to consider compounds as negative by the oral route. The studies the Department is familiar with have generally been with very low doses of nickel, except for one feeding study, which did show lung pathology in a high dose.

And with regard to the ion hypothesis, a recent review of the nickel literature by Dr. Sunderman did note that various nickel compounds, the subsulfide, the carbonyl, are in the body, oxidized to the plus two form, giving supporting evidence for the ion hypothesis.

I think that, given the evidence that there are plus -- that plus two forms of nickel compounds are carcinogenic, and given the evidence that other forms of nickel are metabolized to plus two form, the panel might do well to consider all nickel plus two compounds as carcinogenic.

I also want to relate, when the Air Resources Board asked the air unit of the Department for advice as to what nickel compounds the Air Resources Board should monitor in the air, it was the Department's opinion, in a memo the Panel received, that the Air Resources Board monitor for total nickel because the Department was unable to differentiate between the various species of nickel in terms of the carcinogenic potency.

Now, in terms of your charge of the Panel under Proposition 65, you may find there are air releases or releases into drinking water. I did want to point out there is high gastrointestinal absorption of nickel, which contrasts with gastrointestinal absorption of other metals.

But you may find there are instances where there are releases into the air of nickel compounds or releases into drinking water of nickel compounds.

CHAIRMAN KILGORE: Can you summarize your remarks and move on.

MR. HOLZMAN: Sure. You may find that the analytical techniques will be unable to tell you what compound it was that was released from a particular facility. And by limiting nickel, limiting your judgment to specific nickel compounds, you may preclude the operation of the Proposition in protecting public health.

CHAIRMAN KILGORE: If we took that attitude, we would put all of the compounds in.

MR. HOLZMAN: I am saying that -- I am saying that, with nickel compounds, there is good enough reason to suspect that all nickel compounds are carcinogenic if they are metabolized to plus two-fold.

CHAIRMAN KILGORE: Any quick comments from the floor? Wait a minute.

Can you make it as brief as possible.

MR. SNYDER: Very brief. My name is Clint Snyder and I'm from IBM Corporation.

We have specifically reviewed the question of soluble nickel compounds, particularly as relates to these types of exposures. And we believe that there is inadequate evidence that soluble nickel compounds are carcinogenic.

In particular, probably the best evidence is the fact that there have been injection site challenges in experiments using soluble nickel compounds, and these have

been negative. This is particularly important, because practically every insoluble compound of nickel, except for the sulfide, as mentioned, when challenged, gives injection site challenges -- gives injection site tumors.

However, challenges with a good dose of nickel chloride, nickel acetate, both give no injection site tumors. From our perspective, this is very good evidence that nickel ~~iron~~ is not carcinogenic, because it seems to be that injection site challenges are a very sensitive indicator of nickel carcinogenicity.

CHAIRMAN KILGORE: Thank you.

MR. HOLZMAN: We have evidence of carcinogenesis at sites distal from the injection site.

MR. SNYDER: Yes. That experiment involves one high dose, 360 milligrams per kilogram IV injection.

PANEL MEMBER AMES: Looking at the data base, nickel acetate was tested in water at relatively high levels, 10 milligrams per kilo per day, and was negative in four different tests.

Anyway, for what it's worth.

CHAIRMAN KILGORE: Any other comments from the Panel?

Dr. North could we go back and hear your recommendation again. As I recall, you recommended we accept nickel oxide, nickel dust, nickel carbonyl and

nickel subsulfide.

PANEL MEMBER NORTH: I think, with nickel dust, we should pull in the full name, because we want to be specific as to where the epidemiology studies were carried out that obtained those positive results. So we want to make sure that it's the pyrometallurgical process, and use the term that I stated when I was quoting from the document.

And with respect to the nickel oxide, that frankly is a judgment call. My recommendation was based on the injection site tumors. If I go to this document, I find there are two pages on nickel oxide injection study listing many studies that have been carried out.

And while I haven't reviewed these studies myself, because I didn't realize until this morning that this was going to be a critical issue, it would appear that in at least five of them, there were fairly substantial tumor incidences.

So I would be prepared, on the basis of looking at this table, to say that, for injection, it would appear that we have sufficient evidence in animals.

However, the EPA document says about nickel oxide, taken together, that the data support the evaluation of nickel oxide as having limited evidence as an animal carcinogen. It is not usually EPA's policy to list

sufficient evidence for animal carcinogens as based on injection site tumors.

If our criteria as this Panel is going to include the injection site tumors, then I think we have to make the call the other way.

But I would welcome illumination from my colleagues on the Panel, such as Dr. Spangler, who has far more experience in this area than I do.

CHAIRMAN KILGORE: Dr. Spangler.

PANEL MEMBER SPANGLER: I am not sure I have such vast experience.

PANEL MEMBER NORTH: Should we perhaps defer this then until the next meeting, with respect to nickel oxide, to give a few of us the chance to review the studies in more detail?

CHAIRMAN KILGORE: That's fine.

PANEL MEMBER NORTH: I want to go on the record as very strongly against the proposal to list all nickel or nickel valence two substances. I think there is a very strong argument that we have to treat them separately, because our criteria is known and sufficient evidence in animals.

It is not the possibility that these other substances may be carcinogens and, therefore, regulatory agencies should act in a prudent manner to protect public

health. Our charter is very different. We are asked to list substances as known carcinogens. And I don't believe we can do that, except where there is evidence in animals supporting such a statement.

DR. STRATTON: Dr. Kilgore, in view of the fact that IARC voted this as sufficient evidence for human carcinogenicity and the fact that our Air Toxics Unit is undergoing thorough review of nickel because of their mandates, rather than taking a partial vote at this time, perhaps we might want to reconsider this as a package.

CHAIRMAN KILGORE: Well, perhaps. But I don't see any reason why we can't talk about individual compounds.

Let me point out again that the CAG list of November 1986 only has nickel refinery dust and nickel subsulfide. So they obviously have suffered through some of these problems also.

So let's go back to your proposal again. You are recommending that we put nickel dust. We will leave nickel oxide out, but we will take nickel subsulfide and nickel carbonyl. We will defer nickel oxide until the next meeting.

MR. HOLZMAN: Did you mention nickel acetate, as well?

PANEL MEMBER NORTH: I didn't make a rcommendation on nickel acetate because EPA did not, and it is not

listed.

CHAIRMAN KILGORE: Any objections to that? Everyone agree to that? Okay. So be it.

The last group of compounds we are going to take up are nitrosamines and nitro-containing compounds. And Dr. Ames is going to review these as a group.

Dr. Ames.

PANEL MEMBER AMES: So N-nitroso-N-methylurea and N-nitroso-N-ethylurea are more laboratory curiosities; they are not environmental chemicals of any interest.

They are clearly quite good carcinogens that show carcinogenesis in a number of animals. I think there is no doubt they should be listed as carcinogens, but they are not terribly interesting.

The whole class of nitrosamines are well-known agents, so people have studied these for a long time.

Nitroso dibutylamine is one of -- is a higher homologue model of nitroso diethylamine, which is a more interesting compound. It also is a clear-cut carcinogen in a number of species; no doubt about that. That also is not really very interesting. This is just more laboratory curiosity.

Nitroso methylamine has been used as an anti-cancer agent.

Then the more interesting compounds are

nitrosodiethylamine and nitrosodimethylamine and nitrosopyrrolidine. The nitrosodimethylamine is a very widespread carcinogen. It's a product of nitrite reaction with dimethylamine. Fish have lots of trimethylamine that becomes dimethylamine, and the nitrite will react with that to make diethylnitrosamine. That's been shown to be a carcinogen in a very large number of studies of animals. And nitrosodiethylamine has also been shown to be a carcinogen in a large number of studies.

People are interested in these as human carcinogens, as well, because of several studies, which I won't go into in detail. So the only thing I would like to say is, I suspect that they are quite common in cooked food, because they can also be made, in addition to nitrite reacting with amines, they can be made from NO2 reacting with amines.

NO2 is fairly widespread. Wherever you have a gas flame, you are making NO2. My current hypothesis is that gas ovens are big source of nitrosamines. Gas ovens have a high concentration of NO2. You get lots of nitrosamines in your food. There was a Japanese paper where somebody cooked some squid in different ways, when he cooked it over a gas flame, that nitrosamine content went way up.

These are very potent carcinogens on the list I pointed out before. Nitrosodiethylamine, ten micrograms

per kilo, is ten times less potent than aflatoxin in the major leagues.

Nitrosodimethylamine is 100 micrograms per kilo. Another factor, nitrosodimethylamine is ten times more potent than ethylene dibromide, for example. You find levels of these things all around the place, look, wherever there is nitrite around and some food.

So I think there is no doubt that they are all carcinogens and I suggest we call them all carcinogens.

One last thing. Loren Zeis, who was here before, maybe in the back, had done a big -- she works for the State Health Department -- has done a big compendium of dose response on nitrosodimethylamine, the most thorough studies for any chemical, going down to fairly low doses.

The curve looks like something like this. It bends off quite sharply, but at the lower end, it looks kind of linear. It's certainly not linear over the whole. It folds down sharply. That's one of the chemicals we have been able to do dose response on. If you took linear from the top, you would be way off.

CHAIRMAN KILGORE: Any additional comments from the Panel?

Health Department?

Any comments about the nitroso compounds? Comments from the floor?

I assume then the consensus of opinion is that all these nitroso compounds should be considered as carcinogens and put on the list. To make it appropriate, I will say dibutylnitrosamine, diethylnitrosamine, dimethylnitrosamine, N-nitroso-N-ethylurea, N-nitroso-N-methylurea, N-nitrosopyrrolidine.

We will assume all these compounds will be put on list as reported carcinogens. I would like to apologize for not being able to get any further on our agenda today. But I think it has been well worth the time we spent on it.

I would like to apologize to some of you who came to make presentations that we can't get to today. We sure will get to you next meeting.

The meeting is adjourned.

(Whereupon, the meeting adjourned at 4:45 p.m.)

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REPORTER'S CERTIFICATE

STATE OF CALIFORNIA)
)
COUNTY OF SACRAMENTO)

I, JAN L. BENEDETTI, certify that I am a Certified Shorthand Reporter for the State of California and that I reported verbatim in shorthand writing the foregoing proceedings; that I thereafter caused my shorthand writing to be reduced to typewriting, and the pages numbered 1 through 222 inclusive, constitute a full, true, and correct record of said proceedings.

AGENCY: Safe Drinking Water and Toxic Enforcement Act of 1986 Scientific Advisory Panel

DATE: Augst 28, 1987

IN WITNESS WHEREOF, I have subscribed this certificate in Sacramento, California on this 15th day of September, 1987.

Jan L. Benedetti
CSR No. 4643

II.

Air Resources Board Staff Responses to Summarized Comments on the Draft Part A and the Executive Summary

A) Gene's Plating Works,(GPW), May 3, 1991.

1) **COMMENT:**

GPW feels that the 1.4 tons per year estimate for nickel platers was not based on scientific methods but was supplied by metal plating companies participating in the industry survey compiled by SCAQMD in 1985. This data has no validity and CARB and DHS have no other valid data to indicate emissions of soluble nickel by the electroplating industry into ambient air.

RESPONSE:

We agree that data obtained from the plating industry are preliminary. On page A7 and A11 of the report we reported the results of the SCAQMD survey adding that these emissions may be declining because of the nationwide decline in nickel electroplating. We added several sentences saying the survey provides preliminary information and that the actual emissions may be up to ten times lower (Personal Communication w/Industry Representatives, May 1991).

2) **COMMENT:**

The report suggests that besides nickel carbonyl other forms of nickel may find their way into the atmosphere. Can we continue to regulate on "maybe's" and "what ifs"?

RESPONSE:

Since the DHS and ARB are recommending total nickel be identified as a toxic air contaminant, quantifying the exact species emitted into the air is not essential to identification. Also, the Health and Safety Code in section 39650 states "while absolute and undisputed scientific evidence may not be available to determine the exact nature and extent of risk from toxic air contaminants, it is necessary to take action to protect public health."

3) **COMMENT:**

The GPW questions the inclusion of electroplating industry as one of the minor sources of nickel emissions.

000636

RESPONSE:

We agree that the contribution of electroplating industry to total nickel emissions could be small. However, we have listed all sources and their estimated emissions regardless of their relative contribution.

4) **COMMENT:**

The GPW felt that the two weeks given for a second comment period was inadequate.

RESPONSE:

We believe that the comment period allowed for this report is reasonable. There will also be a 45 day comment period before it goes to the Board and in the risk management phase there will be many opportunities to participate in workshops and comment periods on proposed control regulations.

B) Pacific Gas and Electric, (PG&E), May 3, 1991

1) **COMMENT:**

PG&E believes that ARB/DHS should not proceed with the SRP review of the nickel report until the public is given at least a 30 subsequent day comment period to prepare comprehensive comments on the "soluble nickel" addition.

RESPONSE:

See the response to Comment A4.

2) **COMMENT:**

PG&E believes that the ARB should not identify total nickel as a toxic air contaminant until the conclusions of the National Toxicological Program (NTP) will be published.

000037

RESPONSE:

Nickel is listed as a Hazardous Air Pollutant (HAP) by the new federal Clean Air Act and the Board is required to identify it as a toxic air contaminant (Health and Safety Code Section 39655). The NTP study will provide animal data which will not supercede human findings of the report. In addition the date of publication is unknown. If new information becomes available the public can request the ARB, DHS and SRP to review the risk assessment.

C) Calidria, May 6, 1991.

1) **COMMENT:**

In the Introduction, p.A1, you list asbestos mining and milling as a major source. Calidria feels that asbestos mining and milling should be listed only as a minor source of nickel emissions, or not listed as a source at all.

RESPONSE:

Asbestos mining and milling will be listed in the report as a minor source of nickel emissions.

2) **COMMENT:**

Calidria questions the use of 4500 lbs in Appendix IV as the estimated asbestos emissions from mining. One facility, which may have been a major contributor to the 4500 lbs/year estimates, discontinued operations in December 1987.

RESPONSE:

These asbestos emissions from mining came from the data provided after Calaveras Asbestos Ltd. was closed, therefore the estimated 4500 lbs/year are for Calidria only. However, we recognize that mining emissions differ from year to year and we will revise Appendix IV to indicate the 4500 lbs estimate was for 1987.

3) **COMMENT:**

The nickel emissions from mining and milling are overestimated; based on our estimates nickel emissions from Calidria would be less than 0.0005 tons per year.

000038

RESPONSE:

The nickel emissions estimates for 1987 are based on the asbestos emissions for the same year (see Appendix IV pg.7). Therefore, see the previous response regarding the estimate of 4500 lbs of asbestos for 1987.

D) INCO LIMITED, May 3, 1991

1) COMMENT:

The TSD (Technical Support Document) fails to satisfy the intent of the California legislators that the identification of toxic air contaminants "should utilize the best available scientific evidence" (Health and Safety Code, section 39650(d)).

RESPONSE:

In preparing the TSD the staffs of the ARB and DHS used the best scientific evidence available. The Health and Safety Code, section 39650(e) states "That while absolute and undisputed scientific evidence may not be available to determine the exact nature and extent of risk from toxic air contaminants, it is necessary to take action to protect public health."

2) COMMENT:

Even though nickel is a hazardous air pollutant (HAP) and must be identified as a toxic air contaminant (section 39655), the EPA has not identified any form of nickel as a HAP. Instead, nickel was simply designated as such by the Congress along with almost 200 other chemicals and groups of chemicals.

RESPONSE:

Contrary to Dr. Warner's assertion, California Health and Safety Code, section 39655 states clearly that "Substances which have been identified as hazardous air pollutants pursuant to Section 7412 of Title 42 of the United States Code shall be identified by the state board as toxic air contaminants." Nickel and nickel compounds are hazardous air pollutants pursuant to section 12 of the new Clean Air Act (42 U.S.C. section 7412) and as such "shall be identified....as toxic air contaminants."

000033

3) COMMENT:

The ARB/DHS response to many first-round recommendations and comments, the limited scope and severely limited time allowed for commenting on the revised drafts and reference to section 39655 suggest that ARB has made up its mind about identifying nickel as a toxic air contaminant.

RESPONSE:

Nickel has been in the review process since 1987 and both Parts A and B go significantly beyond the charge in Health and Safety Code section 39660 to provide information about exposure and health effects. In addition, in preparing the Technical Support Document the ARB and DHS provided two comment periods and a workshop and significantly modified the document per those comments. Although this report is currently being reviewed by the Scientific Review Panel, any action to identify nickel as a toxic air contaminant will be done at a public hearing before the Board.

4) COMMENT:

ARB has made mistakes in processing and presentation of the nickel data from the Toxic Air Contaminants Network. These include:

a) failure to use all of the available data

RESPONSE:

The ARB staff compared the 1985-1986 data (the basis of the population weighted estimate) with the 1987, 1988 and 1989 data from the network. The results showed no statistically significant changes between the mean nickel concentrations for 1986 and those of 1987, 1988 and 1989.

b) failure to recognize statistically significant temporal trends at seven of the sampling locations

RESPONSE:

As stated in our previous responses to the first comment period (pg. C18)....Analysis of data from the toxics air contaminant monitoring network indicates that nickel concentrations have increased at some locations and decreased at others. Therefore, no long-term statewide trend in the nickel concentrations has been identified.

000612

c) mixing normal and lognormal statistics in the treatment of the data

RESPONSE:
As stated in our previous responses to the first comment period (pg. C18)...Because of the characteristics of the overall nickel data we believe the data should not be treated as being normally distributed. The staff report has been revised to clarify this and all the references to data being distributed lognormally have been removed from the report.

d) making arithmetic errors in the calculations leading to Table II-2 notably in the standard deviations for the San Francisco Bay and San Joaquin Valley air basins

RESPONSE:
We are unaware of what method Dr. Warner used to calculate the standard deviations and we were unable to substantiate the existence of the errors.

e) incorrectly plotting the values displayed in Figure III-2

RESPONSE:
The commentor does not give the specific values which he believes to be incorrectly plotted; the data in the figure are plotted to approximate values and the staff were unable to locate the specific errors.

f)losing information by averaging monthly means instead of averaging the raw data

RESPONSE:
Since some of the raw data are missing from the data set the monthly means were deliberately averaged to obtain an average of the sites (our 20 monitoring sites are used to estimate a statewide exposure) and subsequent statewide average; no information was lost.

g) using an unexplained and apparently unnecessary statistical procedure (i.e."bootstrapping"), etc.

RESPONSE:
The Bootstrap Method is a well-recognized robust statistical method for estimating variability when there is no identified distribution to the data.

C00041

5) COMMENT:
Table III-2 contains only four of the six values in Table III-4. It is not clear where the other two values came from.

RESPONSE:
Table III-4 contains the mean concentrations of the data: Table III-4 contains the population-weighted exposure estimate. We added the sentence on pg. A23 to clarify the differences.

6) COMMENT:
The population-weighted mean calculated from these data should be 7.1 not 7.3 ng Ni/m3 as shown; using all the basin means from Table III-2, the population-weighted mean is 6.7, not 7.3 ng Ni/m3.

RESPONSE:
The commentor used a different method of calculating the population-weighted means and used different data for the population calculation. For this reason, he got different numbers. The method used in the report is appropriate, and both methods resulted in similar means.

7) COMMENT:
When calculating the statewide population-weighted geometric mean concentration it appears to be about 5.2 ng Ni/m3.

RESPONSE:
As stated in our previous responses to the first comment period (pg. C20)....The nickel concentration data are not lognormally distributed. The geometric mean is a parameter for identifying a lognormal distribution and therefore was not used.

8) COMMENT:
There were some terminology errors in the report describing the forms of nickel released into the ambient air. The ARB and DHS should not be confused the terms "oxidic nickel" and "complex oxides of nickel" with the term "nickel oxide".

RESPONSE:
An appropriate change will be made on pg. A3.

9) COMMENT:
Until the ARB/DHS complete its study of indoor concentrations of nickel and of the nickel species in indoor air, it cannot make a reliable estimate of the excess risk of lung cancer for a lifetime in California. If the species of nickel found indoors have smaller

C00612

carcinogenic potencies than do the species found outside, the population excess lung cancer risk will be substantially lower. If indoor exposure dominate the risk, they should be addressed before exterior sources are addressed.

RESPONSE:
California Health and Safety Code section 39660 requires only that we demonstrate exposure, health effect and consider whether the compound has a threshold. Also, since DHS and ARB are proposing that total nickel be identified, speciation of either outdoor or indoor air is unnecessary. Any consideration of control is a risk management decision and not appropriate to the identification phase.

III.

Department of Health Services Staff Responses to Summarized Comments on the Draft Part B

DEPARTMENT OF HEALTH SERVICES (DHS)
STAFF RESPONSES TO PUBLIC COMMENTS
ON THE APRIL, 1991 (FINAL)
HEALTH RISK ASSESSMENT FOR NICKEL
AND THE TECHNICAL SUPPORT DOCUMENT (TSD)
FOR THE PROPOSED IDENTIFICATION OF NICKEL
AS A TOXIC AIR CONTAMINANT
PREPARED FOR CONSIDERATION BY THE SCIENTIFIC REVIEW PANEL ON MAY 15, 1991

Comments from the Nickel Producers Environmental Research Association, Inc. (NiPERA)

1. Comment: NiPERA submitted two sets of comments on earlier drafts of the proposed identification of nickel as a toxic air contaminant. These were dated August, 1990, and October 1990. The second set of comments incorporated revisions to the first set of comments. These comments were not considered seriously. In addition, DHS and ARB (Air Resources Board) staff misunderstood some revisions. For example, the first set of comments stated that the lifetime risk of lung cancer for Canadian white males was 0.029, and the October comments corrected this to 0.041. [This commenter apparently would have liked DHS staff to use the background lifetime lung cancer risk suggested in its second set of comments.] (NiPERA submittal dated May 3, 1991 (enclosure) pages 1-2).

Response: DHS staff considered all of NiPERA's comments and responded separately to each set of NiPERA comments, in Part C of the TSD. Secondly, a new estimate of background lung cancer rate is now used in the TSD's risk assessment. This new background rate is specific to residents of Ontario, rather than to Canadian white males generally. This changed the estimate from 0.049 to 0.051. NiPERA's own estimate is now 0.052, so there is good agreement.

2. Comment: NiPERA's October comments identified the reason for a discrepancy between U.S. Environmental Protection Agency (EPA) risk estimates and those obtained from the average relative risk approach. This commenter questions why DHS/ARB staff have not been able to reproduce the EPA results (NiPERA, pp. 1-2).

Response: A consultant to DHS contacted the EPA concerning the discrepancy. EPA could not reproduce its own estimates. Part of the problem stems from the computer programs used.

3. Comment: This commenter now offers a "more complete set" of background lung cancer risk values for Canadian white males (NiPERA, pp. 1-2).

Response: See response 1 above.

4. Comment: This commenter (1) continues to advocate use of maximum likelihood estimation (MLE) as opposed to weighted least squares, and (2) disagrees with the statement that "it is inappropriate to use the EPA model since it is in error and is less scientifically rigorous." EPA erred in representing the conditional hazards model that it employed, but did not err in using MLE. MLE is more statistically rigorous than the weighted least

squares method. The conditional hazards model is more realistic and rigorous than a simple approach that applies excess relative risk to background mortality rates. (NiPERA, pp. 2-6).

Response: The difference between the results obtained using weighted least squares and MLE estimation for a regression analysis is very small. Statistical packages are available to do the weighted least squares analysis.

5. Comment: The data in the International Committee on Nickel Carcinogenesis in Man (ICNCM) (1990) report which include 5 more years of follow-up of the Chovil et al. cohort should be used by DHS/ARB for the risk estimates. The comparison by DHS/ARB of the Chovil et al. (1981) analysis and the International Committee on Nickel Carcinogenesis in Man (ICNCM) (1990) report is inappropriate, since a large proportion of the men included in the Chovil et al. analysis were hired after 1951. DHS/ARB staff contend that the estimated risks from the two studies are "consistent" and therefore feel justified in continuing to use the Chovil data (SMR from ICNCM was 8.55, SMR from Chovil was 8.71). Nevertheless, a comparison using data for men hired before 1952 reveals risk estimates over 30% higher than that obtained from the ICNCM report (NiPERA, pp. 3-5). The fact that exposure information from the Chovil et al. study is superior to that in the ICNCM report does not eliminate DHS' responsibility to consider the ICNCM data (NiPERA, pp. 3-5).

Response: As discussed in Parts B and C of the TSD, staff reviewed and considered the ICNCM data. The Chovil data were chosen for the risk analysis because measured exposure estimates were available for a sufficiently early time period. The ICNCM report does not include more exposure measurements. If the staff had unlimited resources and time, every conceivable analysis could be presented in the report. Even if such an analysis was done estimated risks would likely fall within the DHS or EPA range of risks. The best value would still be based on the Chovil paper since the exposure data are better. DHS staff have considered the ICNCM data, and do not believe that risks estimated from the ICNCM data would be considerably different than those estimated from the Chovil data.

6. Comment: In their characterization of risk, DHS/ARB staff mix 70-year "lifetime" exposure with risks associated with lifetimes in excess of 70 years. If 70 years constitutes a "lifetime" exposure, then it follows that 70 years should be used as the "lifetime" for which risk is estimated. If the intent was to lag the effect of exposures on individuals over 70 years old, then this lag should be consistently incorporated in the risk estimation procedure. Any difference in lifetime exposure and lifetime risk should be made clear (NiPERA, p. 4).

Response: DHS staff have used standard methodology in the risk assessment which is to estimate lifetime cancer risks. Seventy years is a reasonable estimate of the average life span in the population. Background rates which are based on lifetables that extend to all age groups reflect the experience of persons who live longer than 70 years and those whose lives are shorter. Since the average life span is considered to be 70 years, the average exposure is considered to be 70 years. It is indeed true that cancers may

be observed in individuals over 70 years old and that these may (or may not) be due to exposure prior to reaching age 70. Therefore, it would not be appropriate to consider, as background rates, population mortality experience only up to age 70.

7. Comment: Risk estimates from animal data are of questionable accuracy. DHS/ARB staff give a value derived from the Ottolenghi et al. (1974) study in rats as the upper limit of the range of estimated lung cancer risks. The repetitive presentation of this estimate as an indication of the "upper range" of cancer risks in inappropriate. The limitations of this estimate are only briefly mentioned once in the document (and by the time the estimate is reported in the Executive Summary there is no indication that the estimate is based upon animal data and represents a 95% upper confidence bound). Presentation of the estimate is misleading and unduly alarming to the general populace. Discussion of it should be confined to Section 7.1.5 of the report (NiPERA, p. 6).

Response: The Department often uses animal data to estimate potential human risks. The Ottolenghi et al. (1974) study was reasonably well-conducted and is adequate for risk assessment purposes. The EPA used this study for estimating the risks to nickel subsulfide and calculated risks similar to those calculated by DHS. In this case DHS staff believe that the human data give the best estimates of risk. However, the animal estimate is a valid one and appears to represent the upper end of the range of risk estimates from exposure to nickel compounds; staff do not agree that the discussion of it is misleading or alarming to the general public.

8. Comment: More complete epidemiologic data and more rigorous statistical methodology give different risk estimates than those reported by DHS/ARB staff. This commenter continues to recommend acquisition of an updated data set for the risk assessment. This commenter also recommends more realistic characterization of "lifetime" risks and increased statistical rigor in the analysis (NiPERA, p. 6-7).

Response: See responses to comments 3, 4, and 5, above.

Comments from Gene's Plating Works (GPW)

1. Comment: This commenter disagrees with the conclusion that all nickel compounds should be considered potentially carcinogenic to humans by inhalation. No data in the document justify including soluble forms of nickel or those used by the metal finishing industry (e.g. nickel chloride and nickel sulfate) as potentially carcinogenic. Several statements in the document seem to reinforce this point of view. This commenter understands that there is a great deal of data that is not favorable to the document's conclusion and has not found its way into the document (GPW, May 3, 1991, p. 1).

Response: The TSD's conclusion is largely a result of information submitted by commenters during the comment period. Several of the commenters indicated that the 1990 ICNCM and IARC reports should be considered in the

health effects document. The conclusion of these reports as discussed in the document is that soluble nickel compounds are human carcinogens. DHS staff have evaluated the available data and agree with this conclusion.

2. Comment: The document indicates that inhalation is the only route of concern, that there is no inhalation data on soluble nickel, and that DHS staff question the carcinogenicity of soluble nickel salts. Therefore, soluble nickel should not be considered until and unless more data are presented (GPW, p. 1).

Response: Inhalation data for soluble nickel compounds in humans are presented in the cited reports by ICNCM and IARC. The commenter admittedly quotes selectively from the TSD, and may have misunderstood the basis for its conclusions. Evidence cited in the ICNCM and IARC reports indicates that soluble nickel compounds are carcinogenic in humans.

3. Comment: All consideration of nickel as a toxic air contaminant should be delayed until the report of a comprehensive study by the National Toxicology Program is available (GPW, p. 2).

Response: Although it would be useful to have the National Toxicology Program studies, it is unlikely that the animal study findings would supersede risk estimates from studies in humans. In addition, it may be several years before the NTP study report is issued.

4. Comment: In addressing a public comment, DHS staff note that they cannot respond without using "unsubstantiable assumptions." Whenever and wherever it suits their purposes, DHS staff use such assumptions (GPW, p. 2).

Response: Although the commenter believes that "unsubstantiable assumptions" cloud the risk assessment, the results of human studies, animal studies, and genotoxicity studies point to a strong and clear risk from nickel compounds. All risk assessments must rely on assumptions. The assumptions DHS uses are standard assumptions used by EPA, DHS, and other regulatory agencies. In this case, the data used to estimate risk are derived from studies of exposed humans. The risk assessment requires fewer assumptions regarding extrapolation than are required for risk assessments based solely on animal data.

Comments from the Pacific Gas and Electric Company (PG&E)

1. Comment: The proposal to provide a single unit risk estimate for all nickel comments is not health protective. Separate unit risks should be provided for nickel subsulfide or nickel refinery dusts versus other nickel. Assuming that all nickel compounds pose the same risk will underestimate the nickel subsulfide risks. This commenter included suggested methods for calculating a range of risk estimates for "other nickel" (PG&E, May 3, 1991, pp. 1-2).

Response: It is currently not possible to estimate the risks from various nickel compounds and adequate data are not available for estimating exposure to different nickel compounds in the ambient air. This area invites future

study. Although the unit risk provided in the TSD may in the future be shown to underestimate the carcinogenicity of some nickel compounds or overestimate that of others, it would not be protective of public health to take no action now in the hope that new compound-specific information will be available in the future.

2. Comment: The Copper Cliffs sinter plant subcohort should only be used to evaluate risks from nickel subsulfide. A more representative cohort should be selected to evaluate other nickel or total nickel exposure risks. DHS has based its total nickel risk estimate on a study of the one subcohort yielding the highest SMR, without seriously evaluating how different nickel species ratios might have contributed to those differences. This commenter disagrees with DHS' contention in Part C of the TSD that the sinter plant subcohort was the "best" available. A larger cohort, with exposures more like those expected in ambient air, would be better. DHS should use the ICNCM report to pick separate cohorts for risk assessment of several subclasses of nickel compounds, or to adjust the risk estimates obtained from the sinter cohort to the different proportions of various nickel compounds in ambient air. In this regard, DHS staff should note a comment on an earlier draft of the TSD previously submitted by another commenter (PG&E, pp. 2-3).

Response: Quantitative speciated exposure to various nickel compounds is not available from any existing epidemiologic study, precluding more exact depictions of risk. There is no way at this time to differentiate the risks posed by various nickel compounds from the epidemiologic data. The Copper Cliffs sinter plant subcohort involved exposure to nickel oxide and nickel subsulfide and has the best defined exposure data for quantitative risk assessment. It is for this reason that this group was chosen for the analysis. The ICNCM report implies that soluble compounds may be more potent. In the opinion of DHS staff the variability in the observed SMRs does not correspond to specific compound types. The variability can be due to other factors such as the lack of exposure information at the other facilities.

3. Comment: The Executive Summary should note that the risk varies with the type of exposure, and is relatively inconclusive at exposures well above those expected to occur in California. A specified passage should be included at a particular place in the Executive Summary (PG&E, p. 4).

Response: DHS staff do not agree with the paragraph proposed for inclusion in the Executive Summary by this commenter. There are methodological reasons for not finding elevated risks at lower exposures in worker studies, (such as the statistical power of the studies). Furthermore, data are not available to clearly separate the potency of sulfidic and oxidic nickel. The ICNCM report indicates that evidence exists for the carcinogenicity of soluble nickel compounds, and that soluble nickel exposure enhances risks associated with insoluble forms of nickel. The report also states that the role that sulfidic nickel exposure played in inducing the high lung and nasal cancer risks found in the refineries is somewhat unclear, primarily because high concentrations of sulfidic nickel were found in association with high levels of other nickel species including oxidic and soluble nickel.

4. Comment: The ARB should not proceed with the identification as toxic air contaminants of nickel compounds other than nickel subsulfide, nickel carbonyl, or nickel refinery dust, until it utilizes the results of the NTP bioassays on nickel sulfate and green nickel oxide. This commenter supports certain comments on an earlier draft of the TSD previously submitted by another commenter, and suggests that they bear on this issue (PG&E, pp. 4-5).

Response: The Department proposes the identification of all nickel compounds due to the conclusions presented in the recent IARC monograph and due to the association of nickel sulfate exposure with human cancer in the ICNCM report. In addition, both soluble and insoluble nickel compounds are carcinogenic in animals or mutagenic in a wide variety of genotoxicity assays. Regarding the NTP bioassays, it is unlikely that the animal study findings would supersede the findings from studies in humans. In addition, it may be several years before the NTP study report is issued. DHS staff have already addressed the previously submitted comments supported by this commenter (see Part C of the TSD).

5. Comment: The use of cohort data should not exclude exercising sound judgement. In this regard, this commenter supports certain comments on an earlier draft of the TSD previously submitted by another commenter. In considering certain data, it should be clear that using the Copper Cliffs sinter plant cohort for risk assessment of nickel subsulfides and another cohort (either the non-sinter plant cohort or the total cohort) for all other nickel compounds would be far more realistic than the current DHS assumption that all nickel is equally hazardous (PG&E, pp. 5-6).

Response: Please see response to comment 2 above.

Comments from D. Warner North

1. Comment: This commenter has participated in the consideration of nickel carcinogenicity by the EPA and the California Governor's Scientific Advisory Panel (SAP) for the implementation of Proposition 65. The evidence for carcinogenicity of nickel compounds and the evidence that the TSD suggests points to ionic (divalent) nickel as the ultimate genotoxic agent of the various nickel compounds is essentially the same as the evidence that was available to the EPA (in 1986) and the SAP (in 1987) when they each decided to classify only selected nickel compounds as carcinogenic (D. Warner North, May 3, 1991, pp. 1-2).

Response: The data presented in the 1990 IARC monograph and in the 1990 ICNCM report represent a more comprehensive picture of nickel compounds than was available to the EPA and the SAP. With Supplement 7 of the IARC Monographs, in 1987, the international agency classified nickel and nickel compounds in Group 1 (carcinogenic to humans) based on sufficient evidence for carcinogenicity in humans and sufficient evidence for carcinogenicity in animals. The monograph stated, "It is still not possible to state with certainty which specific nickel compounds are human carcinogens and which are not." It also noted that "the risk is particularly high in those exposed during certain processes, mainly entailing exposure to nickel subsulphides and oxides". In its 1990 reassessment of the data, IARC states

that there is sufficient evidence in humans for the carcinogenicity of nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry. In its overall evaluation IARC states that nickel compounds are carcinogenic to humans (Group 1), and that metallic nickel is possibly carcinogenic to humans (Group 2B). One important point here is that new evidence recently available indicates that nickel sulfate, a soluble nickel compound, is carcinogenic to humans.

The EPA has not yet changed its classification of nickel compounds with respect to carcinogenicity nor has it reevaluated its potency factors for nickel subsulfide and nickel refinery dust. Dr. Steven Bayard of the EPA has informed DHS staff that the EPA does not have resources allocated to nickel at this time, and that he believes EPA should revisit nickel, primarily because of the IARC and ICNCM publications.

2. Comment: The support for the conclusions regarding the carcinogenicity of various nickel species on page 143 of the TSD's Part B appears to be quite weak. There is no basis for inferring from the epidemiological data that nickel species such as nickel oxide or nickel sulfate are carcinogenic. The carcinogenicity of nickel oxide and soluble nickel salts at the same potency level as nickel subsulfide has been assumed based on "prudence" and some limited evidence from *in vitro* studies and injection bioassays. Although the TSD suggests that the use of total nickel as a surrogate for nickel subsulfide may "slightly overestimate cancer risks" (Part B, page 143), the risk estimates derived from the Ontario sintering plant cohort may be gross overestimates of cancer risks in California (North, p. 3).

Response: This comment misrepresents the discussion in the TSD. The discussion, revolving around a hypothetical situation, states that if the elevated cancer rates seen in the Ontario study were solely due to nickel subsulfide, the potency estimate given in the TSD would underestimate nickel subsulfide's potency. It would be an overestimate of the potency of the nickel found in ambient air, because nickel subsulfide constitutes a small proportion of ambient nickel. The paragraph concludes that, in this hypothetical situation, the potency estimate given in the TSD would overestimate the actual cancer risks. It would probably be better to say that since environmental nickel exposure involves very low proportions of nickel subsulfide, the general effect would be to substantially overestimate cancer risks. It should be noted, again, that this discussion only relates to a hypothetical case.

The conclusions found on page 143 regarding the carcinogenicity of various nickel species are not based solely on epidemiological data or "prudence" and limited *in vitro* and injection bioassay data. Rather, the weight of available evidence, of all types, indicates that to protect public health, all nickel compounds should be considered potentially carcinogenic by inhalation. The document makes this point in the last paragraph on page 143. The word "prudent" is used in the last sentence of the first full paragraph on that page with regard to nickel oxide and nickel subsulfide. Given the weight of evidence that identifies nickel compounds as carcinogens, and the lack of evidence to clearly differentiate their carcinogenic potencies, it is indeed prudent public health policy to consider all nickel compounds as similarly carcinogenic by inhalation.

The limitations of the available data were considered by DHS staff. Although, as noted, some data regarding uptake and bioavailability suggest that soluble divalent nickel compounds might be less bioavailable (and thus less potent carcinogens) than easily phagocytized particles of insoluble compounds, it is not clear that this data is relevant to human inhalation exposure to ambient concentrations. Data from *in vivo* studies involving intratracheal instillation, inhalation, and i.p. as well as i.m. injection were considered for the discussion on pages 142-143. DHS staff considered all available data, including the report of the International Agency for Research on Cancer, before recommending that all nickel compounds be considered potentially carcinogenic to humans by inhalation.

This commenter was probably unfamiliar with the recent IARC monograph and the ICNCM report. The association of nickel sulfate exposure and cancer in humans reported in these documents has modified the scientific opinion on the nature of nickel compounds as a whole. Thus, the conclusion drawn by DHS is not solely for the sake of prudence, but is based on scientific evidence.

3. Comment: The forthcoming results from NTP bioassays will provide a much better basis for a determination of whether to identify nickel oxides and soluble nickel compounds as toxic air contaminants than the information and assumptions set forth in the TSD (North, p. 3).

Response: The forthcoming studies by NTP may definitely shed additional light on the potency of various nickel species. However, the results may not be available for years. Furthermore, it is unlikely that even negative results from the animal bioassays would contradict the positive findings in humans.

Comments from Inco Limited (Inco)

1. Comment: The revised TSD fails to satisfy the intent of the California legislators that the identification of toxic air contaminants (TACs) should utilize the best available scientific evidence. Although Section 39655 of the Health and Safety Code (HSC) requires nickel and nickel compounds to be identified as TACs (because they have been identified as hazardous air pollutants under the federal Clean Air Act), it does not negate the requirement to use the best scientific evidence (Inco, May 3, 1991, cover letter, p. 1).

Response: DHS has considered all available scientific evidence reported in the literature and that submitted to the Department or ARB. The Department has based the risk assessment in the TSD on what it believes is the best study available.

2. Comment: How can DHS justify its prediction that the carcinogenic potencies of all nickel compounds are the same? DHS notes in Part B of the TSD that "there is insufficient data to quantitatively predict the relative carcinogenic potency of specific nickel compounds" (Inco submission ["Comments on the revised technical support document titled Proposed Identification of Nickel as a Toxic Air Contaminant," May 3, 1991], p. 2).

Response: The underlying mechanism of nickel carcinogenicity appears associated with the nickel moiety. A wide variety of nickel compounds have been shown to be carcinogenic including nickel subsulfide, nickel carbonyl, nickel sulfate, metallic nickel and nickel oxide. The range of risks reported for various nickel compounds appear to span a factor of 20, which is well within variability for a single compound. Furthermore the data do not clearly show a carcinogenic potency distinction among the various forms of nickel.

3. Comment: Since DHS concludes in the TSD that nickel oxide is unlikely to be more potent than nickel subsulfide and that soluble compounds are likely to be less potent than insoluble compounds, for exposures involving nickel oxide and/or soluble nickel compounds, ARB/DHS should apply a risk factor smaller than that derived for the sinter plant workers. The oxidic nickel in typical California air is present as complex oxides. Since such nickel is likely to be considerably less toxic than pure nickel oxide, the risk factor should be reduced still further (Inco, pp. 3-4).

Response: If clear data were available indicating a potency distinction among the various forms of nickel, the Department would consider incorporating the information. As indicated in the document, this is an area of suggested future research. Incorporation of smaller factors for certain compounds in the absence of information would be bad policy and would tend to suppress development of such information.

4. Comment: DHS is being too restrictive in looking for evidence of a threshold for respiratory cancer. Why does the TSD not discuss mechanisms based on cytotoxicity and mitogenesis, and why must the evidence be mechanistic? Why not consider practical thresholds? The ICNCM report put forth practical thresholds of 1 mg Ni/m^3 for soluble forms of nickel and 10 mg Ni/m^3 for insoluble forms of nickel. DHS estimates an excess relative risk of 4.61 for exposures of 1 mg Ni/m^3 in the Copper Cliff sinter plant. Many workers exposed to nickel at levels close to this have been subjected to numerous epidemiological studies, but no significant risk of lung cancer has been observed, let alone a relative risk of 4.6. DHS' risk assessment does not predict this outcome; possible reasons for this include (1) that the forms of nickel to which the workers were exposed may not be the same as the forms of nickel in the Copper Cliff sinter plant, and (2) there may be a threshold. Certain data from within the sinter plant itself suggest a threshold effect, although more follow-up is required to resolve this question (Inco, pp. 4-5).

Response: The commenter refers to a statement in the ICNCM report as indicating a practical threshold. The ICNCM report does not call these practical thresholds but rather states that in the cohorts studied which showed excess lung cancer, exposures were greater than 1 mg/m^3 for soluble nickel compounds and greater than 10 mg Ni/m^3 for insoluble compounds. There are methodological limitations in epidemiology which may preclude measuring risks at lower levels of exposure because of the limited power of the studies. The ICNCM report indicates that risks below 1 mg Ni/m3 would be very small. The risk estimated by the Department for ambient air, approximately 2 in one million, is relatively small compared to the risks estimated for other pollutants evaluated in the Toxic Air Contaminants

Program, and is certainly much smaller than risks of the occupationally exposed.

5. Comment: DHS should await the completion of certain NTP bioassays before concluding that all forms of nickel are carcinogenic when inhaled. DHS now assumes that the ambient airborne species of nickel are the same as, and generally in the same proportion as, the bulk species handled in the workplace. The ICNCM report suggests that based on current data, the validity of semi-quantitative comparisons are questionable. Thus DHS should closely monitor NTP activity on nickel subsulfide, high temperature nickel oxide, and nickel sulfate; this might make it possible to extract more useful information from the epidemiological data (Inco, p. 6).

Response: The current data indicate that all nickel compounds are likely to be carcinogenic to humans. The available data for various forms of nickel do not provide convincing evidence of a wide variability in potency. DHS staff will continue to follow the progress of the NTP studies, but need not wait for their completion to find that all nickel compounds are likely to be carcinogenic when inhaled. Unless new data provide adequate information to attribute various potencies to different forms of nickel, DHS staff will continue to recommend a single potency value for all nickel compounds.

Comments from members of the
Metal Finishing Association of Southern California

The following comments were received verbally at a meeting on Friday, May 10, 1991.

1. Comment: Electroplaters generally use only two nickel compounds, nickel chloride and nickel sulfate, both of which are soluble. Why does DHS recommend that soluble nickel compounds be identified as carcinogens by inhalation?

Response: As discussed in the responses to several written comments above, DHS staff have based this recommendation on up-to-date data including the recent IARC and ICNCM reports that point to soluble nickel compounds as being carcinogenic by inhalation.

2. Comment: Why does DHS suggest that all nickel compounds are not carcinogens by ingestion, when there is evidence suggesting that soluble nickel compounds are absorbed from the gastrointestinal tract and may be carcinogenic or genotoxic?

Response: The TSD does not imply that nickel compounds are not carcinogenic by the oral route. The document does not pass judgement on this route. The TSD's risk assessment is explicitly meant to address risks upon inhalation of nickel compounds. The document does not consider the oral route mainly because there is inadequate data on carcinogenicity of nickel compounds by ingestion.

3. Comment: The hypothesis that insoluble nickel is more bioavailable than soluble nickel seems farfetched.

Response: We have reviewed the scientific literature and summarized what data are available on this issue. Some data indicates that the ability of nickel ions to enter cells may be limited, while particles of insoluble nickel compounds may be phagocytized. (These data are not extensive and their relevance to pulmonary exposure to airborne concentrations of nickel is not known.) Once inside a cell, it is thought that particles of compounds that are generally insoluble may slowly release nickel ions, and that these ions may exert carcinogenic effects within the cell. The pH inside phagosomes of macrophages and neutrophils ranges from 3.4 to 4.0. The acidic environment in these vesicles and similar vesicles in other cells may contribute to the release of ions from "insoluble" nickel compounds. In general, the ions of concern are divalent (2+) nickel ions. Nickel in other valence states is thought to be converted to the divalent form within the body.

4. Comment: The TSD's Executive Summary should mention that the NTP bioassay report is coming.

Response: The report summarizes available data. The Executive Summary relates to the document and its findings, rather than to anticipated data or study reports. As indicated above in responses to several written comments, were the NTP findings available today, they would probably not substantially alter the conclusions reached in the TSD. Realistically, the NTP report will probably not be issued for several years.

5. Comment: The Executive Summary should perhaps note that most of the health data are based on nickel from combustion sources and not non-combustion sources like metal plating.

Response: There is health data on a variety of nickel compounds, not just those arising from combustion. DHS staff feel that the Executive Summary does not need to specify the proportion of the health data that was obtained with compounds associated with particular types of sources. As a whole, the health data indicate that all nickel compounds may be carcinogenic when inhaled. The TSD's assessment of the carcinogenic risk associated with expected airborne concentrations of nickel does not find nickel from different sources to pose different unit risks. It possible, however, that emissions from metal plating operations give rise to smaller exposures than do emissions from some other sources.