PART C - PUBLIC COMMENTS AND RESPONSES

REPORT TO THE SCIENTIFIC REVIEW PANEL ON CHLORINATED DIOXINS AND DIBENZOFURANS

Monsanto

Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167
Phone: (314) 694-1000

July 10, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Attention: Dioxin
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

Monsanto is hereby submitting comments on the health effects and exposure assessments for "dioxins", now under consideration by the Air Resources Board.

Much of what we have to say is based on recent information. It is presented here only in summary form because the time allowed for comment proved too short for us to develop comments in appropriate depth. More detailed comments will follow.

Both the health effects and exposure assessments described in the "Report to the Scientific Review Panel on Chlorinated Dioxins [sic] and Dibenzofurans" contain assumptions that we now know to be incorrect. These assumptions overestimate the possible risk from these materials in the air by at least a factor of 100.

In the exposure assessment, all the many chlorodibenzodioxin and -dibenzofuran species are assumed to be equally biologically active. This is known not to be correct, and is contrary to both the recommendations contained in the health effects assessment and practices of U.S. EPA's Chlorinated Dioxins Working Group. In addition, the exposure assessment appears to assume that PCDD's and PCDF's emitted as vapor from incinerators condense and become biologically available as the particulate-bound PCDD/PCDF's are. This assumption is also incorrect: at the low concentrations found, the di- through hexachloro CDD's/CDF's in the vapor phase will tend to remain there and be photodegraded. The first assumption causes biologically relevant exposure to be overestimated by at least 50 times; the effect of the second is hard to ascertain without more information than presented in the report. Contrary to what was stated, it is possible to separate particulate-bound and vapor-phase PCDD/PCDF's; two recent publications describe such experiments.

Although the "Overview" section does not describe these conclusions, the "Risk Assessment" section describes as scenario 3 (pp. 10-22 ret seq.) the relative hazard estimation proposed by EPA's Chlorinated Dioxin Working Group. A position more "conservative than this is not scientifically defensible.

Sincerely,

James D. Wilson, Ph.D.
Planning & Information Director
Environmental Policy Staff

/dkr
cc: Mr. R. Barham
Toxic Pollutants Branch
Attention: Dioxin
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

STATE OF CALIFORNIA GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

August 16, 1985

James D. Wilson, Ph.D.
Planning and Information Director
Environmental Policy Staff
Monsanto Company
800 N. Linbergh Blvd.
St. Louis, MO 63167

Dear Mr. Wilson:

Your letter of July 10, 1985 concerning Report to the Scientific Review Panel on Chlorinated Dioxins and Dibenzofurans has been reviewed. Comments pertaining to Part B have been forwarded to the Department of Health Services. They will prepare responses to your comments which we will include along with your letter in Part C of the revised report. Monsanto will receive the revised report when it is submitted to the Scientific Review Panel.

Some comments in your letter pertained to Part A of the report. In particular, you raised the issue of Photodegradation of chlorinated dioxins and dibenzofurans. Chlorinated dioxins and dibenzofurans in the vapor phase are thought to be susceptable to photodegradation in the atmosphere. Laboratory studies have shown that chlorinated dioxins and dibenzofurans in the vapor phase can be degraded in sunlight. Unfortunately, no studies, to our knowledge, have been conducted documenting the rate and extent of photodegradation in the real world environment. In the absense of hard data on the significance of photodegradation of chlorinated dioxins and dibenzofurans in the atmosphere, we assumed no photodegradation in the risk assessment. This assumption was made to provide maximum protection of public health. If you have information on atmospheric photodegradation of chlorinated dioxins and dibenzofurans which you believe would be of value to us, we would be very interested in reviewing it.

Thank you for your comments.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: Peter Venturini, ARB
Raymond Neutra, DHS

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July 11, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Attention: Dioxin
Air Resources Board
1102 Q Street
P. O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

We appreciate the opportunity to present comments upon the Air Resources Board and Department of Health Services draft reports on polychlorinated dibenzo-p-dioxins (dioxins) and polychlorinated dibenzofurans (furans). We also appreciate both agencies' efforts to protect the health and welfare of the people of California.

The experts with whom we have consulted, particularly L. D. Attaway, Ph.D., agree with the finding that dioxins and furans should be listed as toxic air contaminants. The restriction to dioxins and furans with four to seven chlorine atoms per molecule, with the lateral 2, 3, 7 and 8 positions occupied by chlorine atoms, appears reasonable to them based upon information available at this time. However, the experts recommend that these restrictions be made conditional at this time, until more complete results on the health effects of all of these substances make a more definitive declaration possible.

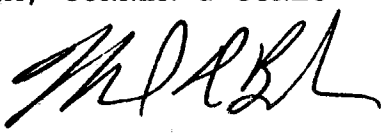
Further, even though we agree with your final determination, the experts believe that you have considerably underestimated the health threat posed by dioxin and furan emissions from municipal solid waste (resource recovery) incinerators. Because these incinerators are likely to be the principal source of these toxic air contaminants, we believe that it is important to evaluate their impact as accurately as possible at this time. We have therefore enclosed with this letter a discussion by Dr. Attaway of recommended amendments to the ARB and DHS analyses which we believe will improve its overall results.

In that discussion, Dr. Attaway refers to a Swedish Environmental Protection Agency moratorium on the construction of new MSW incinerators. Since English translations of these announcements may not already be available to you, we also enclose copies of such translations for your use.

Thank you again for this opportunity. We hope these comments are useful in your continuing work on dioxins and furans.

Very truly yours,

McKENNA, CONNER & CUNEO

By 
Michael D. Berk

MDB:lk
Enclosures

cc: L. D. Attaway, Ph.D.

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RECOMMENDED AMENDMENTS TO ARB/DHS DIOXIN/FURAN ANALYSES

L.D. Attaway, Ph.D.

1. EMISSION RATES

The upper limits on emission rates used in this analysis are too low for both dioxins and furans. In Appendix B to Part A are presented a table giving a "Quantitative Determination of PCDDs in Airborn Particulate and Flue Gas Condensate from Municipal Incinerators", and a similar table for PCDFs. These emission rates are the same as those presented in ARB reference (1), except for an error for PCDF #3, which should be 1.4416 $\mu g/Nm^3$. If these results are complemented with those in references (2, 3), and all emission rates are converted to standard physical conditions, then the following emission range, and average emission rate, result:

	PCDD & PCDF Emission Rate	
	$\mu g/m^3$	$lb/10^6 BTU$
Lowest	0.2	2.2×10^{-7}
Highest	56.0	617.0×10^{-7}
Average	7.7	85.0×10^{-7}

Table 1 - Emission Rate Range in Literature

Because of current controversy over the actual formation mechanism and location (combustion or post-combustion) (2, 3), it is not possible to specify where in this range mass-burn incinerators will operate. However, ARB has chosen for this analysis an upper limit of 8.8 $\mu g/m^3$ (page 4 of Appendix A to Part A). Further, the ARB has stated (page 1 of Appendix A to Part A) that their lower limit "should be considered as the most reasonable scenario" and their upper limit "as the worst plausible scenario." Nothing in the literature we have reviewed leads to this conclusion, and we recommend that an upper limit near 56.0 $\mu g/m^3$ be used in this analysis and represented as just as likely as the lower limit used.

2. SIGNIFICANT PATHWAYS

The ARB/DHS analyses do not consider pathways from MSW incinerators to man other than the direct inhalation pathway. On page III-6 of Part A this narrow focus is based upon previous analyses which allegedly showed other pathways were insignificant relative to direct inhalation. However, more careful evaluation of these pathways leads to a contrary conclusion. In the case of the North County Associates (4) assessment of hand-to-mouth ingestion and skin

absorption via hands of indoor dusts, that analysis failed to reflect the number of times that the human (especially infant) hand touches down on contaminated surfaces. When this is properly reflected (e.g., 100 such touchdowns per day) the following table results (Table 4-5 on page 46 of (5), extended here):

PATHWAY	MAXIMUM UPTAKE (mg/kg/day)		PERCENT OF TOTAL UPTAKE	
	1 Touchdown/Day (NCRRA Results)	100 Touchdowns/Day (Amended Result)	1 Touchdown/Day (NCRRA Results)	100 Touchdowns/Day (Amended Result)
Direct Inhalation	1.0×10^{-10}	1.0×10^{-10}	51.9	2.27
Ingestion				
Soil	3.8×10^{-11}	3.8×10^{-9}	19.8	86.2
Diet	5.7×10^{-12}	5.7×10^{-12}	3.0	0.13
Water	4.4×10^{-11}	4.4×10^{-11}	22.8	1.00
Dermal Absorption	4.6×10^{-12}	4.6×10^{-10}	2.4	10.4
Total Uptake	1.93×10^{-10}	4.41×10^{-9}	100.0	100.0

Table 2 - Estimated Maximum Uptake of Dioxins and Furans By Various Pathways

As can be seen from Table 2, appropriate reflection of the number of hand touchdowns per day completely reverses the relative importance of the direct inhalation and soil ingestion pathways as evaluated by the NCRRA model. We do not necessarily hold with the results of Table 3 -- for example, the ingestion by diet analysis is also inadequate -- but we are simply emphasizing that the ARB should not dismiss other pathways based upon these other analyses. Please also see reference (6) for a review of the Brooklyn Navy Yard analysis.

We would recommend that the ARB address the pathways (originating with air emissions) shown in Table 3 below with screening models to determine their relative importance. Those which remain as possibly significant should then be subjected to a more full-blown analysis. The Swedish Environmental Protection Agency (7) has recently imposed a one-to-two year ban on the construction of new MSW incinerators, largely because of foodchain contamination by dioxins and furans; so these pathways should not be rejected out-of-hand.

3. HIGH-TO-LOW DOSE EXTRAPOLATION

Although the multi-stage model used in the DHS analysis (Part B) for extrapolating from high to low doses is usually more conservative than other models, in this case it was not for 2,3,7,8-TCDD. Even so, it was used by the DHS in its risk assessment. We suggest it would be more appropriate to use the more conservative Weibull model results.

1. DIRECT INHALATION

2. INHALATION OF RESUSPENDED INDOOR DUST AND OUTDOOR SOIL

3. INGESTION OF DEPOSITIONS TO INDOOR DUST AND OUTDOOR SOIL

4. DERMAL ABSORPTION OF DEPOSITIONS TO INDOOR DUST AND OUTDOOR SOIL

5. FOOD CHAIN:

   - DEPOSITION ON ANIMAL FORAGE FOODS
   - DEPOSITION ON SOILS NEAR FORAGE FOODS
   - CONTAMINATION OF SURFACE AND GROUNDWATERS
   - CONTAMINATION OF FOOD PROCESSOR PRODUCTS
   - DEPOSITION ON HUMAN FOOD CROPS

Table 3 - Pathways of Possible Concern for Air Emissions

4. CARCINOGENIC MECHANISM FOR 2,3,7,8-TCDD

2,3,7,8-TCDD is suspected of being both an initiator and a promoter of cancer (page 10-2 of Part B). Both aspects of its carcinogenicity should be reflected in the DHS risk assessment. For one approach to treating 2,3,7,8-TCDD promoter effects, see reference (6).

5. NON-CANCER AND SYNERGISTIC EFFECTS

The above recommended treatment of 2,3,7,8-TCDD as a promoter (as well as an initiator) of cancer addresses a synergistic relationship between 2,3,7,8-TCDD and other carcinogens. Its is therefore appropriate to consider at least this synergism between 2,3,7,8-TCDD and other substances.

On page 10-1 of Part B it is stated: "Therefore, there is a safety factor of over 1000 incorporated in Longstreth and Hushon's ADI. The airborne concentration necessary to give an exposure equivalent to the ADI is approximately 0.33×10^{-2} nanograms of 2,3,7,8-TCDD per cubic meter. This ADI is near or above the highest exposure level projected by the ARB for PCDDs and PCDFs (see Section 10.4 and Part A)." The ADI referenced here is 1 pg/kg/day.

However, the maximum exposure level projected by the ARB for PCDDs and PCDFs is 1.3×10^{-2} ng/m^3 (page III-3 of Part A) or 3.94 times the above equivalent exposure. Since the safety factor of 1000 has been introduced by Longstreth and Hushon in order to be conservative, it is not appropriate to use its inclusion in the ADI as grounds for ignoring the possibility of toxic effects. Furthermore, when maximum expected emission rates for PCDDs/PCDFs are increased to reflect their possible range (see item 1 above), when possible underestimates of ambient concentrations are amended (see item 6 below), and when ambient concentration uncertainty due to PCDD/PCDF sources other than MSW incinerators is reflected (see item 7 below), ambient concentrations will be even higher.

At these ambient concentrations consideration of synergisms between PCDD/PCDFs and other pollutants becomes appropriate. At the very least, the additivity approach suggested by EPA (8), ACGIH (9) and NSF (10) should be used (summation of ratios of ambient concentrations to acceptable ambient concentrations and comparison with unity). The minimum set of other pollutants which should be considered are those emitted by MSW incinerators. A partial list is shown in Table 4 (4); please note that the majority of the organics and metals in Table 4 are currently under consideration by the ARB for listing as toxic air contaminants (11)--indicated with an (*) in Table 4. The list in Table 4 should be extended as appropriate to include all the air pollutants now ARB candidates for listing under the AB1807 program; these are shown in Table 5 (11), with those emitted by MSW incinerators underlined.

ORGANICS

Polycyclic Aromatic Hydrocarbons (PAH)*
Polychlorinated Biphenyls (PCB)*
Polyvinyl Chloride (PVC)*
Polychlorinated Dibenzo-p-Dioxins (Dioxins)*
Polychlorinated Dibenzofurans (Furans)*

METALS

Carcinogens
- Arsenic*
- Beryllium*
- Cadmium*
- Chromium*
- Nickel*

Others
- Antimony
- Copper
- Mercury*
- Molybdenum
- Manganese*
- Lead*
- Selenium
- Tin
- Vanadium
- Zinc

CRITERIA POLLUTANTS

Sulfur Dioxide (Plus Sulfates)
Nitrogen Dioxide
Carbon Monoxide
Hydrocarbons
Ozone (Precursors Emitted)
Particulate Matter

Table 4 - Toxic Air Pollutants Emitted
By Municipal Solid Waste Incinerators (4, 11)

*On List Of Compounds To Be Considered By California Air Resources Board As Toxic Air Contaminants Under AB 1807.

LEVEL 1A

Asbestos	Formaldehyde
Benzene	Inorganic Arsenic
Cadmium	Nickel
Carbon Tetrachloride	Polycyclic Aromatic Hydrocarbons (PAH)
Chloroform	Polychlorinated Biphenyls
Chromium	Dioxins
Ethylene Dibromide	Furans
Ethylene Dichloride	Vinyl Chloride
Ethylene Oxide	

LEVEL 1B

Inorganic Lead	Perchloroethylene
Manganese	Radionuclides
Methyl Cloroform	Trichloroethylene
Methyl Chloride	

LEVEL 2

Acetaldehyde	p-Dichlorobenzene	Nitrobenzene
Acrolein	Dialkyl Nitrosamines	Nitrosomorpholine
Acrylonitrile	1,4-Dioxanes	Phenol and Chlorinated
Allyl Chloride	Epichlorohydrin	Phenols
Benzyl Chloride	Hexachlorocyclo-	Phosgene
Beryllium	pentadient	Propylene
Chlorobenzen	Maleic Anhydride	Oxide
Chloroprene	Methyl Bromide	Vinylidene Chloride
Cresol	Mercury	Xylene

Table 5 - California Air Resources Board Candidates For Listing As Toxic Air Contaminants (11)

NOTES:
(1) Level 1: Considered of Concern And For Which Sufficient Information Exists To Pursue Listing
Level 2: Considered To Be of Potential Concern

(2) Underlined Substances Emitted by MSW Incinerators.

6. EMISSION CHARACTERISICS

It would appear that some of the emission characteristics for the nine sources may need clarification. For example, in the ARB memorandum on diffusion modeling for the present study (Table 1 of [12]) the Irwindale facility is given a stack height of 107 meters. However, the stack is to be located on the bottom of an abandoned quarry above the lip of which the stack reaches only 45.7 m (13). It is not clear whether or not this condition has been reflected in the ARB diffusion modeling; if not, its amendment will lead to significant increases in ground level concentrations. Further, the simple downwash/turbulence routines used in the ARB diffusion analysis are probably inadequate in this complex situation. Other emission parameters also appear to be different for this facility.

7. SENSITIVITY/UNCERTAINTY ANALYSIS

There is great uncertainty in the data and models employed in this analysis by the ARB and DHS. It is therefore essential to perform a careful sensitivity/uncertainty analysis of the overall final results in order to fully understand their meaning. We recommend this be done by describing the uncertainty (distributions) of each major variable, and then combining these analytically or via Monte Carlo techniques to assess the overall uncertainty. The uncertainty introduced by not being able to include sources other than MSW incinerators, as well as already existing human tissue, mothers' milk and foodchain burdens (14), should be addressed.

REFERENCES

1. California Air Resources Board, Air Pollution Control at Resource Recovery Facilities. 24 May 1984.

2. Center for the Biology of Natural Systems, The Origin and Methods of Controlling Polychlorinated Dibenzo-p-Dioxin and Dibenzofuran Emissions from MSW Incinerators. Queens College, CUNY, Flushing, N.Y. For presentation at Air Pollution Control Association Annual Meeting, Detroit, MI., 2Ø June 1985.

3. Center for the Biology of Natural Systems, Environmental and Economic Analysis of Alternative Municipal Solid Waste Disposal Technologies, Volume II: The Origins of Chlorinated Dioxins and Dibenzofurans Emitted by Incinerators that Burn Unseparated Municipal Solid Waste, and An Assessment of Methods of Controlling Them. Queens College, CUNY, Flushing, N.Y., 1 December 1984.

4. North County Resource Recovery Associates, Risk Assessment for Trace Element and Organic Emissions, North County Recycling and Energy Recovery Center, San Marcos, CA. Prepared by Henningson, Durham & Richardson, Santa Barbara, CA. April 1984.

5. North County Resource Recovery Associates, Risk Assessment for Trace Element and Organic Emissions. Response to Environmental Defense Fund Evaluation of September 2Ø, 1984. Prepared by Henningson, Durham & Richardson, Santa Barbara, CA. November 1984.

6. Center for the Biology of Natural Systems, Environmental and Economic Analysis of Alternative Municipal Solid Waste Disposal Technologies, Volume I: An Assessment of the Risks due to Emissions of Chlorinated Dioxins and Dibenzofurans from Proposed New York Incinerators. Queens College, CUNY, Flushing, N.Y. 1 May 1984 revised 27 August 1984.

7. Swedish Environmental Protection Agency
   Technical Department
   Disposal and Recycling Unit
   a. Telex to Swedish Embassy, Washington, DC, 12 April 1985
      Attention: Elizabeth Lagerlof.
   b. Letter to Public Utilities Commission for Environmental Protection, 12 February 1985.
   c. Memorandum on Dioxin Emissions from Waste Combustion, 11 February 1985.

8. U.S. Environmental Protection Agency, Proposed Guidelines for the Health Risk Assessment Of Chemical Mixtures and Request for Comments; Notice. In: Federal Register, Volume 5Ø, No. 6, 9 January 1985, p. 117Ø.

9. American Conference of Governmental Industrial Hygenists, TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment and Biological Exposure Indices with Intended Changes for 1984-1985.

10. National Research Council, Drinking Water and Health, Volume 3. Washington, DC. 1980.

11. California Air Resources Board, List of Compounds To Be Considered Under AB1807, 4 April 1985.

12. California Air Resources Board, Cummulative Impacts of Polychlorinated Dibenzodioxins and Dibenzofurans from Resource Recovery Facilities in the South Coast Air Basin, April 1985.

13. Woodward-Clyde Consultants, Risk Analysis of Health Effects from Emissions of Trace Metals and Organics from the Proposed Irwindale Resource Recovery Facility. Santa Ana, CA. April 1985. Submitted to California Energy Commission.

14. Rappe, Christopher, et. al., Identification of 2,3,7,8-Substituted Polychlorinated Dioxins (PCDDs) and Dibenzofurans (PCDFs) in Environmental and Human Samples. Presented at the 189th National Meeting, American Chemical Society, Miami, Florida, April 19-May 3, 1985.

12 April 1985

Technical Department
Disposal and Recycling Unit
Departmental Director S. Modig

Swedish Embassy
Washington
Att.: Elisabeth Lagerlöf

Telex:

The Environmental Protection Agency, which, in compliance with the environmental protection law, makes no independent decisions in licensing matters, has, as a consulted party, stated, in a licensing matter with the Public Utilities Commission for Environmental Protection, that no license for new incinerative plants should be granted until certain questions have been investigated. The reason involves the dioxin emission from waste combustion.

In our memo, which is part of our statement to the Commission, we have stated the following:

"Concerning the consideration of new waste incinerative plants, the Agency suggests that they await the results of ongoing research and development, particularly in regards to steps to continuously maintain good combustion efficiency, the plants' emergency systems, the refining of smoke gas and the treatment of waste water."

We further stated:

"In 1986, significantly more information will be available for determining which disposal demands should be made on a new waste incinerative plant and consequently, the plant's design and emission filtering steps. Such a delay ought not cause any major inconveniences for the handling of the waste either."

The Public Utilities Commission has not yet reached a decision on the matter.

The embassy will receive our memo by mail.

Sincerely,

On behalf of the Environmental Protection Agency,

Staffan Modig

12 February 1985

Environmental Protection Agency
Technical Department
Disposal and Recycling Unit
Departmental Director S. Modig

Public Utilities Commission
for Environmental Protection
Box 2121
10313 STOCKHOLM

Statement regarding Södertörn District Heating Co.'s and Södertörn Refuse Collection Co.'s application for waste combustion license, etc.

The Environmental Protection Agency made its first statement on this matter on October 12, 1984. Thereafter the Public Utilities Commission has suggested that the Agency render an account of the Research results that are now available concerning the emissions of chlorodibenzo-dioxins, dibenzo-furans, et al. in waste combustion, information about ongoing research concerning those emissions and an account of the Agency's opinion about the emissions.

In an enclosed memo the Agency supplies the requested account.

From this account it is evident that dioxins have been found in mother's milk and in fish in amounts which, if generally toxic, would exceed the limit for "tolerable daily intake" in normal consumption. A quantification of the existence of dioxins in the environment and where they come from is, however, not possible with today's knowledge. Waste combustion in Sweden and sources outside of Sweden are, however, significant. These circumstances and others presented in the memo are reasons for partially altering the position on this matter.

It is furthermore evident from the enclosed memo that in well maintained incinerative plants of modern construction the emission of chloro-dibenzo-dioxins and dibenzo-furans ought to be kept at a low level. The risk estimate that has been made does not indicate any significant danger for that population which is considered to be the most exposed. The high toxicity of the dioxins and the uncertainty of the risk estimate make it, however, extremely urgent to limit the dioxin emission

as much as possible in new plants. Despite the given information, there is no reason for questioning the permissibility of the planned waste incinerative plant.

In order to secure such operational conditions which lead to low emissions it is required that a plant be equipped with sufficient supervision, with equipment for supplementary oil burning or the equivalent thereof so as to ensure that the entire volume of smoke gas is heated to a sufficiently high temperature, and with other filtering equipment in addition to electrical filters/obstruction filters, e.g. smoke gas condensation. It is, however, at the present moment uncertain what form these measures should take. Several investigations are currently being conducted to clarify these relationships and full-scale experiments are in the planning stages as well. Until at least some of these investigations are concluded it is not possible to formulate the demands for a limitation of the necessary dioxin emissions. It is particularly urgent to underline the importance of intensified supervision and control, supplementary oil burning, and smoke gas purification via condensation for the dioxin emissions. The implementation of the condensation treatment with lime insemination + electrical filter and obstruction filter will most likely produce a dioxin removal as well.

With reference to what has been said above, the Agency thinks that prior to making a final decision about emissions limits and other conditions, the company should investigate the possiblities of continously securing low emissions of dioxins through the use of different technical devices.

The results of the investigations in Umeå (supervision, supplementary oil burning) and Avesta (condensation) are expected this summer, while the evaluations of the condensation technique, in full scale in Uppsala and in pilot scale in Högdalen, will not be ready until next summer. EPA's own investigation of the implementation of supplementary oil burning is expected to be concluded late this fall. It should be up to the company to determine when to act on the matter, depending on the results of the aforementioned investigations and other possible ones abroad, or on ones the company itself might want to conduct.

If the results from Umeå and Avesta are sufficiently clarifying and a condensation technique is selected, a supplement to the application should be available in as early as six months.

In other combustion matters, the question of quicksilver removal in condensation has been considered. At the investigation of one plant the Agency has moved to a separation level of 80%. The Agency therefore wants to supplement their earlier motion with a demand for an emission limit of quicksilver. This limit should be placed at 80% removal.

In summary, the Agency's investigation of dioxins indicates that the planned waste incinerative plant is permissible, but that further investigation is needed in order to design a plant with the lowest possible emission of dioxins. The Agency also specified a demand for a limit of quicksilver emissions at 80% removal.

Otherwise, the Agency's motion remains the same as the statement of 12 October 1984.

On behalf of the Environmental Protection Agency,

Lars Lindau

Staffan Modig

11 February 1985

Swedish Environmental Protection Agency
Technical Department
Disposal and Recycling Unit

MEMO ON DIOXIN EMISSIONS FROM WASTE COMBUSTION

The content of this memo is mainly based on information from Swedish and foreign sources.

General Information About Chlorodibenzo-p-dioxins And Dibenzo-furans

Polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) are two series of aromatic substance groups, which consist of 210 different substances in all. The number of chlorine atoms in these groups can vary between one and eight and exist in different positions in the molecule. There are, thus, 75 different PCDD-isomers* and 135 different PCDF-isomers. 12 of these chlorinated compounds are extremely toxic. In Appendix 1, the molecules are shown graphically, as is the placement of the chlorine atoms. The key to the abbreviations used is presented as well. Below, the term dioxin(s) is used as a comprehensive term for chlorinated dioxins and furans in general.

The most toxic of the 210 compounds are considered to be 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). It is mainly this substance which has been the subject for studies regarding toxicity, etc.

The first time 2,3,7,8-TCDD was mentioned in literature was in 1872. It was not until the 1950's that research started on the toxicity of dioxins. When dioxins exist in very small amounts, very low levels must be detected. With the testing and analyzing techniques in use today it is possible to analyze quantities on a pikogram-level (10^{-12}g).

Dioxins can occur as a pollutant in technical products (pesticides, and others).

2,3,7,8-TCDD has been found in pesticides containing 2,4,5-T (e.g. Agent Orange). Agent Orange has the capacity to contain about 50 mg/kg of 2,3,7,8-TCDD. During the Vietnam War (1962-1971) the amount of 2,3,7,8-TCDD spread was estimated at ca. 168 kg as a pollutant included in Agent Orange (1). In comparison it can be said that at the accident in Seveso, Italy in 1976 ca. 2.5 kg of the isomer 2,3,7,8-TCDD were instantly released.

*Translator's note: The word "isomer" was used throughout the original Swedish document, even though in most cases "congener" was the appropriate noun. The word "isomer" has been left in the English text.

2,4,5-T has during about 20 years, up until 1977, been spread on wooded and cultivated soil in Sweden. During the 1950's, about 20 tons/year were spread and during the 1970's until its prohibition, about 80 tons/year. With a content of 2,3,7,8-TCDD of 1 ppm, about 80 g/year of this dioxin was thus spread in the 1970's.

Apart from waste incinerative plants for household waste, dioxin can be brought into the environment by combustion of other kinds of waste (particularly waste, hazardous to the environment, containing chlorine) and industrial processes where chlorinated products are used. In accidents with PCB-containing transformers and condensers, dioxin can be emitted. The burning of, in particular, chlorophenol impregnated firewood can also be a source of dioxin emission. Similarly, dioxin can occur as a pollutant in chemical products (PCB, PBB, hexachlorophene, chlorophenols, etc.) other than 2,4,5-T. Other sources that have been discussed are the burning of oil, coal, peat and other bio-fuels, and the operation of motor vehicles.

The Formation Of Dibenzo-p-dioxins and Dibenzofurans In Waste Combustion

Dioxins are formed in many different ways. There are 3 principally different reasons for the occurence of dioxins in connection with waste combustion.

1. Dioxins occur in the waste (and are not destroyed completely in the combustion).

2. Dioxins are formed during the combustion process from certain chlorinated organic compounds.

3. Dioxins are formed during the combustion process "from scratch" via a complex system of thermal reactions between organic materials and chlorine in some form.

At the end of the 1970's, when it was determined that dioxins could also occur in the smoke gas from waste incinerative plants, several researchers tried to find our how the formation of dioxins occurs. Experiments were conducted at laboratory scale using different additions to the fuel. So far this has only resulted in the development of testing and analyzing techniques, but the question of formation mechanisms has not been ultimately solved. Efforts to find some connection between content of dioxins and other parameters such as HCl, SO_2 and CO have been made, but no simple connection has yet been found.

Measurements carried out on waste incinerative plants have in some instances showed that the level of dioxins was higher at combustion temperatures around 500^{o}C than at temperatures exceeding 800^{o}C.

Toxicity

The section below is based on a research application to the Agency from Ulf Ahlborg, SML.

The toxicity of the different isomers is of a highly varying degree. The most studied bond is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The toxicity in TCDD is very high, as is the species variation. Thus, the acute toxicity varies fom 0.6 - 2 µ/kg for guinea pigs, to 1157 - 5000 µ/kg for Syrian gold hamsters. Other isomers vary in toxicity, but in general, one can say that the precondition for a high toxicity is that the molecule is chlorinated in a symmetrical lateral position, i.e., in the positions 2,3,7,8. Lower chlorinated dioxins have a lower toxicity. Higher chlorinated dioxins still have a high, although decreasing, toxicity, but the fully chlorinated octachlorodioxin is relatively low in toxicity.

2,3,7,8-tetrachlorodibenzofuran (TCDF) and 2,3,4,7,8-pentachlorodibenzofuran have an acute toxicity which is somewhat lower than TCDD's (LD50 for guinea pigs 5 - 10 µ/kg). At present, the same relations are assumed to apply as for isomers of dioxins.

Only TCDD has been studied extensively in animal experiments. These have, on the one hand, shown that TCDD is cancer producing (2, 3, 4), and, on the other hand, that the most sensitive parameter is reproduction disturbances in apes (5) and rats (6).

The risk estimate for TCDD has either been left out of the cancer studies and through extrapolation therefrom led to a tolerable daily intake with the acceptance of one cancer case per 10^6 inhabitants (7), or a safety factor (200 - 1000) on NOEL (no effect level) has been applied in the reproduction or cancer studies. These risk estimates have led to acceptable daily intakes in the magnitude of 1 - 5 pg/kg body weight. These acceptable daily intakes refer to a lifelong exposure, but no particular considerations have been made regarding infants. Generally speaking, infants are considered to have a higher sensitivity to toxic substances since their toxification (SIC) mechanisms are not fully developed.

Concerning chlorinated dioxins and dibenzofurans, there exist data which offer particular reasons for assuming that infants can constitute a particularly sensitive risk group.

A risk estimate for a mixture of dioxins and dibenzofurans can, at present, not be made on the basis of data concerning the toxicity of individual isomers. In risk evaluations tentatively made in different countries, the term TCDD-equivalents has had to be used. Researchers used TCDD's toxicity as a starting point and related the other isomer's toxicity to this by comparing data concerning acute toxicity, enzyme induction, binding of receptors etc., with TCDD, and in this manner gave each isomer or group of isomers a certain weight, which then can be weighed together for an appraisal of the potential toxicity of a test or an obtained level. In one case they also started out from carcinogenicity. The procedure necessarily implies a significant uncertainty for the following reasons:

1. The large species variation which TCDD's toxicity shows implies significant uncertainty in the appraisal of where man is in this respect. A series of accidents have occurred where people were exposed to TCDD or mixtures in which TCDD was a component. In many of these accidents the exposed people and their state of health was monitored during time periods as long as 30 years. In an examination of this material, done in connection with the preparation of a draft to a WHO/IPCS document about PCDDs and PCDFs, it was found that man should probably not be considered as belonging to the most sensitive species when it comes to the effects of these substances. Such an assumption can, however, not be described in quantitative terms since the exposure data are extremely uncertain.

2. The effects on which the weighting of different isomers' toxicity were based do not necessarily correlate to the long term effects in areas with low doses.

3. The effect mechanism for TCDD is not known. Several theories have been constructed but these have not yet been able to satisfactorily explain species variation in sensitivity.

4. In most cases the appraisal is based on in-vitro testings. No consideration has been given to the varying toxicokinetics of the different isomers, mainly because this is unknown.

Some of the methods and weight factors that have been used are shown in Table 1.

Degradation Ability

2,3,7,8-TCDD can be degraded through biodegradation as well as through photodegradation (degradation through the influence of ultraviolet light). The informaton from literature, however, does not make it possible to determine the speed of the degradation in different environments. At the accident in Seveso in 1976, the soil and vegetation were tested immediately after the accident and the tests were analyzed with regard to the existence of 2,3,7,8-TCDD. In the vegetation tests levels as high as 50 µ/g were measured. Studies indicate that the half-life of 2,3,7,8-TCDD in the ground is 10-12 years. One year after the accident in Seveso no trace of TCDD could be detected either in the meat of apples, peaches or pears, nor in corn growing in the vicinity of the factory that had emitted the dioxin cloud. TCDD was, however, found on the peels and this could be interpreted in such a way that the contamination was not due to absorption by the plant but to particles that stick to the surface. A corresponding condition can be assumed to exist for deposition on pasture land. Grazing cows can in this manner get dioxin in their system via deposition on grass.

TABLE 1

Isomers	Level	Method 1	Method 2	Method 3	Method 4
PCDDs					
Cl 1-2		0	0	0	0
Cl 3		0	0	0	0
2,3,7,8-TCDD	1	1	1	1	1
other TCDDs	1	0	.01	.01	.01
2,3,7,8-PeCDDs	1	1	1	.2	.1
other PeCDDs	1	0	.01	.002	.1
2,3,7,8-HxCDDs	1	.03	1	.04	.1
other HxCDDs	1	0	.01	.004	.1
2,3,7,8-HpCDDs	1	0	1	0	.01
other HpCDDs	1	0	.01	0	.01
OCDD	1	0	1	0	0
PCDFs					
Cl 1-3	1				0
2,3,7,8-TCDF	1	.33	.02	.1	.1
other TCDFs	1	0	.0002	.001	.1
2,3,7,8-PeCDFs	1	.33	.02	.1	.2
other PeCDFs	1	0	.0002	.001	.2
2,3,7,8-HxCDFs	1	.01	.02	.1	.1
other HxCDFs	1	0	.0002	.001	.1
HpCDFs	1	0	.02	0	.01
OCDF	1	0	.02	0	0
TOTAL TCDD-EQUIVALENT		2.7	5.1406 4.1006	1.559	2.24

Method 1: Eadon, 1982 (acute toxicity)
Method 2: Ontario Government, 1982 (combined effects)
a: OCDD = 1 and HpCDFs and OCDF = 0.02
b: OCD = HpCDFs = OCDF = 0
Method 3: EPA, 1984 (cancer extrapolation)
Method 4: Danish Environmental Agency, 1984 (enzyme induction)

Existence In The Environment

Research goes on at several institutions the world over to, among other things, determine the background level and what level existed earlier. This is being done through analyzing human fat tissue and mother's milk, through analyzing reference tests on herring, seal and sea birds in the Baltic Sea/Gulf of Bothnia, and through analyzing fish in the collection at the Natural History Museum as well as through analyzing sediments (9). Dioxins were identified in all the tests. The levels in the 9 tests on mother's milk and in some tests on fish exceed the above mentioned "acceptable daily intake". Any general conclusion can, however, not be drawn until there exists more complete material which describes the levels in the environment.

Dioxins have been traced in sediments 50 years back in time in research done at Siskiwit Lake on Isle Royale in the United States (10). The author of the article states that this pollution is due to atmospheric precipitation since the lake is situated on a high level in relation to other lakes and there can be no inflow of polluted water. To trace this precipitation is often very difficult, since the source that caused it may be situated far from where it fell to the ground. The investigation shows an increasing level of PCDD in the three tests from the years 1935, 1953, and 1982.

Considering the stability of the dioxins and that they are emitted in gas phase or adsorbed on fine particles, the dioxins could be spread very far from the disposal source. We, therefore, probably have a contributing intransport of dioxins from other countries in a similar way as for sulphur, quicksilver and DDT.

Investigation And Research Concerning Emissions From Waste Combustion

Tests and analyses of PCDDs/PCDFs in smoke gas from a few waste incinerative plants have been done both in Sweden and abroad. These tests indicated a large spread of the levels of PCDDs/PCDFs.

In Sweden, analyses of PCDDs/PCDFs were done earlier at incinerators in Lovsta, Hogdalen, Sotenas and Eksjo. The combustion efficiency at these places was very poor, with high levels of carbon monoxides in the smoke gas. This manner of operating was the normal way earlier, since waste combustion most often was a way to diminish the volume of the waste, and the energy in the waste was not used for production of district heating. In addition, measurements were made under the DRAV-project in Linkoping and Malmo. These measurements showed that the level of total TCDD was low, below 1 ng per normal cubic meter of dry gas converted to the condition at $0^{o}C$ and a carbon dioxide level of 10% (1ng/Nm^3). These incinerators were then tuned and optimized, and were operated efficiently, as is evident from the fact that the CO level was below 100 mg/Nm^3.

The Institute For Water And Air Protection Research (IVL) in 1979 conducted an investigation of organic substances which were emitted from 4 municipal waste incinerative plants (11). In this investigation the incinerators were forced to operate at low temperatures in order to find out if organic emissions increased. This way of operating with low combustion temperature produced increased emissions of organic substances.

At the end of 1984, measurements of PCDDs/PCDFs were made at waste incincerators in Avesta and Umea. The results from these measurements are expected to be available in February/March. At the plant in Umea, measurements were made at the start-up and shut-down operations of the incinerator as well. In Hogdalen new measurements have been made. The final results from these tests are also expected within a short while. In Appendix 2 data are shown from the measurements made under the DRAV-project and from one measurement made in Avesta.

High levels were found in some measurements in Italy and Holland (12, 13). The results from the measurement in Italy have indicated levels of PCDD (total dioxins) as an average at 1100ng/m^3 and in the Dutch measurement at 500 ng/m^3.

PCDDs/PCDFs In Ashes And Slag

Dioxin analyses in Sweden have mainly been done on emitted smoke gas. The occurence of pollutants in ashes and slag has been examined on a larger scale in Germany. They have analyzed ashes and slag from most of the plants. Dioxins that are in the ashes and the slag will be deposited on municipal disposal sites. Since PCDDs and PCDFs are considered to be very firmly bound to the particles (8), it means that the risk from leaching is small.

A German study (14) shows the average level in results from 80 tests on flue ashes from 25 plants in Europe. This information, however, does not make it possible to determine the removal level in the dust for dioxins. It is, however, safe to assume that a significant amount will be separated, especially when using obstruction filters.

Exposure Estimates

In most analyses done on smoke gas emitted from waste incinerative plants, the level of 2,3,7,8-TCDD has been much below 1 ng/Nm^3. For the plants in Malmo and Linkoping, which were investigated under the DRAV-project, the level was at 0.05 ng/Nm^3. In the estimation of the deposited amount of 2,3,7,8-TCDD per m^2 during 6 months, the value of the emission was set at 0.5 ng/Nm^3. The calculation was made in the same fashion as for a 50 MW incinerator burning wood chips in regards to the dust. The calculating method was produced by Ulf Hogstrom in Uppsala.

Other assumptions for the deposition calculations are that the combustion capacity is 10 tons per hour (corresponds to 75000 tons per year), the height of the stack is 80 m, and that the size of the particle is less than 1 micrometer.

With the above inputs to the calculation, we reach a deposited amount per m^2 per 180 days of 0.01 ng. This result comprises both wet and dry deposition. The level per m^3 of air in the most heavilly afflicted area between 1-4 km from the disposal source is 5×10^{-7} ng/m^3.

The daily intake can be divided up into, on the one hand, inhaled quantities and, on the other hand, via food.

The inhaled quantity becomes 1×10^{-5} ng at an inhalation volume of 20 m^3/day and a level on the ground of 5×10^{-7} ng/m^3.

The intake via food can be calculated by assuming that a cow eats grass from 60 m^2 per day, that 20% of the 2,3,7,8-TCDD secretes into the milk, and that the milk production per day is 20 liters. With these assumptions the amount of dioxin per liter of produced milk becomes 0.006 ng. The intake per day at 1 liter milk consumption provided that it comes from a cow that grazes only in the vicinity of a waste incinerative plant, and that this milk does not pass through a dairy, becomes 0.006 ng. The total intake may increase if the individual also consumes meat and vegetables produced in the area connected with the plant.

Risk Evaluation

As mentioned above, the toxicological evaluations made in several countries have resulted in an "acceptable daily intake" of 1-5 pg/kg body weight of TCDD. The starting point has been the cancer effect (one case per 10^6 inhabitants) or the effect on growth with a safety factor of 200-1000. Researchers have furthermore started out from 2,3,7,8-TCDD and for other toxic dioxins they have calculated so called TCDD equivalents, i.e., the level that has the same effects as 2,3,7,8-TCDD.

The only way of exposure of any significance is intake via food. Dioxins have been found in fish from the Baltic Sea. The levels in milk from dairies have so far been below the detection limit. The tests are made on milk with a low fat content. The levels in the few tests made on mother's milk are, however, above the limit for "acceptable daily intake".

Above, a calculation has been made of the exposure from an individual waste incinerative plant burning about 75,000 tons of waste per year. The most exposed group is estimated to be individuals who drink milk from cows grazing in the vicinity of the plant. If the emission rate is 0.5 ng/Nm^3 2,3,7,8-TCDD, i.e., a level which today's Swedish plants can attain, and if they drink one liter of milk per day, the intake will be about 0.006 ng/day, i.e., 10-50 times below the above indicated acceptable level. For those individuals there must then be added the intake of other dioxins, plus background and intake from other sources.

For the general population, the contribution from a waste incincerative plant with the above mentioned emission level becomes very small, because the dioxins are diluted with large quantities of milk from other areas in the treatment at the dairy.

The Waste Combustion Situation

Waste combustion has occurred in Sweden for about 80 years. The Lovsta plant in Stockholm started operating in 1906. In the beginning of the 1960s when close to 200,000 tons were burned, an estimated 1800 tons of dust were emitted every year. Today, the annual emission of dust from all plants is estimated at 600 tons.

Waste combustion today comprises about 1,2##,### tons of waste per year. Of this amount, about 1,###,### tons have been sanctioned with considerably stricter conditions than before. Current applications under consideration and recently investigated plants comprise another 35#,### tons/year. The requirements on the plants have the effect that, despite increased quantities of waste for combustion, the emission of dust and other known pollutants have not increased, except for quicksilver, compared to what was emitted from wste combustion before 198#.

Earlier, the control and the demands that were made on the plants were much lower than today. The composition of the waste is mainly assumed to have been the same since the beginning of the 195#s but with an increase in the share of plastic. At that time the plants did starting and stopping operations every day which have been proven to increase the emission of organic compounds considerbly. The demands that today are made on waste combustion with the stating of lowest temperature in a combustion zone, supervisory equipment, continuous operation, different fuel with starting and stopping operations, etc., should, according to current knowlege, be enough to keep the dioxin and dibenzofuran emissions at an acceptable level.

Measures To Limit Or Avoid Dioxin Emissions

Swedish and foreigh experience suggest that the best way to minimize dioxin emissions is to assure oneself of good combustion conditions.

There can be assumed to exist a connection between dioxin disposal and combustion temperature. The demands that the EPA makes in licensing matters specify that the total amount of smoke gas must have a temperature of at least 8##^{o}C. The temperature indication must not be interpreted as an average temperature over a certain time.

All Swedish incincerative plants are, which follows from Appendices 3a, b, c, equipped with electrical filters or textile obstruction filters. Today's demands are that the emission of particles (dust) can, at its highest, reach 5# mg/Nm^3. Many plants show considerably lower levels. The more efficient the filters, the more efficiently the fine dust particles are removed. There is much evidence that a significant share of the dioxins is adsorbed on fine particles. A textile obstruction filter has a higher ability than an electical filter to separate fine particles.

An important measure to decrease emissions is to supply the plant with operation-safe supervisory instruments, like carbon monoxide meters, in order to be able to directly follow and correct errors that occur. The level of carbon monoxide (CO) in the smoke gas is a direct measurement of the plant's combustion efficiency. When the level of CO is below 1##-25# mg/Nm^3 organic emission is normally small as well. Continuous operation is another step which has as a consequence decreased emissions since starting and concluding operations mean an increased level of pollution in the smoke gas. Trained personnel are also an important factor from the viewpoint of emissions. Knowledge of the plant's function and why and when certain steps should be taken have proved to be of the utmost importance for the size of emissions. Starting and concluding burning with a different fuel and supplementary oil burning are other measures that can decrease the emission of pollutants.

The DRAV-measurements at some combustion plants have shown that during about 1% of the operation time, the temperature is below 800°C. Other plants may have higher frequency of operational disturbances. In order to sustain a high combustion temperature, even during operational disturbances, supplementary oil burners may be installed. An investigation of the significance of such an installation is being conducted in Umea. A report from this investigation is expected in March of 1985. Considering that the produced energy is utilized, an introduction of supplementary oil burning will not mean any large increase in cost. As an alternative, after-burning or the supplying of oxygen can be considered. The smoke gases contain, apart from dioxins, hydrogen chloride and quicksilver et al. In order to limit these emissions there is a plant with lime insemination in the smoke gas and seperation in the electrical filter or in the obstruction filter. An alternative under investigation at the present moment is condensation of the smoke gases. A part scale (20%), as well as a full scale project are being planned. Both these techniques will further separate dioxins. Low temperature causes some of the dioxins to be condensed so that they can be separated. An estimate of the degree of separation is not possible but must be determined in tests.

Conclusions

As mentioned above, the toxicological evaluations made in several countries have reached the conclusion of an "acceptable daily intake" of 1-5 pg/kg body weight of TCDD. The starting point has been the cancer effect (one case per 10^6 inhabitants) or the effect on growth and a safety factor of 200-1000. Furthermore, they started out with 2,3,7,8-TCDD and for other toxic dioxins they have estimated so called TCDD-equivalents, i.e., the amount that has the same effect as 2,3,7,8-TCDD.

The only route for dioxin exposure that has significance is intake via food. Dioxins have been found in fish in the Baltic Sea. Measurements on milk from dairies have so far remained under the limit for detection. Those tests were done on milk with low levels of fat. The few times mother's milk has been tested, however, the levels are above the limit for "acceptable daily intake".

A quantification of the existence of dioxins in Sweden is not possible to make with today's knowledge. An important source is, however, waste combustion in Sweden. But sources outside of Sweden may also be of significance. Dioxins are such stable substances that they are surely transported from afar. Other sources discussed are other combustion plants for oil, coal, peat and other bio-fuels, and also, the operation of motor vehicles.

The measurement of dioxins in waste combustion indicates large variations. It is clear, however, that levels smaller than 1 ng/Nm^3 for TCDD and 0.05 ng/Nm^3 for 2,3,7,8-TCDD can be attained at today's best plants. These levels ought to be reached during long periods of time as well, but this then implies significant efforts in supervision and control.

The installation of supplementary oil burning will probably be a complement to maintaining high combustion efficiency. This will result in low levels of dioxin in emissions and should lead to lower levels than those mentioned above. The installation of equipment for purification of smoke gases, for example, condensation equipment, increases further the possibility of attaining low levels.

In regard to the complexity and the significance of the problems with emission and the existence of dioxins, the EPA plans to appoint a special group to discuss and evaluate problems and coordinate efforts. The group is to consist of representatives from the EPA, the Fishery Agency, the Food and Drug Administration and the Department of Health, Education and Welfare. It is safe to assume that relatively comprehensive research and investiations in which different problems regarding dioxins will be illuminated will be made in the near future. In the recent past, research and investigation activities, especially the DRAV-study, have pointed out different measures to improve combustion conditions, and thereby decrease the risk in the emission of dioxins. Mentioned above are continuously registering carbon monoxide meters, significantly increased supervision of the temperature, starting and concluding burning with other fuels and training personnel, etc. Such measures can be taken quickly and at a relatively low cost. EPA plans to hold discussions in the near future with the Association of Refuse Collection regarding these matters with the goal of having the aforementioned measures carried out at all plants. When the results from the investigations in Umea are available, the Agency intends to bring up the question of the introduction of supplementary oil burning as a further step at existing plants. The smoke gas from waste combustion contains, besides different dioxins, hydrogen chloride and quicksilver. In order to limit the emission of these waste products, there are plans to refine smoke gas, especially via condensation, in existing plants as well. These systems will limit dioxin emission as well. Such measures can, however, not be taken until the ongoing experiments are concluded. The above suggested steps at existing plants are urgent and will limit the preconditions for the creation and emission of dioxins.

Concerning the consideration of new waste incinerative plants, the Agency suggests that they await the results of ongoing research and development, particularly in regards to steps to continuously maintain good combustion efficiency, the plants emergency systems, the refining of smoke gas and the treatment of waste water. The experiments in Umea and Avesta, and in other countries as well, regarding combustion techniques, supplementary oil burning etc., the work with condensation of smoke gases at partial scale at the waste incinerative plants in Hogdalen and Avesta as well as the work at the waste incinerative plant in Uppsala to construct a condensation plant in full scale, will produce conclusive information on how a new waste incinerative plant should be constructed and equipped, and what demands should and can be made in regard to dioxin emission. In 1986, significantly more information will be available for determining which disposal demands should be made on a new waste incinerative plant and, consequently, the plant's design and emission filtering steps. Such a delay ought not cause any major inconveniences for the handling of the waste either. Few waste incincerative plants are currently under investigation, and only a few more applications are expected. Alternative treatments of waste exist and can be used.

EPA wishes, however, to stress that waste combusiton is a suitable treatment for waste and that it should be possible to find a solution for the problem of dioxin. The alternatives for disposal of waste may be worse from an environmental standpoint. If the above measures to secure good combustion conditions and good operational supervision are taken, the Agency sees, at the present time, no reason to interfere with existing waste incinerative plants in any other way than indicated above.

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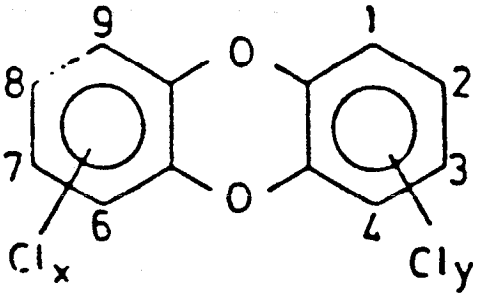
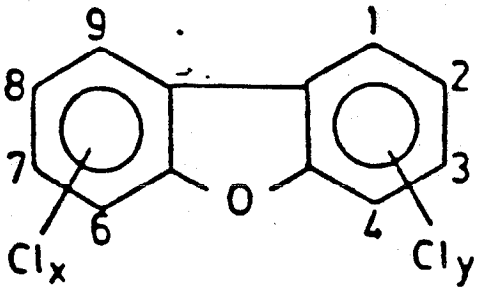
APPENDIX 1

Polychlorinated dibenzo-p-dioxins and dibenzofurans



PCDDs



PCDFs

x + y = 1 - 8

The most toxic PCDD and PCDF isomers

PCDDs		PCDFs	
2,3,7,8-Tetra-CDD	(TCDD)	2,3,7,8-Tetra-CDF	(TCDF)
1,2,3,7,8-Penta-CDD	(PnCDD)	1,2,3,7,8-Penta-CDF	(PnCDF)
1,2,3,6,7,8-Hexa-CDD	(HxCDD)	2,3,4,7,8-Penta-CDF	(PnCDF)
1,2,3,7,8,9-Hexa-CDD	(HxCDD)	1,2,3,6,7,8-Hexa-CDF	(HxCDF)
1,2,3,4,7,8-Hexa-CDD	(HxCDD)	1,2,3,7,8,9-Hexa-CDF	(HxCDF)
		1,2,3,4,7,8-Hexa-CDF	(HxCDF)
		2,3,4,6,7,8-Hexa-CDF	(HxCDF)

APPENDIX 2

	SYSAV	Linköping		Avesta	
				1	2
	obeh.	RDF	RDF	CO 3400	CO max 200
2,3,7,8 TCDD	0,01	0,03	0,02	2,3	1,2
TCDD	0,15	0,6	0,3	180	82
2,3,7,8 TCDF	0,5	0,2	1	15	6,8
TCDF	2	4,5	4	615	258
1,2,3,4,8/12378 PnCDF	0,15	0,3	0,3	66	34
2,3,7,8 PnCDF	0,45	0,3	0,9	66	34
PnCDF	3	4	6	850	340
1,2,3,7,8-PnCDD	0,015	0,04	0,03	33	14
PnCDD	0,15	0,1	0,1	650	258
HxCDD				345	163
HxCDF	26	113	225	570	233
HxCDD				270	136
HxCDF				260	156

DATA ON WASTE COMBUSTION 1985

TREATMENT PLANT / MUNICIPALITY (a) not in operation 1985)	PLANTS FORMATION AND TECHNICAL EQUIPMENT — COMBUSTION — OVENS — MANUFACTURE AND NO. U1–U5: MANUFACTURE TYPE 1	MANUFACTURE TYPE 2	DIM. CAPACITY AND CURRENT IN TON/H RESP. Mcal/ton waste per oven and year — UGN 1 DIM.	UGN 1 CURRENT	UGN 2 DIM.	UGN 2 CURRENT	UGN 3 DIM.	UGN 3 CURRENT	UGN 4 DIM.	UGN 4 CURRENT	UGN 5 DIM.	UGN 5 CURRENT	COOLING OF FURNACE WALLS: AIR	WATER	OTHER	MIXED	ROSTER: WIDTH M	ROSTER: TYPE	REMARKS OBSERVATIONS
AVESTA	U1–U2 Bruun & Sörensen		3.1 / 2200	3.3 / 2500	3.1 / 2200	3.3 / 2500	---	---	---	---	---	---	•				1.6	Vipprost	
BOLLNÄS a)	U1 Generator		5 / 2000	---	---	---	---	---	---	---	---	---		•					Fluidbad
BORLÄNGE	U1 K+K Ofenbau AG		6.6 / 3700	6.6 / 3700	---	---	---	---	---	---	---	---	•	•			3.0	Tvärroster	Planroster
BORÅS	U1–U2 Landsverk	U3 Vølund	3.8 / 1800	2.1 / 2600	3.8 / 1800	2.1 / 2600	4.0 / 2200	3.7 / 2600	---	---	---	---				•	1.7 2.1	Framskjut	Planroster
EKSJÖ	U1 Generator		2.5 / 2000	3.3 / 2405	---	---	---	---	---	---	---	---		•					Fluidbad
GRAAB GÖTEBORG	U1–U3 von Roll		15.0 / 2200	13.4 / 2325	15.0 / 2200	13.4 / 2325	15.0 / 2200	13.4 / 2325	---	---	---	---	•				3.3	Tvärroster	Planroster
HALMSTAD	U1, U2 Martin		5.5 / 2200	4.1 / 2600	5.5 / 2200	4.1 / 2600	---	---	---	---	---	---				•	2.1	Återskjut	Planroster
HÖGDALEN STOCKHOLM	U1, U2 VKW	U3 Martin (Under byggnad 1984)	15.6 / 2200	11.5 / 2100	15.6 / 2200	11.5 / 2100	---	---	---	---	---	---		•			3.5	Valsroster	Roterande
KARLSKOGA a)	U1 K+K Ofenbau AG		6.0 / 2500	---	---	---	---	---	---	---	---	---	•				2.4	Tvärroster	Planroster
KINDA a)	Widmer Ernst		2.2 / 2500	---	---	---	---	---	---	---	---	---	•				2.0	Tvärroster	Planroster
KÖPING	U1, U2 Landsverk		5.0 / 2500	4.2 / 2400	5.0 / 2500	4.2 / 2400	---	---	---	---	---	---				•	2.1	Framskjut	Planroster
LANDSKRONA a)	U1, U2 Generator		2.5 1) / 4500	---	---	---	---	---	---	---	---	---							1) Briketter Fluidbad
LIDKÖPING a)	U1, U2 Generator		4.8	---	---	---	---	---	---	---	---	---		•					Fluidbad
LINKÖPING	U1, U2 von Roll		6.9 / 2500	6.9 / 2500	12.0 / 2500	12.0 / 2500	---	---	---	---	---	---	•	•			2.8 4.0	Tvärroster	Planroster
LULEÅ	U1, U2 Landsverk		4.5 / 3140	3.3 / 2500	4.5 / 3140	3.3 / 2500	---	---	---	---	---	---	•				2.0	Framskjut	Planroster
LÖVSTA STOCKHOLM	U1–U5 Landsverk, Vølund		10.0 / 1600	4.8 / 2700	10.0 / 1600	4.8 / 2700	10.0 / 1600	4.8 / 2700	11.0 / 1600	4.8 / 2700	15.0 / 2200	9.5 / 2700				•	1.9 2.4	Framskjut	Planroster
MORA	U1 Bruun & Sörensen		3.1 / 2200	2.9 / 2096	---	---	---	---	---	---	---	---	•				1.6	Vipprost	
SUNDBYBERG	U1, U2 Landsverk		2.5 / 2000	2.3 / 2175	2.8 / 2000	2.3 / 2175	---	---	---	---	---	---				•	1.5	Framskjut	Planroster
SUNDSVALL a)	U1 Götaverken		---	---	---	---	---	---	---	---	---	---							Fluidbad
SYSAV MALMÖ	U1, U2 Martin		8.5 / 2100	10.5 / 2500	8.5 / 2100	10.5 / 2500	---	---	---	---	---	---		•			4.0	Återskjut	Planroster
SÖDERHAMN a)	U1 Kamake Torsk 1)		1.5	---	---	---	---	---	---	---	---	---	•					Roterande trumma	1) GASIFICATION OVEN FOR RDF
TROLLHÄTTAN	U1 Bruun & Sörensen		3.3 / 2500	3.1 / 2300	---	---	---	---	---	---	---	---				•	1.6	Vipproster	
UMEÅ	U1, U2 von Roll		5.7 / 2500	5.7 / 2500	5.7 / 2500	5.7 / 2500	---	---	---	---	---	---	•	•			2.1	Tvärroster	Planroster
UPPSALA	U1 och U4 Widmer Ernst	U2 Landsverk; U3 Bruun & Sørensen	15.0 / 2500	15.0 / 2300	3.5 / 2400	3.2 / 2300	5.0 / 2400	4.0 / 2100	10.0 / 2500	10.0 / 2100	---	---	•	•			1) 1.5 2.0	Överskjut Framskjut Vipprost	1) 1.5 resp 4.2
VÄSTERVIK a)	U1, U2 Generator		---	---	---	---	---	---	---	---	---	---		•					Fluidbad

APPENDIX 3a

DATA ON WASTE COMBUSTION 1983

TREATMENT PLANT / DISTRICT (o) not in operation)	PLANTS FORMATION AND TECHNICAL EQUIPMENT: SMOKE GAS REFINING (GAS AT 10% CO_2) – MULTICYCLE	ELECTROFILTER	WET	DRY		MANUFACTURER	MAX CAPACITY AND MEASURED – RAW GAS – MAX CAP.	RAW GAS – MEASURED	DUST IN RAW GAS – MAX CAP.	DUST IN RAW GAS – MEASURED	FILTER CLEANING MANUAL – TIMES/YEAR	STACK – HEIGHT ABOVE GROUND IN METERS	AREA m²	SMOKE GAS SPEED m/s	INTERNAL MATERIAL	SLAG – EXTINGUISHING	OTHER TREATMENT	STOKING		DEALT WITH AS SLAG	DEALT WITH SEPARATELY	REMARKS OBSERVATIONS
AVESTA		•				Svenska Fläkt	400	350	3.8	1.7	2	70	5v 0.8	9.7	corten	•	C-TR	C	C		•	
BOLLNÄS o)	•				•	Industrifilter						65						Silo			•	
BORLÄNGE		•				Industrifilter	930		10.0			86	1.1	26	corten	•	TR-N	Silo	Uttag under		•	
BORÅS		•				Industrifilter	2187	1367	8.0	1.3	0	82	5.5	15	brick	•	SK-N	Silo	Uttag under	•		
EKSJÖ	•				•	Svenska Fläkt	236					60		29	corten		TR		C	•		
GRAAB GÖTEBORG		•				Svenska Fläkt	1700	1500	10.0	4.5	2	120	3x2	24	corten	•	TR	Bunker	Skopa	•		
HALMSTAD		•				Bischoff	835	477	8.0	1) 2.0	2	70	1.1	19.5	corten	•	SK-N	C		•		1) MEASURED 1972
HÖGDALEN STOCKHOLM	•	•				Svenska Fläkt	2600	1900	7.0	< 3.0	1	113	2x1.8	9	corten	•	TR	Bunker	Skopa	•		
KARLSKOGA o)		•				Svenska Fläkt						70		26		•	C			•		
KINDA o)		•				Bacho Lurgi						80				•	C			•		
KÖPING		•				Bacho Lurgi	887	536	7.0	3.4	1	70	1.1	20	SIS 1312	•	SK-TR-C.	C	C		•	
LANDSKRONA o)	•				•	Industrifilter																
LIDKÖPING o)	•			•	•	Industrifilter	420		30			70	0.4		corten		SK-TR-C	Silo	C		•	
LINKÖPING		•				Ratamüle	970 1430					80 60	1.2 1.6	25 25	corten	•	TR	Bunker	Skopa	•		
LULEÅ			•			Bacho OVM-18 Kaskadskrubber	1200	750			K 1)	30	1.1	15	plast	•	SK-N	Slaggrum	Skopa Traktor	•		1)Kontinuerlig vattenrening
LÖVSTA STOCKHOLM		• •				U1-U4 Sv Fläkt U5 -"-	3170 2160		2.0 3.0		K K	68 80	2x2.2 4.5	15 18	corten brick	•	TR-SK	Bunker	Skopa		•	
MORA		•				Industrifilter	384	318	3.8		3	80	2.3	8	corten	•	SK	C	C	•		
SUNDBYBERG	•	•				Svenska Fläkt	397		4.0		1	84	3.1	1)	brick	•	SK-N	Silo	C		•	1) MORE HEATERS CONNECTED
SUNDSVALL o)		•				Svenska Fläkt						100		30	corten				C		Silo	
SYSAV MALMÖ	1) •	•		•	•	Svenska Fläkt Bisholl (elfilter)	1300	1100	7.0	4.0	6	84	2) 1.5	18	corten	•	SK	Bunker	Skopa	• 3)	•	1)Grovcyklon 2)Per pipe 3)Cyklonaska
SÖDERHAMN o)																						
TROLLHÄTTAN	•				1) •	Industrifilter	378	487			52	60	0.8	16	corten	•	SK	Silo	Skopa	•		1)STARTED OPERATION 1983
UMEÅ		•				Svenska Fläkt	883	887	6.0	6.0	1	82	1.2	8-25	corten	•	TR-N	C	C	•		
UPPSALA		•				Research Cottrell(U1A,M) Svenska Fläkt(U2,4,3)	1) 700	2) 870	5.0 5.0	26 1.4/2.0	1	100	4.0 1.1	19 21	corten	•	TR	C	C	•		1)1980/1320 2)1670/1075
VÄSTERVIK o)	•				•	Bacho						70		8-25	corten	•	Skraptransport					

APPENDIX 3b

DATA ON WASTE COMBUSTION 1983

TREATMENT PLANT / DISTRICT (a) NOT IN OPERATION 1983)	OPERATION DATA REGARDING QUANTITIES OF WASTE, SLAG AND ASHES 1983 — WASTE — BURNT IN THE PLANT: Household waste etc.	Industrial waste	Separated RDF (waste fuel)	Firewood chips bark	Waste hazardous to the environment	Risk waste	Total amount of burnt waste	Normal amount of burnt waste	Rejected waste due to no avail plant	SLAG: Amount of slag Dry-T Wet-V	Amount of slag in kilo per ton wet waste	Separated amount for recycling	Replacement for separated material	Deposition or recycling D-A	SEPARATED DUST[1]: Ashes Dry-T Wet-V (ton/år)	Ashes in kg per ton waste wet	Deposition or recycling D-A	REMARKS OBSERVATIONS (1) Percentage of water)
AVESTA	15.8	1.8	9.7	0.7			27.2	37	4.8 [1]	3.8	137			0	480 T	18	0	1) Explosion Accidents
BOLLNÄS a)																		
BORLÄNGE			6.8	37.0			43.8			4.0 V	92			0	1170 T	27	0	
BORÅS	27.8	7.6		3.8		0.1	39.2	30		9.0 V	250			0	850 T	22 T	0	
EKSJÖ			4.5 [1]	21.8			28.3											1) Production in own plant
GRAAB GÖTEBORG	170.9	69.6					240.5	260	7.8 [1]	71.7	289			0		se slagg	0	1) [illegible]
HALMSTAD	27.8	7.0				0.1	34.9	37	3.0	9.8 V	281			0			0	
HÖGDALEN STOCKHOLM	127.4 [1]	4.0 [1]				·	131.4	150	7.5 [2]	37.6 V	288			0		se slagg	0	1) Waste is weighed 2) Leaks in tube
KARLSKOGA a)																		
KINDA a)																		
KÖPING	22.3	3.2	2.0	1.1			28.6	·		7.5 V	262			0	1000	35	0	
LANDSKRONA a)																		
LIDKÖPING a)																		
LINKÖPING	56.7	28.0	8.0 [1]	85.3			145.0			28.0	193			0			0	1) Production in own plant
LULEÅ	18.5						18.5	20	0.8	4.0	218			0	48		Pumpas till avl verk	
LÖVSTA STOCKHOLM	47.1						47.1			13.9 V	296			D+A	1100 T	23	0	
MORA																		
SUNDBYBERG	9.7	0.3		3.4			13.4	10	0.2	3.8 V 30%	281			0	414 V	31		
SUNDSVALL a)																		
SYSAV MALMÖ	131.1	40.3	11.0			0.3	182.7	180		47.8 T	261			0	4000 T	22	0	
SÖDERHAMN a)																		
TROLLHÄTTAN	9.5			0.9			10.4	16	5.6 [1]	2.9	279			0				1) Reconstruction
UMEÅ	58.9			5.9			64.8			21.4 V 33%	330			0	V		0	
UPPSALA	130.7	12.1	9.0	0.1		0.2	152.1		6.7	39.3 V	258			0	[1]		0	1) Weighed with slag
VÄSTERVIK a)																		

STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

August 20, 1985

Mr. Michael A. Berk
McKenna, Conner & Cuneo
Twenty-Eighth Wilshire Blvd.
Los Angeles, CA 90010

Dear Mr. Berk:

Your Comments on Chlorinated Dioxins and Dibenzofurans

Your letter of July 11, 1985 concerning the Report to the Scientific Review Panel on Chlorinated Dioxins and Dibenzofurans has been carefully reviewed. Comments pertaining to Part B of the report have been forwarded to the Department of Health Services. They will prepare responses to your comments, which we will include along with your letter in Part C of the revised report. McKenna, Conner, and Cuneo will receive a copy of the revised report when it is submitted to the Scientific Review Panel.

The majority of the comments prepared by Dr. Leland Attaway deal with topics contained in Part A of this report. We have prepared responses to some of the issues raised in these comments.

EMISSION RATES

A wide range of dioxin emission rates have been cited in the literature for waste-to-energy facilities. We based the range of expected emission rates on facilities of a configuration and design consistent with those being proposed for construction in California. We believe that the most likely emission rate will fall somewhere within the range contained in the report.

The high estimate you mention is based on a single very high test result. The 56 ug/m^3 emission rate seems to be an isolated case as it is nearly twice as high as any other value found in the literature. Cavallaro, who presents this value in a

1982 paper, examined six incinerators. This value was six times greater than the next highest emission rate determined by Cavallero and over one hundred times the lowest dioxin emission rate sited in this study.

An incinerator in Hamilton, Canada was investigated by Ozvacic and found to have a high chlorinated dioxin and dibenzofuran emission rate (29 ug/m^3). Ozvacic found that this was a poorly operated facility. Corrective action was taken which reduced chlorinated dioxin and furan emissions to 8.1 ug/m^3. Tests of waste-to-energy facilities have generally shown lower total chlorinated dioxin and dibenzofuran emission rates than the more recent test of the Hamilton facility.

A few very high values skew the average chlorinated dioxin and dibenzofuran emission rate you calculated upward. For example, if the two highest and two lowest measured emission rates sited in Air Pollution Control at Resource Recovery Facilities are dropped when calculating an average, the value drops from 7.7 ug/m^3 to 0.9 ug/m^3. A review of existing source test results strongly suggests that a well designed and managed facility would be very likely to have an emission rate within the range presented in the report.

SIGNIFICANT PATHWAYS

This report does discuss ingestion and dermal exposure as other possible routes of chlorinated dioxin and dibenzofuran exposure. The investigations of this issue we sited conclude that exposure due to ingestion and dermal exposure may equal that due to air exposure. There is no accepted methodology for quantifying the exposure due to these pathways which makes any assessment of the risk posed by these pathways open to question. We did not intend to dismiss these pathways, and included them to show that the risk posed by dioxin emissions may be greater than air exposure alone. We plan to give more emphasis to these alternative exposure pathways in the final report.

EMISSION CHARACTERISTICS

At the time the modeling analysis was performed, we were unaware of the relationship between the stack at Irwindale and the surrounding terrain. We are in the process of evaluating the effect of the lower stack height (45.7 m) on exposure. Preliminary results indicate that the change in stack height will not affect the maximum exposure level which is used in the risk assessment. The facilities examined in the modeling study were

selected to provide an estimate of the ambient levels which might be expected to occur in Los Angeles. The analysis was not intended to serve as a risk assessment for any proposed facility currently under review.

Thank you for your comments.

Sincerely,

for William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: Peter Venturini, ARB
Raymond Neutra, DHS

Southern California Edison Company

P. O. BOX 800
2244 WALNUT GROVE AVENUE
ROSEMEAD, CALIFORNIA 91770

EDWARD J. FAEDER, Ph.D.
MANAGER OF ENVIRONMENTAL OPERATIONS

TELEPHONE
(818) 302-2009

July 11, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Attention: Dioxin
Air Resources Board
1800 15th Street
P.O. Box 2815
Sacramento, CA 95812

SUBJECT: Report to Scientific Review Panel on
Chlorinated Dioxins and Dibenzofurans

Southern California Edison Company has reviewed the Air Resources Board report concerning the health risks of airborne polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) and we would like to submit these brief comments on the methods used to assess the carcinogenic potency of these compounds and the risks they pose to public health.

This evaluation of PCDDs and PCDFs is different from previous evaluations of toxic air contaminants in several ways. The assessment of potential public health risks is not based upon actual measurements of these compounds in the ambient air, but is instead based upon a presumed mixture of PCDDs and PCDFs resulting from 9 hypothetical (nonexistent) resource recovery facilities which have been presumed to be located within the South Coast Air Basin. Regulations governing the evaluation of toxic air contaminants indicate that the process should include "the range of risk to humans resulting from current or anticipated exposure." However, we feel that this type of anticipated risk estimate must be differentiated from risks calculated from actual air quality monitoring and exposure data. The actual risks resulting from these resource recovery facilities will depend on where, when and if they are sited and become operational within the state. The hypothetical nature of these risk estimates should be pointed out in the report. The actual risks from PCDD and PCDF sources at present and in the future may be quite different from those presented.

The PCDD and PCDF evaluation is also different from previous ones in that the compounds being evaluated are actually broad groups of several related compounds which vary in chemical structure and toxicological effects. This creates two problems:

1) Since carcinogenicity data are available for only a few of the many forms of PCDDs and PCDFs, some method must be devised to estimate the carcinogenic potency of compounds for which little or no toxicity data are available.

2) Information on PCDDs and PCDFs found in ambient air is limited: therefore some method must be devised to estimate the total amount and the specific mix of the various PCDD and PCDF isomers which people are exposed to at present and in the near future.

These problems are both dealt with in the development of "TCDD Equivalent Proportions" presented in Section 10.4 of your report. This section estimates carcinogenic potencies, the mix of compounds resulting from resource recovery facilities, and the resulting risk to the public from the siting of 9 of these facilities in the South Coast Air Basin. Because the mixture of these compounds emitted from specific sources and found in ambient air is not known at this time, we believe it would be more appropriate to deal with the two problems separately. The toxicity of various classes of PCDDs and PCDFs should be determined, and then these potency estimates can be combined with emissions data to determine the extent of risk from specific facilities or source categories.

ARB presents three scenarios for estimating the toxicity of the various forms of PCDDs and PCDFs. In Scenario 1, all PCDDs and PCDFs are assumed to be equivalent to 2,3,7,8 tetrachlorodibenzodioxin (2,3,7,8 TCDD) in structure and carcinogenic potential (alternatively, the compounds are acknowledged to have different structures but are nevertheless assumed to have a potency equivalent to 2,3,7,8 TCDD). These assumptions are clearly inappropriate given the available data on chemical structure and toxicologic potency.

Scenario 2 assumes that 2,3,7,8 TCDD and the hexachlorodibenzodioxins (HxCDD) chlorinated in the 2,3,7,8 positions each have the carcinogenic potency which they have demonstrated in animal bioassays. It is furthermore assumed that all pentachlorodioxins (PeCDD) and dibenzofurans (PeCDF) and heptachlorodibenzodioxins (HpCDD) and dibenzofurans (HpCDF) which are chlorinated in the 2,3,7,8 positions are of equal carcinogenic potency as 2,3,7,8 TCDD.

This scenario also incorporates inappropriate assumptions. The results from the bioassay on HxCDD demonstrate that the carcinogenicity of these compounds is not solely determined by chlorination at the 2,3,7 and 8 positions; hence the 38 fold reduction in carcinogenic potency of 2,3,7,8 HxCDD as compared to 2,3,7,8 TCDD.

The basic problem faced by ARB and DHS is to estimate a carcinogenic potency for compounds when there are no carcinogenicity data available. The most logical approach would be to use all available toxicologic data on this class of compounds in the estimation of such a potency factor.

The EPA's Chlorinated Dioxin Work Group has compiled toxicity endpoint information for this class of compounds, including carcinogenicity, acute lethality, enzyme induction, receptor binding and others. The data indicate that chlorination at the 2,3,7 and 8 position is an important indicator of toxicity. However, the data also show that the degree of total chlorination (as one progresses from tetrachloro to octachloro 2,3,7,8 derivatives) is also an important determinant of toxicity. Thus, just as the addition of two chlorines reduces the carcinogenic potency of TCDD by 38 fold, the available toxicity data indicate that one would expect the 2,3,7,8 HpCDDs to show a lesser biological potency than the less chlorinated HxCDDs. The same would be true for the dibenzofurans. The potency of the 2,3,7,8 PeCDDs would be expected to lie somewhere intermediate between TCDD and HxCDD. The toxicity data also indicate that the dibenzofurans would be expected to have less biological potency than their similarly chlorinated dibenzodioxin counterparts.

An approach available to the ARB is that taken by the EPA's Chlorinated Dioxin Working Group whereby all toxicity endpoints are assessed, including acute toxicity data and in vitro bioassay data. These data are then used to estimate the carcinogenic potency of a particular isomer. The ARB has included this approach as Scenario 3 in the report but state that they favor Scenario 2 because it "takes a health conservative approach".

We feel that this graded toxicity estimate is the preferred approach given the absence of carcinogenicity data for the majority of chlorinated dioxins and dibenzofurans. The <u>best scientific judgement</u> approach utilized by the Chlorinated Dioxin Working Group (and outlined in ARB's Scenario 3) should be adopted for use in estimating these potencies, rather than adopt a <u>worst case</u> scenario and assume that all 2,3,7,8 cogeners are as potent as TCDD (unless evidence is available to the contrary).

The multistage model, it should be noted, produces highly conservative risk predictions. The exposure estimates included in this report are themselves likely to be highly conservative. Choosing this conservative definition of carcinogenic potency (i.e. Scenario 2), repeatedly applying these highly conservative assumptions, will result in an unreasonably high risk estimate. SCE therefore recommends that Scenario 3 be used for estimating cancer potencies of those isomers for which the data are not available.

Thank you for the opportunity to provide comments during the development of this important document.

Sincerely,

Edward J. Farley

STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

August 9, 1985

Dr. Edward J. Faeder, Ph.D.
Manager Manager of Environmental Operations
Southern California Edison Co.
PO Box 800
Rosemead, CA 91770

Dear Dr. Faeder:

Subject: Your Comments on Chlorinated Dioxins and Dibenzofurans

Your letter of July 11, 1985, concerning Report to the Scientific Review Panel on Chlorinated Dioxins and Dibenzofurans, Part B has been forwarded to the Department of Health Services. They will prepare responses to your comments, which we will include along with your letter in Part C of the revised report. Southern California Edison will receive the revised report when it is submitted to the Scientific Review Panel.

Thank you for your comments.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: P. Venturini, ARB
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THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48640

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July 11, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Attention: Dioxin
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

In response to the June 12, 1985, notice of opportunity to review and comment on reports pertaining to chlorinated dioxins and dibenzofurans, The Dow Chemical Company is submitting the following comments. Due to the short period of time available for comment, we were not able to provide a more detailed critique. However, we believe the following comments will hopefully assist your agency in understanding and clarifying the numerous references reviewed in the Health Effects Report.

On page 1-3 of the Executive Summary, the DHS Health Effects Report states the following: "In addition, because of structure activity considerations and the lack of chronic exposure studies on penta and hepta CDD and CDF isomers, DHS has concluded that these isomers must also be considered potential human carcinogens." This rationale whereby only (1) structure-activity relationships and (2) the lack of chronic exposure studies are the sole basis for considering these other isomers to be potential human carcinogens is inadvisable and unconventional, as this approach has typically not been used by regulatory agencies. The categorization of a chemical as a potential human carcinogen has been typically made only after actual experimental data from laboratory animal studies are available and interpreted as indicative of a positive carcinogenic response in the laboratory animals. Furthermore, in keeping with the general theme in the draft document whereby DHS agrees with the general concepts regarding the categorization of the experimental evidence of carcinogenicity of 2,3,7,8-TCDD for laboratory rodents, it would appear more scientifically appropriate for DHS to not distort or deviate from the conventional format of requiring validated experimental data as the basis for categorization of a substance as a potential human carcinogen. This is particularly important in this case since a large number of distinct compounds are being implicated as carcinogens.

In the case of the 2 Hexa CDD's that have been bioassayed for carcinogenic potential in laboratory animals, there appears to be rather substantial differences among the diagnoses rendered by different pathologists who have examined the same liver sections. The examination of Squire (1983) reported only neoplastic nodules with no actual cancer induction in the female rats given the Hexa CDD's. In view of the fact that Squire is the only pathologist who has had occasion to histopathologically examine the tissues from animals used in the bioassays of 2,3,7,8-TCDD and Hexa CDD's, his data would appear to be the most valid for comparative assessment of carcinogenic potency of the chlorinated dioxins. As the examination of Squire reported only neoplastic nodules with no actual cancer induction with the Hexa CDD's, this raises the question as to the appropriateness of DHS utilizing these data for the mathematical modeling of carcinogenic risk assessment for these Hexa CDD's, especially when the DHS has characterized the Hexa CDD's bioassay as suggesting only a tumorigenic response (page 8-12 of draft).

Based on the weight of the evidence as presented in the DOHS proposal indicating that 2,3,7,8-TCDD has caused the carcinogenic response in laboratory animals through an indirect mechanism of action (such as promotion) and in view of the fact that 2,3,7,8-TCDD has been shown to have essentially no potential for interaction with DNA, it would be scientifically more valid to use a threshold-based approach or one of the less conservative models in the risk assessment for 2,3,7,8-TCDD.

On pages 8-6 to 8-9 of the draft document, the results of the NTP bioassay of 2,3,7,8-TCDD in rats and mice are discussed. Both the text and Tables 8.1-4 and 8.1-5 list certain tumor type tabulations in a manner that incorrectly implies that all of these tumor types were considered to be related to treatment with TCDD. If one closely evaluates the actual data in the NTP report of this bioassay, one finds substantial variability in spontaneous tumor incidences among the various control subgroups. The variability in spontaneous tumor incidences indicate that not all of the tumor types listed in Tables 8.14 and 8.15 were related to treatment with 2,3,7,8-TCDD.

The issue of decreased bioavailability of chlorinated dioxins adsorbed onto particles such as soil or dust particles should be more adequately factored into the draft proposal. Table 10.3-2 and Figure 10.3-1 are based on air exposures but calculated from gavage exposures (NTP, 1982a). Thus the bioavailability of chlorinated dioxins on dust is a critical component of the calculation. Recent data generated by Dr. Michael Gallo of Rutgers University indicates a relative lack of absorption of a toxic dose of chlorodioxins when present in a soil matrix. This new information should be obtained from Dr. Gallo for inclusion in the document, particularly since these data would indicate an "order of magnitude" difference in dose to the subject.

The section of the draft document on Risk Assessment outlines three scenarios offered by DHS as proposed methods of estimating cancer risk for the assumed mixture of chlorinated dioxins and furans. For reasons outlined above, there are scientifically valid and substantive reasons to not utilize the proposed nonthreshold mathematical modeling for purposes of risk assessment of these mixtures.

However, if certain revisions were made in accordance with the reasons stated above, a revised version of the assumptions in Scenario 3 would be more scientifically valid when compared to the assumptions in Scenarios 1 and 2.

The assumptions in both Scenarios 1 and 2 are flawed and contradicted by the composite of the known scientific data regarding the comparative toxicity and biologic activity of the chlorinated dioxins and furans. The assumption in Scenario 1 (assuming that all PCDD/PCDF isomers are as potent as 2,3,7,8-TCDD) and Scenario 2 (assuming that PCDD's and PCDF's that are chlorinated on the 2,3,7,8 positions and have at least one ring position unchlorinated are as potent as 2,3,7,8-TCDD) are contradictory to what is known about the relative toxicity/biologic activity of these PCDD's and PCDF's. The EPA paper by Bellin and Barnes (1984) as well as the paper by Kociba and Cabey (1984) indicate substantial differences in toxicity/biologic activity among these PCDD's and PCDF's. For example, the compilation of relative toxicities of PCDD's and PCDF's prepared by Bellin and Barnes of EPA indicate a 1000x differential between 2,3,7,8-TCDD and the 2,3,7,8 Hepta CDD's or the 2,3,7,8 Hepta CDF's.

Thus, the available scientific data do not support the assumptions made in either proposed Scenario 1 or Scenario 2. A revised application of the assumptions in Scenario 3 more adequately reflects the actual scientific data on the relative toxicity/biologic activity of the PCDD's and PCDF's.

In addition, the Health Effect Report could be improved by inclusion of several additional reported references, a more complete reporting of the results of some of the studies considered and a different view of the concept of confounding. In addition, some of the specific comments in the Report could lead to a misinterpretation of the study conclusions.

Several missing literature articles, which we referenced to your agency in our earlier correspondence (Nov. 14, 1984), can be itemized: 1) The American Medical Association Review which should be a part of Section 2. 2) The Fingerhut presentation at Rockefeller symposium was reported to the board as being in press in 1984 and considerably updates Fingerhut and Halperin (1983) reported on page 8-24. 3) A Cook (1984) publication was provided to the Board with reference to Ekland (1983). These studies reviewed the soft tissue sarcoma reports of Hardel and noted the probability of observer bias which is not discussed on page 8-19.

There are several examples of selective use of literature perspective in the Health Effect Report. Examples, but not an inclusive list, is presented here for clarification of the point.

The Townsend (1982) study (Pg. 6-7) is reported to have stated "the power to detect risks of 1.5 or more was only 50%---." However, the full quote would read: "the power to detect a crude adds ratio of 1.5 or greater varied from less than 50% for Still-births, Indicator Malfunction and Infant Deaths to 80% or greater for all Conceptus Deaths, all Unfavorable Outcomes, and for Spontaneous Abortions."

The Townsend study was also judged likely to be inaccurate due to the use of historical data but the Hardell reports which used similar historical data were not downgraded in a like fashion.

The Zack and Gaffy (1983) study attributed bladder cancers to other exposures and did not include a smoking history. Since lung and bladder tumors are specifically discussed on page 8-22, these facts should also be reported.

On page 8-24, the Report notes that Bond et al. (1983) reported increased ulcers and diseases of the digestive system, but omits the fact that such increases were not dose related. A summary comment on this study notes that "the study might have missed the most affected workers" without acknowledging the equal probability of missing the least affected workers.

The authors of the Report have misused the Concept of Confounding in Section 6.2. Several of the negative studies are dismissed because they suffer from serious problems in "their failure to rule out that multiple exposures to various agents did not have significant confounding effect on the outcomes studied." The confounder would have to be protective if such logic were to be considered valid.

A limited number of specific comments that have been identified are listed below.

Page 1-3 - Line three states "shown elevated risks." Since debate is continuing on these data, it should state, "reported elevated risks."

Page 8-18 - Section 8.2.1 line 5 notes a history of "heavy" exposure. The exposures recorded in this study were variable, not consistently heavy.

Page 8-25 - Reports one study as "carefully conducted." It is our opinion that most studies are carefully conducted even though some of the conclusions are subject to debate.

Risk assessment is a complex procedure requiring a large number of assumptions, most of which are made with very little scientific guidance. In the interest of protecting human health, these assumptions generally take the most conservative position. This is done as a matter of policy in the absence of a rigorous scientific understanding.

This compounding of conservative assumptions results in assessments which are, at best, extreme upper limits on risk and do not translate into actual number of cases of cancer per year. These estimates also have a tremendous amount of uncertainty due to the possible choices of assumptions. One measure of the uncertainty in the estimates is the difference between the "best estimate" of risk for the multistage model and the upper 95% confidence limit. However, this difference represents only one of the uncertainties in the entire process. As an example of the impact of assumptions, the DHS document estimates risks ranging from less than 1 up to 1400 per million as a result of differing assumptions on the carcinogen potency of the untested PCDD's and PCDF's and depending upon whether "best estimates" or 95% upper bounds are used.

DHS has explicitly listed the assumptions to be made and the specific options that were taken. They have also stated in a number of cases that a conservative position was taken as a matter of policy because of scientific uncertainty. The uncertainty in these estimates can be reduced, however, when assumptions can be replaced by data. It has been generally recognized that when these data are available, they should be used (EPA, 1984; NAS, 1983; OSTP, 1984).

In particular, the following assumptions listed in Section 10 of the DHS document need re-examination:

1. Use of the most sensitive sex, species, study.

This assumption is often made as a matter of policy to protect public health. It must be clearly stated, however, that the resulting estimates cannot be literally translated into actual cancer cases per year. Instead, the numbers represent only worst case scenarios.

2. Route of exposure.

In the absence of pharmacokinetic data, equivalency of routes of exposure is sometimes assumed. In the case of inhalation exposure to PCDD's and PCDF's, the assumption of 100% bioavailability of the active compound is very questionable. There are data indicating that this family of compounds tend to bind to particles and are not 100% biologically available Poiger and Schlalter, 1980 (Appendix E, reference), Gallo, personal communication.

3. Surface Area.

In the absence of data, it is often assumed that man is approximately six times more sensitive than a rat and 13 more sensitive than a mouse to exposure expressed on a mg/kg/day basis. This is based on man's lower metabolic rates and lower surface area/body weight ratio. In the case of 2,3,7,8-TCDD, there are indications that man is likely less sensitive than rats to the toxic effects of the compound. Therefore, the risk assessment for TCDD should incorporate, at most, equal sensitivity on a mg/kg/day basis. Equal sensitivity is the general assumption made for most other toxicological endpoints. Increased sensitivity for carcinogenic effects in man has been assumed as a policy decision but is not appropriate for TCDD.

There are other assumptions listed in Chapter 10 which we generally do not agree with on a conceptual basis, but the pro and con arguments are presented in the DHS document and have been discussed at length in the past. These assumptions include lack of thresholds, appropriateness of modeling in general.

A set of assumptions which should be further addressed are set out in the three scenarios described in the DHS document and are discussed in an earlier section of these comments.

Two additional references which may be of assistance are enclosed:

(1) Bellin, J. and D. Barnes. April, 1985. Chlorinated Dioxins Workgroup Position Document. Interim Risk Assessment Procedures for Mixtures of Chlorinated Dioxins and Dibenzofurans (CDD's and CDF's).

(2) Kociba, R. J. and O. Cabey. 1984. Comparative Toxicity and Biologic Activity of Chlorinated Dibenzo-p-Dioxins and Furans Relative to 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD). Presented at the 4th International Symposium on Chlorinated Dioxins and Related Compounds, October 16-18, 1984, and published as Proceedings in Chemosphere.

In evaluating the Part A report, it was not possible to evaluate the conclusions since the input data and a description of the model structure was not provided.

Dow Chemical would like to thank you for this opportunity to review and comment on your draft reports prior to their submittal to the Scientific Review Panel (SRP). It would be appreciated if you would transmit these comments to the SRP as part of your draft report. If either members of your agency or the SRP would like to discuss our comments, please contact Bryant Fischback in our Western Division at 415-432-5051.

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Enclosure

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CHLORINATED DIOXINS WORKGROUP POSITION DOCUMENT
April, 1985

INTERIM RISK ASSESSMENT PROCEDURES FOR MIXTURES OF CHLORINATED DIOXINS AND -DIBENZOFURANS (CDDs and CDFs)*

I. Summary

EPA increasingly is confronted with the need to determine the risks inherent in exposure to materials such as soot, incinerator flyash, industrial wastes, and soils. Exposure to these materials often involves the potential for exposure to a mixture of chlorinated dibenzo-p-dioxins (CDDs) and chlorinated dibenzofurans (CDFs). Recognizing that there is much to learn about these chemicals, the Chlorinated Dioxins Work Group (CDWG) is proposing an interim method for assessing the human health risks posed by mixtures of CDDs/CDFs.

The CDWG has discussed several approaches for making such assessments and has concluded that a direct biological assessment of the toxicity of complex mixtures of CDDs/CDFs is preferred. Therefore, research to develop appropriate methods of this type should be supported. In the interim, however, the CDWG believes that a reasonable estimate of the toxic risks can be made by taking into account the distribution of CDD/CDF congeners or homologues that are estimated to have the greatest toxic potential. This document describes the recommended procedure for generating the "2,3,7,8-TCDD equivalents" of complex mixtures of CDDs/CDFs, based upon congener- or homologue-specific data and for using such information in assessing risk.

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* Refer to Appendix for precise nomenclature used in this paper.

The recommendations are summarized in the right most column in Table III.

The CDWG acknowledges that this procedure is not based on a thoroughly established scientific foundation. It represents a consensus recommendation on science policy. Consequently, assessors and risk managers are urged to use informed discretion when deciding to what situations the procedure can be appropriately applied.

II. The Need for a Procedure for Assessing the Risk Associated wit Exposure to Complex Mixtures of CDDs/CDFs

During the late 1970s, the Agency was faced with assessing the human health significance of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). In preparation for the cancellation hearings for the herbicides 2,4,5-trichlorophenoxyacetic acid and silvex, the Agency generated risk assessments for several toxic responses for 2,3,7,8-TCDD. The quantitative cancer risk assessment produced by the Cancer Assessment Group was later adapted for use in the Water Quality Criteria (WQC) Document for 2,3,7,8-TCDD. In addition to carcinogenicity concerns, the WQC contains an assessment of systemic toxicity, based on reproductive effects produced by 2,3,7,8-TCDD. The Agency's concern for CDDs and CDFs has expanded more recently. For example, the current draft of the Health Assessment Document prepared for the Air Program contains a quantitative risk assessment for a mixture of hexachlorodibenzo-p-dioxins (HxCDDs), based upon carcinogenicity studies conducted by the National Cancer Institute.

However, as early as the late 1970s, it became clear that exposure situations existed in the country which involved more than simply

2,3,7,8-TCDD. Specifically, data on emissions from combustion sources (e.g., hazardous waste and municipal waste incinerators) and contents of waste from certain industrial production processes indicated that the majority of the 75 CDDs and 135 CDFs can be detected in the environment.

Given the high potency and strong structure-activity relationships exhibited in in vivo and in vitro studies of CDDs and CDFs, the CDWG recognizes that the potential risks posed by the congeners other than 2,3,7,8-TCDD need to be addressed.* Detailed consideration of the toxicity of the vast majority of the CDDs/CDFS is limited by the lack of toxicology studies on most of the congeners. Further, it is unlikely that many expensive long-term test results will be available soon. For example, research on 2,3,7,8-TCDD has been underway for more than two decades at an estimated cost in the hundreds of millions of dollars. Although this chemical has been investigated to a much greater extent than any of the other CDDs/CDFs, unanswered questions remain. As noted below, the CDWG believes that it would be unwise, uneconomical and unnecessary to conduct such extensive testing on each of the CDD/CDF congeners prior to conducting an assessment of their risks.*

* In the early 1980s, the Agency developed an approximate method for assessing the risks of the emission of CDDs/CDFs associated with the high temperature incinceration of PCBs and combustion of municipal waste (USEPA, 1980; USEPA, 1981); cf. Table III. The procedure presented in this document is a refinement of that approach.

III. Approaches to Hazard Assessment for CDD/CDF Mixtures

A. Overview.

1. Preferred Practical Approach -- Toxicity Assay of Mixtures

In the first instance, an assessment of the toxicity of a mixture of chemicals is best accomplished by direct evaluation of its toxic effects, e.g., by determining the effects of chronic exposure in an experimental animal. Such an assessment is time consuming and costly and would theoretically have to be performed for each of the many mixtures of environmental importance. Therefore, this idealized approach is not likely to be achieved in the near future.

An alternative, practical approach to hazard assessment of a mixture is an assay that indirectly provides a measure of the mixture's potential toxicity. In the case of mixtures containing CDDs and CDFs, short term assays are under development that directly determine the 2,3,7,8-TCDD-like response which can be used as a measure of the toxicity of the mixture as a whole. Such assays, which take advantage of the similar toxic manifestations induced by CDDs and CDFs, have been used to assess the potential health hazards of exposure to CDD/CDF-contaminated soot from PCB fires (Eadon, 1982; Gierthy, 1984; Gravitz, 1983), and predicting the potential toxicity of incinerator flyash (Sawyer, 1983). The development of such "mixture assays" is progressing rapidly. While additional work is required to more fully validate the assay findings for specific toxic endpoints, especially chronic effects, data have been presented that indicate

correlations with subchronic effects of CDDs/CDFs (Safe, 1984). The CDWG recognizes the importance of this approach in implementing its regulatory strategy for 2,3,7,8-TCDD-like chemicals and encourages research in this area.

2. Alternative Approach -- Additivity of Toxicity of Components

In the absence of more fully developed "mixture assays", however, the CDWG recognizes the viability of a second approach to assessing the risk posed by a mixture of CDDs/CDFs. First, components in a mixture of CDDs and CDFs are identified and quantified. Then, the toxicity of the mixture is estimated by adding the toxicity contributed by each of its components.

In the case of most environmental mixtures, however, this method cannot be directly applied, since congener-specific analyses for the 75 CDDs and 135 CDFs potentially present in the mixture are seldom available. In addition, there is little information available on the toxic potency of most of these congeners. Therefore, this approach is not viable at this time and is not likely to be feasible in the near future.

3. An Interim Approach -- 2,3,7,8-TCDD Toxicity Equivlance Factors (TEFs)

The CDWG recognizes a third alternative for estimating the risks associated with exposure to complex mixtures of CDDs/CDFs. First, as in approach #2, information is obtained on the concentrations of homologues and/or congeners present in the mixture. Then, reasoning on the basis of structure-activity relations and results of short term tests, the toxicity of each of the components is estimated and expressed as an "equivalent amount of 2,3,7,8-TCDD". Combined with

estimates of exposure and known toxicity information on 2,3,7,8-TCDD, the risks associated with the mixture of CDDs/CDFs can be assessed. Key to the approach are the 2,3,7,8-TCDD Toxicity Equivalence Factors (TEFs) which are derived in Section IV below.

The general approach of TEFs outlined here is not unique: several organizations have used similar approaches; cf. Table III.

The CDWG recommends that the TEF procedure be adopted as a matter of science policy on an interim basis. The approach will enable the Agency to deal with many, but not all, of its roblems; e.g., which Superfund sites should be given administrative priority, to what extent a hazardous waste site should be cleaned up, which manufacturing wastes can be delisted as EPA hazardous wastes, and how to esimate the risks associated with the emission of CDDs/CDFs from combustion sources.

The remainder of this document discusses the TEF approach in greater detail, illustrates its use in risk assessment, and identifies additional research, the results of which would strengthen the basis of this interim approach.

IV. The 2,3,7,8-TCDD Toxicity Equivalence Factors (TEFs) Approach to Assessing the Toxicity of Complex Mixtures of CDDs/CDFs

2,3,7,8-TCDD is one of 75 CDDs. Exceptionally low doses of this compound elicit a wide range of toxic responses in many animals; e.g., adverse reproductive effects, thymic atrophy, and a "wasting syndrome" leading to death. EPA's Cancer Assessment Group (CAG) has determined that there is sufficient evidence to treat 2,3,7,8-TCDD qualitatively as a potential human carcinogen. The CAG quantitative asesssment indicates that the chemical is the most potent animal carcinogen evaluated by the Agency to date. Limited data suggest that some of the 74 other CDDs may have similar toxic effects, again at low doses.

Moreover, these toxicity concerns are not restricted to CDDs. Limited experimental data, supplemented by strong structure/activity relationships in in vitro tests that are correlated with in vivo toxic effects of these compounds, indicate that some CDFs exhibit "2,3,7,8-TCDD-like" toxicity (Bandiera, 1984; Safe, 1984).

The cellular biochemical mechanisms leading to the toxic response resulting from exposure to CDDs and CDFs are not known in complete detail. However, over the last few years experimental data have accumulated which suggest that an important role is played by an intracellular protein, the Ah receptor. This receptor binds halogenated polycyclic aromatic molecules, including CDDs and CDFs. In animals, the binding of 2,3,7,8-TCDD-related compounds to this receptor has been correlated with the expression of several systemic toxic effects including sensitivity to acute toxic effects (LD_{50} values), thymic involution, chloracnegenic

response, and the induction of several enzyme systems, some of which have been linked to carcinogenic pathways (Poland and Knutson, 1982; Bandiera et al., 1984).

Table I contains information on a variety of endpoints: acute toxicity, carcinogenicity, reproductive effects, receptor binding, enzyme induction, and in vitro cell transformations. The data are normalized to unity for 2,3,7,8-TCDD. For example, 2,3,7,8-substituted HxCDDs have about 5% the Ah receptor binding strength of 2,3,7,8-TCDD, they are about 70% as potent in the ability to induce the enzyme AHH; and their carcinogenic potency is about 4% that of 2,3,7,8-TCDD. For these effects the LOELs or NOELs for 2378-congeners are about one hundred-fold lower than those for the non-2378 congeners. Kociba (1984) has recently presented similar data.

The structure/activity generalizations based on the data in Table I bear out the generalizations in the literature concerning the congeners that are most likely to be of toxic concern (Poland, 1982; Gasiewicz, 1982; Bandiera et al., 1984). That is, congeners which are substituted in the lateral 2, 3, 7, and 8 positions are likely to exhibit toxic effects at lower doses than other congeners. This includes the fifteen tetra-, penta-, hexa- and heptachlorinated CDDs and CDFs listed in Table II.*

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* The CDWG is aware that some investigators (e.g., Grant, 1977; Olie, 1982; Commoner, 1983; and Ontario, 1983) have broadly defined the congeners of conern to include all those tri- to hepta- congeners

which are substituted with at least three chlorines in the four lateral (2,3,7 and 8) positions. The CDWG has reviewed the toxicity data and does not find it to argue strongly for this extended range of concern. Further, the increased level of complexity invoked by including these additional congeners is to suggest a greater level of accuracy and resolution than the CDWG believes is warranted.

The CDWG is also aware that receptor binding data suggest a relatively high toxicity for 1,2,4,6,7-PeCDF. Examination of stereochemial models point out that the 4/6 positions on CDFs are arguably "more lateral" than the 2/8 positions (Bandiera et al, 1984). However, this increased receptor binding acitivity is not reflected in an increased potency of 1,2,4,6,7-PeCDF as an enzyme inducer (cf. Table I), an endpoint which has been shown to correlate with subchronic toxicity (Safe, 1984). Therefore, the CDWG is not treating 1,2,4,6,7-PeCDF as a "2378-congener" at this time; however, additional data could lead to a change in this position.

The associated "2,3,7,8-TCDD equivalent factors" were assigned as follows. The relative carcinogenicity responses (Table I) for 2,3,7,8-TCDD and the mixture of two 2378-HxCDDs* provide the TEF for 2378-HxCDD. The relative toxicity of 2378-PeCDD was taken to be the root mean square of the 2378-TCDD and 2378-HxCDD values. The remaining assignments in Table II and Table III (righthand column) are based on a rough assessment of the data in Table I, subject to these constraints:

1. The CDFs are likely to be less toxic than their corresponding CDDs, based on compartive toxicity data of 2,3,7,8-TCDD and 2,3,7,8-TCDF in various species (Moore, et al, 1979).
2. As a matter of judgment, the CDWG believes that the uncertainties in the procedure limit discrimination of relative toxicity to order of magnitude estimates.

In the same vein, TEFs for the non-2378 isomers are assigned values which are 1% of the TEFs of the 2378-isomers in the same homologous group.

While it could be argued that the hepta- congeners are of lesser concern, the CDWG recognizes that in some mixtures the hepta congeners predominate; therefore, they are not entirely excluded.

The general approach of estimating relative toxicities discussed here has been taken by other groups in reaching decisions regarding risk. Table III lists the TEFs used by these other workers.

* Refer to Appendix for nomenclature

The TEFs assigned (except for the HxCDDs) do not rest on the results of long term animal studies. Generally, they are based on estimates of the relative toxicity in in vitro tests whose relationship to the chronic effects of concern is largely presumptive. However, experimental results continue to supplement the view that the short term assays are providing important fundamental information on the toxicity of the CDDs/CDFs. For example, for the higher chlorinated CDFs, induction of certain enzymes correlates rather well with thymic atrophy and body weight reduction noted in subchronic rat studies (Bandiera et al., 1984; Safe, 1984).

It should also be noted that the structure/activity relationships are not uniformly consistent and cannot be said to have established, at this point, a causal relationship between the Ah-receptor and all forms of toxicity of CDDs and CDFs. For instance, it has recently been noted that the development of porphyria in mice does not correlate with Ah phenotype and that genes other than Ah influence the development of 2,3,7,8-TCDD-induced hepatotoxicity in mice (Greig, 1984).

In summary, in the view of the CDWG, there is a sufficient scientific support for the TEF approach to estimating risks associated with CDDs/CDFs that the Agency should adopt the approach, on an interim basis, as a matter of science policy.

V. Applications to Risk Assessment

In general, an assessment of the risk to human health of a mixture of CDDs and CDFs involves the following steps:

1. Analytical determination of CDDs and CDFs in the sample.
2. Multiplication of congener concentrations in the sample by the TEFs in Table III express the concentration in terms of 2,3,7,8-TCDD equivalents.
3. Summation of the products in step 2 to obtain the "2,3,7,8-TCDD equivalence" of the sample.
4. Determination of human exposure to the mixture in question, expressed in terms of equivalents of 2,3,7,8-TCDD.
5. Combination of exposure from step 4 with toxicity information on 2,3,7,8-TCDD (usually carcinogenicity and/or reproductive effects) to estimate risks associated with the mixture.

In cases in which the concentrations of the fifteen congeners of concern are known:

$$\text{2,3,7,8-TCDD Equivalents} = \sum (\text{TEF of each 2378-CDD/CDF congener} \times \text{the concentration of the respective congener}) + \sum (\text{TEF of each non-2378 CDD/CDF congener} \times \text{the concentration of the respective congener})$$

samples of this calculation for several environmental mixtures are provided in Table IV.

In cases where only the concentration of homologous groups is known; i.e., no isomer-specific data are available, different approaches are possible. For example, the assumption that the 2378-congeners of concern constitute all of the CDDs and CDFs present in the mixture is likely to provide an upper bound estimate of the toxicity. Alternatively, one could assume that the occurrence of each of the congeners in the

mixture has equal probability (Olie, 1982; Commoner, 1982). For instance, 2,3,7,8-TCDD is one of 22 possible TCDDs and would constitute about 4% of a mixture of equally probable isomers. In other situations, particular knowledge of chemical reaction parameters, process conditions, and results from related studies, (e.g., congener distributions in emissions from combustion sources) might enable one to estimate the relative occurrence of 2378-congeners. However, one must be careful to explicitly explain and justify whatever assumptions are made.

The calculated "2,3,7,8-TCDD equivalents" can then be used to assess the health risk of a mixture. As an explicit example, consider a municipal solid waste (MSW) combustor whose particulate emissions, the CDD/CDF mixture in question, were exactly like the electrostatic precipitator (ESP) catch cited in columns 5 and 6 of Table IV. The sample is estimated to contain 28 ppb 2378-TCDD equivalents; i.e., 28 picograms of 2378-TCDD equivalents per milligram of mixture. Suppose that an exposure analysis indicates that a person living downwind from the incinerator receives an average daily dose of 1 ng of the mixture/kg body weight. This exposure estimate is combined with the upper bound carcinogenic potency of 2,3,7,8-TCDD (1.6×10^5 per mg/kg-day (U.S. EPA 1984)) to generate the upper 95% limit of the excess risk of developing cancer for a person living downwind from the facility emitting the mixture under consideration, assuming lifetime exposure:

Upper 95% limit of excess cancer risk = [potency] x [exposure]
= [1.6×10^5 per mg TCDD/kg-day] x [28 pg TCDD/mg mixture x 10^{-9} mg TCDD/pg TCDD x 1 ng mixture/kg-day x 10^{-6} mg mixture/ng mixture
= 10^{-9}

Use of the different assumptions regarding relative toxicities (see Table III) influence the calculation of 2,3,7,8-TCDD equivalents only slightly. For example, using analytical data from an Agency study on emissions from a particular municipal waste combustor (EPA 1984), the 2,3,7,8-TCDD equivalents calculated using the assumptions listed in Table III are generally within an order of magnitude.

VI. Comparison with Other Approaches to Determining 2,3,7,8-TCDD Equivalents

A limited number of *in vivo* and *in vitro* approaches have been employed in assessing the toxicity of complex mixtures of CDDs and CDFs. While the results from these attempts are not definitive, it is instructive to compare those results with the results from the TEF approach proposed here.

Fadon (1982) investigated the toxicity of CDD/CDF contaminated soot associated with a fire involving PCB containing electrical equipment. Using the results from acute *in vivo* toxicity (LD_{50}) studies in which the soot was the test substance, the researchers determined that the soot had the acute toxicity expected of material containing about 60 times the amount of 2,3,7,8-TCDD actually found by GC/MS analysis.

Table V illustrates the results of employing the TEF approach through three different procedures, each of which depends upon the results of GC/MS analysis of the soot. In the first instance (A, in Table V), the analytical data have been consolidated to totals with a homologous class. These concentrations are treated as if they consisted completely of 2378-members of the class and, therefore, are multiplied by the TEF appropriate for the 2378-members of the class. The resulting 2,3,7,8-TCDD equivalent estimate from this procedure is about 80.

In procedure B, the assumption is made that the occurrence of each of the congeners in a homologous class is equally probable; e.g., the concentration of 2,3,7,8-TCDD is 1/22 (about 5%) of the concentration of the total TCDDs. This approach leads to an estimate of the total 2,3,7,8-TCDD equivalents of 8.

A rather unique data base exists in the case of the soot from this fire in that an extensive isomer-specific analysis of the sample is available (as cited in DesRosiers, 1984). Therefore, the full array of TEFs from Table III can be applied. This procedure (C in Table V) results in an estimate of roughly 40 for the total 2,3,7,8-TCDD equivalents in the sample.

As might be expected, the most conservative of these procedures, A, leads to the highest estimate. The fact that the approach, B, leads to a lower estimate than the isomer-specific results, C, reflects the fact that the 2378-congeners are present in somewhat higher than "equal probability" proportions. Given the complexity of the analysis involved, the approximate nature of the TEF method, and the vagaries of the bioassay, a major feature of note in Table V regarding the soot samples is that the results of procedures A, B, and C span a range of only one order of magnitude and bracket the bioassay estimate.

In a separate study, Sawyer et al. (1983) published results of homologue-specific CDD and CDF concentrations in flyash from four municipal solid waste combustors (MSW) which are amenable to treatment by the TEF methodology. In addition, extracts from the flyash samples were analyzed by three bioassay techniques (AHH induction, EROD induction, and receptor binding).

These data, taken in toto, suggest that the TEF approach is likely to be a useful, inter tool for the rough estimation (1-2 orders of magnitude, of the tox. .ty of complex mixtures of CDDs and CDFs. Additional scrutiny should accompany the application of these particular TEF procedures (i.e., A,B or C) to any specific sample.

VII. Research Needs

As noted above, the CDWG recommends that research be conducted to develop bioassays that will directly assess the toxicity of complex mixtures of CDDs/CDFs. In addition, research should be conducted which will provide a firmer basis for the TEF approach and guide appropriate modifications thereof. This research should be aimed at

1. Validating and completing the entries in Table I.
2. Investigating additional short term assays which can test the mechanistic hypothesis which underlies the TEF approach; of Section IV.
3. Investigating correlations between the short term assays, longer term assays, and human health effects.

APPENDIX

The following terminology and abbreviations are used in this document:

1. The term "congener" refers to any one particular member of the same chemical family; e.g., there are 75 congeners of chlorinated dibenzo-p-dioxins.
2. The term "homologue" refers to a group of structurally related chemicals which have the same degree of chlorination. For example, there are eight homologues of CDDs, monochloroinated through octochlorinated.
3. The term "isomer" refers to substances which belong to the same homologous class. For example, there are 22 isomers that constitute the homologues of TCDDs.
4. A specific congener is denoted by unique chemical notation. For example, 2,4,8,9-tetrachlorodibenzofuran is referred to as 2,4,8,9-TCDF.
5. Notation for homologous classes is as follows:

Dibenzo-p-dioxin	D
Dibenzofuran	F

No. of Halogens	Acronym	Example
2	D	2,4-DCDD
3	Tr	
4	T	1,4,7,8-TCDD
5	Pe	
6	Hx	
7	Hp	
8	O	
1 through 8	CDDs and CDFs	

6. Dibenzo-p-dioxins and -dibenzofurans that are chlorinated at the 2,3,7 and 8 positions are denoted as 2378 congeners; e.g., 1,2,3,7,8-PeCDF and 2,3,4,7,8-PeCDF are both referred to as "2378-PeCDFs".

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TABLE I

POTENCIES OF DIOXINS RELATIVE TO 2,3,7,8-TCDD

CHEMICAL	GUINEA PIG LD_{50} (ref)	CARCINO-GENICITY (ref)	REPROD. TER. EFFECTS (ref)	RECEPTOR BINDING (ref)	ENZYME AHH (ref)	INDUCTION EROD (ref)	CELL KERATIN. (ref)	FLAT CELL ASSAY (XB) (ref)
CDDs:								
Mono thru tri	$<10^{-4}$(e)	--	--	.001-.01(e)	<.001(f)	—	.01(e)	--
2378-TCDD	1 (a)	1(b)	1(c) 1(i)	1(e)	1(e)	1(g)	1(e)	1(j)
TCDDs	<.001(a)	—	<.001(k)	<.01-.16(e)	<.001-.02(g)	—	<.001-.01(e)	
2378-PeCDD	.67 (a)	--	--	1(e)	.02-.2(g)	--	.5(e)	--
PeCDDs	.002(a)	—	--	--	<.001(g)	--	--	--
2378-HxCDDs	.03 (a)	.04(b)	.01(c)	.05(e)	.001-.1(g)	--	.005(e)	--
HxCDDs	--	—	--	--	<.001(g)	--	--	--
2378-HpCDDs	.004(a)	--	--	--	.002-.004(g,f)	--	--	--
HpCDDs	.002(a)	--	--	--	<.001(f)	--	--	--
OCDD	--	—	<.00001(k)	--	<.001(f)	--	--	--
CDFs:								
Mono thru tri	--	--	--	≤.001-.02(d,h)	<.001(d)	<.001(d)	<.001(e)	
2378-TCDF	.28;.5(a)		.03-.13(i,k)	.3/.25(e/h)	.01-.04(f,h)	.1(h)	.05(e)	.1(j)
TCDFs	--	--	--	.001-.05(d,e)	≤.001(d)	≤.005(d)	--	--
2378-PeCDF			--	.13/.7/.6(d/e/h)	<.3(d)	.1(d)	--	--
12467PeCDF				.15(h)	.002(h)	<.001(h)	--	--
PeCDFs				.001-.1(d,e)	≤.001(d)	≤.001(h)	--	--
2378-HxCDFs	.017(a)	--	--	.04-.5(e,h)	.05-.2(h)	.1-.5(h)	--	--
HxCDFs	--	--	--	.001(e,h)	.002(h)	.006(h)	--	--
2378HpCDFs	--	--	--	--	.004(g)	--	--	--
HpCDFs	--	--	--	<.001(h)	<.001(f)	--	--	--

a. McKinney and McConnell, 1982; b. USEPA 1984a; c. Murray et al., 1979; Schwetz et al., 1973; Weber et al., 1984.; d. Bandiera et al., 1984; e. Knutson and Poland, 1980; f. Bradlaw et al., 1979; g. Bradlaw et al., 1980; h. Bandiera et al., 1984; i. Hassoun et al., 1984; j. Gierthy and Crane, 1985; k. Weber et al., 1984;

TABLE II

CDD/CDF ISOMERS OF MOST TOXIC CONCERN[a/]

DIOXIN		DIBENZOFURAN	
Isomer	TEF[b/]	Isomer	TEF
2,3,7,8-TCDD	1	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.2	1,2,3,7,8-PeCDF	0.1
		2,3,4,7,8-PeCDF	0.1
1,2,3,6,7,8-HxCDD	0.04	1,2,3,6,7,8-HxCDF	0.01
1,2,3,7,8,9-HxCDD	0.04	1,2,3,7,8,9-HxCDF	0.01
1,2,3,4,7,8-HxCDD	0.04	1,2,3,4,7,8-HxCDF	0.01
		2,3,4,6,7,8-HxCDF	0.01
1,2,3,4,6,7,8-HpCDD	0.001	1,2,3,4,6,7,8-HpCDF	0.001
		1,2,3,4,7,8,9-HpCDF	0.001

a/ In each homologous group the relative toxicity factor for the isomers not listed above is 1/100 of the value listed above.

b/ TEF = toxic equivalency factor = relative toxicity assigned.

TABLE II

CDD/CDF ISOMERS OF MOST TOXIC CONCERN[a/]

DIOXIN		DIBENZOFURAN	
Isomer	TEF[b/]	Isomer	TEF
2,3,7,8-TCDD	1	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.2	1,2,3,7,8-PeCDF	0.1
		2,3,4,7,8-PeCDF	0.1
1,2,3,6,7,8-HxCDD	0.04	1,2,3,6,7,8-HxCDF	0.01
1,2,3,7,8,9-HxCDD	0.04	1,2,3,7,8,9-HxCDF	0.01
1,2,3,4,7,8-HxCDD	0.04	1,2,3,4,7,8-HxCDF	0.01
		2,3,4,6,7,8-HxCDF	0.01
1,2,3,4,6,7,8-HpCDD	0.001	1,2,3,4,6,7,8-HpCDF	0.001
		1,2,3,4,7,8,9-HpCDF	0.001

a/ In each homologous group the relative toxicity factor for the isomers not listed above is 1/100 of the value listed above.

b/ TEF = toxic equivalency factor = relative toxicity assigned.

TABLE III

SOME APPROACHES TO ESTIMATING RELATIVE TOXICITIES OF PCDDs and PCDFs

BASIS/ COMPOUND/	SWISS[a]	GRANT[b] OLIE[c] COMMONER[d]	NEW YORK STATE[e]	ONTARIO[f]	FDA[g]	CA[h]	EPA[i] 1981	EPA Current Recommend
(Basis)	enzyme		LD_{50}	various effects	various effects			Carcin.
Mono and di	0	0	0	0	0	0	0	0
237-TrCDD	0	0.1*	0	1*	0	0	0	0
other TrCDDs	0	0	0	0	0	0	0	0
2378-TCDD	1	1*	1	1*	1	1	1	1
other TCDDs	0.01	0	0	0.01	0	0	1	0.01
2378-PeCDDs	0.1	0.1*	1	1*	-**	1	0	0.2
otherPeCDDs	0.1	0	0	0.01	-**	0	0	0.002
2378-HxCDDs	0.1	0.1*	0.03	1*	0.02	1	0	0.04
other HxCDDs	0.1	0	0	0.01	0.02	0	0	0.0004
2378-HpCDDs	0.01	0.1*	0	1*	0.005	1	0	0.001
other HpCDDs	0.01	0	0	0.01	0.005	0	0	0.00001
OCDD	0	0	0	0	<0.00001	0	0	0
2378-TCDFs	0.1	0.1*	0.33	0.02*	0	1	0	0.1
other TCDFs	0.1	0	0	0.0002	0	0	0	0.001
2378-PeCDFs	0.1	0.1*	0.33	0.02*	0	1	0	0.1
other PeCDFs	0.1	0	0	0.0002	0	0	0	0.001
2378-HxCDFs	0.1	0.1*	0.01	0.02*	0	1	0	0.01
other HxCDFs	0.1	0	0	0.0002	0	0	0	0.0001
2378HpCDFs	0.1	0.1*	0	0.02*	0	1	0	0.001
other HpCDFs	0	0	0	0.0002	0	0	0	0.00001
OCDF	0	0	0	0	0	0	0	0

*: congeners with chlorine atoms at 3 of the 4 lateral positions.

**: these isomers were not considered.

a = Swiss government, 1982
b = Grant, 1977
c = Olie et al., 1982; 1983
d = Commoner, 1984
e = Eadon, 1982
f = Ontario, 1982
g = USDHHS, 1983
h = California, 1982
i = USEPA, 1981

TABLE IV
PCDDs/PCDFs IN SOME ENVIRONMENTAL SAMPLES

ISOMER	TEF	AIR PARTICS, St. Louis [5]		MSW ESP DUST [5]		LAKE SEDIMENT [5]		1982 MITORGANITE [4]		MSW FLYASH [6] ONTARIO		OSLO	
		Conc. (ppb)	TCDD Eqts. (ppb)	Conc. (ppb)	TCDD Eqts. (ppb)	Conc. (ppb)	TCDD Eqts. (ppb)	Conc. (ppt)	TCDD Eqts. (ppt)	Conc. (ppt)	TCDD Eqts. (ppt)	Conc. (ppt)	TCDD Eqts. (ppt)
TCDDs	1	0.2	0.2	5	5	0	0	206	206	541	541	ND	-
PeCDDs	0.2	1	0.2	10	2	0.1	0.02	-	-	467	93	11	2.2
HxCDDs	0.04	1.2	0.048	160	6.4	0.34	0.014	2768	110.7	591	24	51	2
HpCDDs	0.001	25	0.025	120	0.12	0.5	0.001	7600	7.6	434	0.43	119	0.12
OCDD	0	170	-	260	-	1.3	-	60000	-	467	-	186	-
TCDFs	0.1	-	-	40	4	0.13	0.013	-	-				
PeCDFs	0.1	-	-	80	8	0.14	0.014	-	-				
HxCDFs	0.01	-	-	280	2.8	0.38	0.004	-	-				
HpCDFs	0.001	-	-	160	0.16	1.13	0.001	-	-				
OCDF	0	-	-	40	-	0.14	-	-	-				
Total TCDD Eqts.			0.5		29		0.07		324		658		4

. USEPA 1984b.
. Cooper Engineers, 1984.
. Rappe, 1984.
4. Lamparski et al., 1984
5. Czuwa and Hites, 1984.
6. Tong et al., 1984
7. des Rosiers, 1984.

TABLE IV (Continued)

ISOMER	TEF	THERMAL DEGRADATION PRODS. FROM DIELECTRIC FLUIDS [1] Run 8-13-40 Conc. (ng)	TCDD Eqts.	Run 8-30-61 ASKL Conc. (ug)	TCDD Eqts.	JAP. MSW[2] Pt. A TEF Conc. (lb/MMBTU(x10^{-6}))	TCDD Eqts.	Pt. B TEF Conc. (lb/MMBTU(x10^{-6}))	TCDD Eqts.	COMMERCIAL CPs 246TCP[3] Conc. (ppm)	TCDD Eqts.	PCP[3] Conc. (ppm)	TCDD Eqts.	SOOT FROM PCB PCB FIRE[7] Conc. (ppm)	TCDD Eqts.
TCDDs															
2378	1	0	0	0	0	0.1	0.1	0.58	0.58	<.1	-	<.1	-	0.6	0.6
other	0.01													0.6	.01
PeCDDs															
2378	0.2	0	0	0	0	0.07	0.014	0.47	0.094	<.1	-	<.1	-	2.5	.5
other	0.002													2.5	.01
HxCDDs															
2378	0.04	0	0	0	0	0.04	0.002	0.36	0.014	<1	-	2.5	0.1	1.1	.04
other	0.0004													3.6	0
HpCDDs															
2378	0.001	0	0	330	0.33	0.02	<.001	0.08	<.001	<1	-	175	0.18	3	0
other	0.00001													4	0
OCDD	0	0	0	37	0	0.01	0	0.04	0	<1	-	500	-	2	-
TCDFs															
2378	0.1	690	69	1400	140	1.31	0.131	1.25	0.125	1.5	0.15	<.1	-	12	1.2
other	0.001													16	.01
PeCDFs															
2378	0.1	43	4.3	6400	640	0.38	0.038	0.46	0.046[4]	17.5	1.75	<.1	-	358	35.8
other	0.001													312	.3
HxCDFs															
2378	0.01	7	0.07	910	9.1	0.06	0.006	0.06	0.006	36	3.6	<.3	-	670	6.7
other	0.0001													295	.03
HpCDFs															
2378	0.001	0	0	29	0.029	0.01	<.001	0.02	<.001	4.8	0.005	19	0.019	285	.29
other	0.00001													172	0
OCDF	0	0	0	3.4	0	0.004	0	0.01	0	<1	-	25	-	40	-
Total TCDD Eqts.			73		789		0.3		0.87		5.5		0.3		45

TABLE V

ISOMER	TEF	PROP. FACTOR	PCB FIRE SOOT[a] (ppm) Conc.	TCDD Eqts. A[c]	TCDD Eqts. B[c]	TCDD Eqts. C[d]	MSW FLYASH (ppb) [b] SAMPLE 1 Conc.	SAMPLE 1 TCDD Eqts. A	SAMPLE 1 TCDD Eqts. B	SAMPLE 2 Conc.	SAMPLE 2 TCDD Eqts. A	SAMPLE 2 TCDD Eqts. B
Total TCDDs	1	1	1.2	1.2			85	85		2.7	2.7	
2378 TCDD	1	0.05	1.2		0.2	0.6	85		4.3	2.7		0.1
other TCDDs	0.01	0.95	1.2		- [e]	-	85		0.8	2.7		-
Total PeCDDs	0.2	1	5.0	1.0			213	42.6		6.6	1.3	
2378 PeCDDs	0.2	0.07	5.0		0.1	0.5	213		3.0	6.6		0.1
other PeCDDs	0.002	0.93	5.0		-	-	213		0.4	6.6		-
Total HxCDDs	0.04	1	4.7	0.2			354	14.2		11.6	0.5	
2378 HxCDDs	0.04	0.3	4.7		0.1	-	354		4.3	11.6		0.1
other HxCDDs	0.0004	0.7	4.7		-	-	354		0.1	11.6		-
Total HpCDDs	0.001	1	7	-		-	184	0.2		5.7	-	
2378 HpCDDs	0.001	0.5	7		-		184		0.1	5.7		-
other HpCDDs	0.00001	0.5	7		-		184		-	5.7		-
Total TCDFs	0.1	1	28	2.8			209	20.9		7.0	0.7	
2378 TCDFs	0.1	0.03	28		0.1	1.2	209		0.6	7.0		-
other TCDFs	0.001	0.97	28		-	-	209		0.2	7.0		-
Total PeCDFs	0.1	1	670	67			549	54.9		17.8	1.8	
2378 PeCDFs	0.1	0.07	670		4.7	35.8	549		3.8	17.8		0.1
other PeCDFs	0.001	0.93	670		0.6	0.3	549		0.5	17.8		-
Total HxCDFs	0.01	1	965	9.7			1082	10.8		32.1	0.3	
2378 HxCDFs	0.01	0.19	965		1.8	6.7	1082		2.1	32.1		0.1
other HxCDFs	0.0001	0.81	965		0.1	-	1082		0.1	32.1		-
Total HpCDFs	0.001	1	460	0.5			499	0.5		10.9	-	
2378 HpCDFs	0.001	0.25	460		0.1	0.3	499		0.1	10.9		-
other HpCDFs	0.00001	0.75	460		-	-	499		-	10.9		-
TOTAL TCDD EQUIVALENTS (TEF):												
TEF estimate:				84	8	45		229	20		7	1
AHH bioassay:				-	-	-		4			-	-
EROD bioassay				-	-	-		5			-	-
Receptor binding bioassay:				-	-	-		32			4	-
Acute toxicity bioassay:				58	-	-		-			-	-
RELATIVE TCDD EQTS. (TEF/Bioassay):												
AHH bioassay:				-	-	-		57	5		-	-
EROD bioassay:				-	-	-		46	4		-	-
Receptor binding bioassay:				-	-	-		7	0.6		2	0.2
Acute toxicity bioassay:				1.4	0.1	0.8		-	-		-	-

a: des Rosiers, 1984, assuming only homologue-specific concentrations are known (for isomer-specific analyses see Table IV.

b: Sawyer et al., 1983.

c: A = estimated assuming 2378-isomers constitute 100 % of a homologous group.
B = estimated assuming occurrence of all isomers in a homologous group is equally probable (thus using the proportionality factor in column three).

d: estimated by utilizing isomer-specific analyses (see Table IV)

e: values rounding off to less than 0.1 are omitted.

TABLE V - continued

ISOMER	TEF	PROP. FACTOR	MSW FLYASH (ppb) [b] SAMPLE 3 Conc.	SAMPLE 3 TCDD Eqts. A	SAMPLE 3 TCDD Eqts. B	SAMPLE 4 Conc.	SAMPLE 4 TCDD Eqts. A	SAMPLE 4 TCDD Eqts. B
Total TCDDs	1	1	12.9	12.9		2.4	2.4	
2378 TCDD	1	0.05	12.9		0.6	2.4		0.1
other TCDDs	0.01	0.95	12.9		0.1	2.4		-
Total PeCDDs	0.2	1	37.5	7.5		7.9	1.6	
2378 PeCDDs	0.2	0.07	37.5		0.5	7.9		0.1
other PeCDDs	0.002	0.93	37.5		0.1	7.9		-
Total HxCDDs	0.04	1	75	3		9.7	0.4	
2378 HxCDDs	0.04	0.3	75		0.9	9.7		0.1
other HxCDDs	0.0004	0.7	75		-	9.7		-
Total HpCDDs	0.001	1	41.9	-		9.1	-	
2378 HpCDDs	0.001	0.5	41.9		-	9.1		-
other HpCDDs	0.00001	0.5	41.9		-	9.1		-
Total TCDFs	0.1	1	8.2	0.8		4.4	0.4	
2378 TCDFs	0.1	0.03	8.2		-	4.4		-
other TCDFs	0.001	0.97	8.2		-	4.4		-
Total PeCDFs	0.1	1	19.8	2.0		21.0	2.1	
2378 PeCDFs	0.1	0.07	19.8		0.1	21.0		0.1
other PeCDFs	0.001	0.93	19.8		-	21.0		-
Total HxCDFs	0.01	1	38.7	0.4		21.6	0.2	
2378 HxCDFs	0.01	0.19	38.7		0.1	21.6		-
other HxCDFs	0.0001	0.81	38.7		-	21.6		-
Total HpCDFs	0.001	1	20.6	-		16.6	-	
2378 HpCDFs	0.001	0.25	20.6		-	16.6		-
other HpCDFs	0.00001	0.75	20.6		-	16.6		-
TOTAL TCDD EQUIVALENTS (TEF):								
TEF estimate:				27	2		7	0.4
AHH bioassay:				4	-		2	-
EROD bioassay:				5	-		2	-
Receptor binding bioassay:				65	-		11	-
Acute toxicity bioassay:				-	-		-	-
RELATIVE TOTAL TCDD EQTS. (TEF/BIOASSAY):								
AHH bioassay:				7	0.5		4	0.2
EROD bioassay:				5	0.4		4	0.2
Receptor binding bioassay:				0.4	0.03		0.6	0.04
Acute toxicity bioassay				-	-		-	-

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COMPARATIVE TOXICITY AND BIOLOGIC ACTIVITY OF CHLORINATED DIBENZO-P-DIOXINS AND FURANS RELATIVE TO 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)

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ABSTRACT

An assessment of the comparative toxicity and biologic activity of the various chlorinated dibenzo-p-dioxins and furans indicates a range of potency extending from $\sim 10^{-1}$ to $<10^{-6}$ relative to TCDD.

INTRODUCTION

The purpose of this paper will be to perform a comparative assessment of the toxicity and biologic activity of certain of the chlorinated dibenzo-p-dioxins and furans relative to TCDD. As TCDD has been most comprehensively studied, it has been used as a reference for the other dioxins and furans.

For the sake of brevity, only limited reference will be made to specific data available in previous publications (1,2,3). The emphasis herein will be on the comparative assessment of the various isomers as measured by certain differential responses in studies of toxicity and/or biologic activity.

COMPARATIVE TOXICITY AS MEASURED BY ACUTE LETHALITY IN LABORATORY ANIMALS

Tables 1 and 2 list the comparative single oral dose LD_{50} values for sixteen different dioxins and five different furans relative to TCDD. Evaluation of the data available from as many as seven different laboratory animals in which these studies have been performed indicates some rather substantial differences in single dose oral LD_{50} values. This holds true when evaluated on the basis of interspecies response (for the same isomer) or intraspecies response (for the same species of animal tested). For example, the interspecies differential response for TCDD as measured by single oral dose LD_{50} data indicates an LD_{50} value for the guinea pig of 0.6-2 µg/kg, whereas in the hamster it is 1157-5051 µg/kg. The intraspecies differential response to different isomers is typified by the greater than six orders of magnitude difference between the LD_{50} values of 0.6-2 µg/kg for TCDD and the LD_{50} value of $>15\times10^{6}$ µg/kg for the 1,3,6,8-tetrachlorodibenzo-p-dioxin when tested in the same species (guinea pig).

The limited data presently available on the furans indicates some parallelism to the dioxins in regard to those structural characteristics associated with toxicity or the lack of toxicity as measured by acute oral lethality.

RELATIVE BIOLOGIC ACTIVITY AS MEASURED BY IN VITRO TESTS SUCH AS ENZYME INDUCTION OR EPITHELIAL KERATINIZATION

Several groups of researchers (4,5,6,7,8,9,10,11,12) have utilized certain in vitro tests whereby the biologic activities of various dioxin and furan isomers have been ranked relative to TCDD. Tables 3 and 4 are tabulations of the comparative biologic activities as measured by in vitro enzyme induction or epithelial keratinization for various dioxins and furans relative to TCDD.

Due to the everexpanding data base now being generated with various in vitro test systems, the tabulation in Tables 3 and 4 is understandably not intended to be all inclusive. More recent data such as that from the laboratory of Safe (11, 12) or Gierthy (10) will likely be presented in companion papers at this symposium. The comparative assessment in Tables 3 and 4 indicates the considerable range of biologic activity for the dioxin isomers and furan isomers that have been evaluated for biologic activity as measured by in vitro enzyme induction or epithelial keratinization.

For the chlorinated dioxins, the 1,2,3,7,8,9-Hexa-, the 1,2,3,4,7,8-Hexa-, the 1,2,3,4,7-Penta-, the 1,2,3,7,8-Penta-, the 1,3,7,8-Tetra- and the 2,3,7-Trichloro-dioxins exhibited some biologic activity relative to TCDD. Of the lesser number of chlorinated furans tested, the 2,3,7,8-Tetra-, the 1,2,3,7,8-Penta- and the 2,3,4,7,8-Pentachloro-furans exhibited biologic activities in the range of one to two orders of magnitude less than TCDD.

COMPARATIVE ASSESSMENT FOR CHLORACNEGENIC ACTIVITY IN THE RABBIT EAR BIOASSAY

The rabbit ear bioassay has been used to evaluate the acnegenic potential of a limited number of chlorinated dioxins and furan isomers listed in Table 5.

As expected, TCDD exhibited the greatest activity, with a positive rabbit ear bioassay noted when a 0.04 ppm concentration was tested. No acnegenic response occurred with TCDD when tested at a lower concentration of 0.004 ppm. A mixture of two unspecified hexachlorodioxins gave a positive response, but at a higher concentration of 10-50 ppm. A mixture of 1,3,6,8- and 1,3,7,9-tetrachlorodioxin gave a positive acnegenic response at a concentration of 5000 ppm and a negative response at a concentration of 50 ppm. The remaining dioxin and furan isomers listed in Table 5 are reportedly negative for acnegenesis in the rabbit ear bioassay.

COMPARATIVE EVALUATION OF TERATOGENICITY AND RELATED END POINTS

Stucies to evaluate the potential for teratogenicity and related end points have been performed on the chlorodioxins and furans listed in Table 6. A comparative evaluation of the quantitative Lowest-Observed-Effect-Levels (LOEL) and No-Observed-Effect-Levels (NOEL) as defined in studies using the mouse or the rat is included. Relative to the data on TCDD, most of those tested thus far have been considerably less active. The exceptions are a mixture of two unspecified hexachlorodioxins and also the 2,3,7,8-tetrachlorofuran which exhibited some fractional activities relative to TCDD.

COMPARATIVE ASSESSMENT OF MUTAGENIC, CLASTOGENIC AND RELATED END POINTS

In regard to mutagenic and clastogenic potential, numerous studies of various types have been conducted with TCDD that indicate little or no potential for mutagenesis, clastogenesis or interaction with DNA. These various studies on TCDD and other chlorodioxins have been recently reviewed (2,3) and, for the sake of brevity, will only be briefly reviewed herein.

Table 7 is a compilation of data from various chlorodioxins (other than TCDD) and furans that have been evaluated. For both the chlorodioxins and furans listed in Table 7 there is an overall concurrence indicative of a relative lack of potential for mutagenesis, clastogenesis or related end points evaluated in these various types of tests.

COMPARATIVE ASSESSMENT OF CARCINOGENICITY AND LONG-TERM TOXICITY

In regard to carcinogenicity and long-term toxicity, the data base presently available is essentially that reviewed in previous papers (2,3). Thus, for the sake of brevity, only a brief review of these data will be given here.

At this time, these chlorodioxins have animal bioassay data that can be summarized as follows:

1) The unsubstituted dibenzo-p-dioxin given to rats and mice at 10,000 or 5,000 ppm in the diet elicited no carcinogenic response (13).

2) The 2,7-dichlorodibenzo-p-dioxin was also given to rats and mice at 10,000 or 5,000 ppm in the diet. No carcinogenic response was noted in either species, except for a suggestive response in mice given the 10,000 ppm level (14).

3) TCDD has elicited a tumorigenic response in rats during lifetime ingestion of 0.07 - 0.1 μg/kg/day and in mice during lifetime ingestion of 0.07 - 0.3 μg/kg day (15,16,17). Daily dose levels of 0.001 - 0.014 μg/kg/day (rats) or 0.001 - 0.003 μg/kg/day (mice) of TCDD were tolerated for a lifetime without eliciting any increase in tumors in these studies. In the lifetime study with TCDD wherein both carcinogenicity and other chronic toxicity were evaluated (15), a lifetime No-Observed-Effect-Level of 0.001 μg/kg/day was defined for the rat species.

4) A mixture of the 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxins has been given by gavage to rats and male mice (5, 2.5 or 1.25 μg/kg/week) and female mice (10, 5 and 2.5 μg/kg/week).

The initial report of this bioassay (18) reported a carcinogenic response at the higher dose level for the female rat, the male mouse and the female mouse. However, several re-examinations of the histologic slides from this study have been stimulated by the results of a re-examination (19) rendering differing diagnoses for certain of the tumors in the study.

The various studies with 2,3,7,8-TCDD on tumor initiation, promotion and cocarcinogenesis have been reviewed previously (2,3). One of the most pertinent of these studies (20) found TCDD to be a promoter of rat tumors initiated by diethylnitrosamine. Another study (21) using the hairless HRS/J strain of mouse (those capable of chloracnegenic-like reaction of the skin), found that TCDD was a promoter of skin tumors initiated by either Dimethylbenzanthracene or Methyl-N-Nitrosoguanidine.

Other mechanistic studies (22) indicated a relative lack of binding of TCDD to DNA (4-6 orders of magnitude less than for most chemical carcinogens). Likewise, TCDD did not stimulate unscheduled DNA synthesis when tested in rat hepatocytes (23) or in a human cell line (24).

Overall, there is a substantial amount of data available on TCDD, including the results from the lifetime bioassays, the mechanistic studies describing it as a promoter, as well as the studies finding little or no potential for either mutagenesis or DNA interaction. Evaluation of all these pertinent data supports the concept of a nongenetic (possible promoter) mechanism of carcinogenesis for TCDD.

SUMMARY

Of all the chlorinated dibenzo-p-dioxins and furans, the 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has been evaluated most extensively in regard to its biologic activity and toxicologic properties. Thus, TCDD has been used as the reference for comparative evaluation of the other dioxins and furans.

A compilation of the results of various studies wherein single dose oral LD_{50} data have been generated for sixteen different dioxins and five furans relative to TCDD in as many as seven different animal species indicates marked differences in acute toxicity when evaluated on the basis of interspecies differential response (same isomer, different animal species) or on the basis of intraspecies differential response (same animal species, different isomers).

Marked differences in response have also been noted for those chlorinated dibenzo-p-dioxins and furans that have been comparatively evaluated in studies of the potential for chloracnegenesis, teratogenesis or carcinogenesis.

When evaluated for comparative biologic activity as measured by various in vitro tests for enzyme induction or epithelial keratinization, a similar wide range of differential response has been noted for the various chlorinated dibenzo-p-dioxins and furans.

Overall, this assessment of the comparative toxicity and/or biologic activity of the various chlorinated dibenzo-p-dioxins and furans indicates a range of potency extending from $\sim 10^{-1}$ to $<10^{-6}$ relative to TCDD.

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TABLE 1

COMPARATIVE SINGLE ORAL DOSE LD_{50} VALUES FOR CHLORODIBENZO-P-DIOXIN ISOMERS

	Oral LD_{50} Values (μg/kg)							
Chlorodibenzodioxin	Guinea Pig	Mouse	Rat	Monkey	Hamster	Rabbit	Dog	References
2,3,7,8-Tetra	0.6-2	114-284	22-45	70	1157-5051	115	>300,<3,000	(25.26.27.28.29)
Unsub		>50,000	>1,000,000					(30) (32)
2,3-Di			>1,000,000					(32)
2,7-Di		>2,000,000	>1,000,000					(25)
2,8-Di	>300,000	8,470,000	>5,000,000					(26) (31)
1,3,7-Tri		>15,000,000	>5,000,000					(31)
2,3,7-Tri	29,444	>3,000	>1,000,000					(26) (32)
1,2,3,4-Tetra			>1,000,000					(32)
1,3,6,8-Tetra	>15,000,000	>2,987,000	>10,000,000					(33)
1,2,3,7,8-Penta	3.1	337.5						(26)
1,2,4,7,8-Penta	1,125	>5,000						(26)
1,2,3,4,7,8-Hexa	72.5	825						(26)
1,2,3,6,7,8-Hexa	70-100	1250						(26)
1,2,3,7,8,9-Hexa	60-100	>1440						(26)
1,2,3,4,6,7,8-Hepta	>600							(26)
Octa		>4,000,000	>1,000,000					(25)

TABLE 2

COMPARATIVE SINGLE ORAL DOSE LD_{50} VALUES FOR CHLORODIBENZOFURANS COMPARED TO TCDD

	Oral LD_{50} Values (µg/kg)							
Chlorodioxin/furan	Guinea Pig	Mouse	Rat	Monkey	Hamster	Rabbit	Dog	References
2,3,7,8-Tetradioxin	0.6-2	114-284	22-45	~70	1157-5051	115	>300,<3000	(25,26,27,28,29)
Chlorodibenzofuran								
2,8-Di		>15,000,000	>15,000,000					(31)
2,4,8-Tri		>15,000,000	>5,000,000					(31)
2,3,7,8-Tetra	5-10	>6000	>1000	1000				(34,35)
2,3,4,7,8-Penta	<10							(36)
2,3,4,6,7,8-Hexa	120							(36)

TABLE 3

COMPARATIVE BIOLOGIC ACTIVITY (IN VITRO) OF CHLORODIBENZO-P-DIOXINS RELATIVE TO TCDD

Chlorodibenzo-p-dioxin	AHH Activity in Rat Hepatoma Cells	AHH Activity in Chick Embryo Liver	ALA Synthetase in Chick Embryo Liver	Keratinization of X8/3T3 Cells
2,3,7,8-Tetra	1/1	1/1	1/1	1/1
Unsub.	Inactive	Inactive	Inactive	Inactive
1-Chloro		Inactive	Inactive	
1,3-Di	Inactive			
1,6-Di	Inactive	Inactive		Inactive
2,3-Di	Inactive	Inactive	Inactive	Inactive
2,7-Di	Inactive	Inactive	Inactive	Inactive
2,8-Di	Inactive	Inactive	Inactive	
1,2,4-Tri		Inactive	Inactive	
2,3,7-Tri	1/920-1/3060	1/1666	Active	1/100
1,3,7,8-Tetra	1/57-1/242	1/12		1/100
1,2,3,8-Tetra	1/1666-1/5900			
1,2,3,4-Tetra	Inactive	Equiv.	Inactive	
1,3,6,8-Tetra	Inactive	Inactive	Inactive	Inactive
1,2,3,7,8-Penta	1/5-1/53			1/2
1,2,3,4,7-Penta	1/21-1/132	Active	Active	
1,2,4,7,8-Penta	Inactive			
1,2,3,6,7,9-Hexa	Inactive			
1,2,4,6,7,9-Hexa	Inactive	Inact./Equiv.	Inact./Equiv.	
1,2,3,4,7,8-Hexa	1/10-1/20	Active	Active	
1,2,3,7,8,9-Hexa	1/114-1/523	1/5		1/200
1,2,3,6,7,8-Hexa	1/71-1/947			
1,2,3,4,6,7,9-Hepta	1/10,200			
1,2,3,4,6,7,8-Hepta	1/282-1/367			
Octa (99.2%)	1/1666-1/4594			
Octa (>99%)	1/53,000	Inactive	Inactive	
	(Refs. 4,5)	(Refs. 6,7,8)		(Ref. 9)

Biologic Activity expressed as fractions relative to TCDD (1/1).

TABLE 4

COMPARATIVE BIOLOGIC ACTIVITY (IN VITRO) OF CHLORODIBENZOFURANS RELATIVE TO TCDD

Chlorodioxin/furan	AHH Activity in Rat Hepatoma Cells	AHH Activity in Chick Embryo Liver	Keratinization of X8/3T3 Cells
2,3,7,8-Tetra Dioxin	1/1	1/1	1/1
Chlorodibenzofuran			
Unsub.	Inactive	Inactive	Inactive
2,8-Di	Inactive	Inactive	
2,4-Di		Inactive	
2,4,8-Tri		Inactive	
2,3,8-Tri	1/20,714		
2,4,6-Tri	Inactive		
1,4,6,8-Tetra	Inactive		
1,3,6,7-Tetra		Inactive	
2,3,6,8-Tetra	Inactive		
2,4,6,8-Tetra	Inactive		
2,3,7,8-Tetra	1/92	2/3	1/20
1,2,3,7,8-Penta		1/7	
1,3,4,7,8-Penta	1/1,928		
2,3,4,7,8-Penta		7/10	
1,2,4,7,8-Penta	1/31,428		
1,2,3,4,6,8,9-Hepta	1/24,286		
	(Ref. 4)	(Ref. 7)	(Ref. 9)

Biologic Activity expressed as fractions relative to TCDD (1/1).

TABLE 5

RABBIT EAR BIOASSAY FOR CHLORACNEGENIC ACTIVITY

Chlorodioxin or Furan		Response to Conc. (ppm) Positive	Negative	Reference
2,3,7,8-Tetra Dioxin		0.04	0.004	(25)
Unsub.	"		Unspecif.	(32)
2,7-Di	"		100,000	(25)
2,8-Di	"		Unspecif.	(31)
2,3-Di	"		Unspecif.	(32)
1,3,7-Tri	"		Unspecif.	(31)
1,2,3,4-Tetra	"		50	(25)
1,3,6,8- 1,3,7,9-Tetra (mixture)	"	5000	50	(1)
Unspecified Hexas (mixture of 2)	"	10-50		(25)
Octa	"		100,000	(31)
2,8-Di	Furan		Unspecif.	(31)
2,4,8-Tri	"		Unspecif.	(31)

TABLE 6

COMPARATIVE EVALUATION OF QUANTITATIVE DATA ON
FETOTOXICITY/TERATOGENICITY OF CHLORODIBENZO-P-DIOXINS AND FURANS

Chlorodibenzo Dioxin or Furan		Fetotoxicity/Teratogenicity Dosage (ug/kg/day) LOEL	NOEL	Reference
Mouse Studies:				
2.3.7.8-Tetra	Dioxin	1.0	0.1	(37)
1,2,3,4-Tetra	"		1000	(30)
Octa	"		20,000	(30)
2,3,7,8-Tetra	Furan	10-30		(44)
Rat Studies:				
2,3,7,8-Tetra	Dioxin	0.125-0.25	0.03-0.125	(38,39)
2-Mono	"		2000	(38)
2,3-Di	"		2000	(38)
2,7-Di	"	1000	500	(38)
2,7-Di	"		100,000	(25)
2,8-Di	"		not specif.	(31)
1,3,7-Tri	"		not specif.	(31)
1,3,6,8-Tetra	"		3,000,000	(40)
1,2,3,4-Tetra	"		800	(38)
Unspec. Hexas (mixture of 2)	"	1-10	0.1	(25)
Octa			500,000	(25)
2,8-Di	Furan		not specif.	(31)
2,4,8-Tri	"		not specif.	(31)

TABLE 7

COMPARATIVE DATA ON EVALUATION OF POTENTIAL FOR MUTAGENESIS, CLASTOGENESIS AND RELATED END POINTS

Chlorodioxin or Furan		Tests and Results
2,3,7,8-Tetra	Dioxin	See (2,3) for Reviews
Unsub.	Dioxin	No chromosomal aberrations in rats (41)
2,7-Di	Dioxin	No chromosomal aberrations in rats (41)
2,8-Di	Dioxin	No cytogenetic or dominant lethal effects in Chinese hamster or mouse; No mutagenic response in Salmonella sp. (31)
1,3,7-Tri	Dioxin	Same tests and results as given above for 2,8-Di Isomer (31)
Octa	Dioxin	No mutagenic response in strains TA1530, TA1531, G46; "doubtful mutagenicity" in strains TA1532 and TA1534 (42)
Unsub.	Furan	No mutagenic response with 8/8 strains of Salmonella sp. (43)
2,8-Di	Furan	No mutagenic response with 11/11 strains of Salmonella sp. (43)
		No cytogenetic or dominant lethal effects in Chinese hamster or mouse; No mutagenic response in Salmonella sp. (31)
3,6-Di	Furan	No mutagenic response with 10/10 strains of Salmonella sp. (43)
2,4,8-Tri	Furan	No cytogenetic or dominant lethal effects in Chinese hamster or mouse; No mutagenic response in Salmonella sp. (31)
2,3,7,8-Tetra	Furan	No mutagenic response with 5/5 strains of Salmonella sp. (43)
Octa	Furan	No mutagenic response with 9/9 strains of Salmonella sp. (43)

STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

August 9, 1985

Mr. John A. Harris
Manager, State Environmental Regulatory Affairs
Environmental Quality
2030 Willard H. Dow Center
Midland, MI 48674

Dear Mr. Harris:

Subject: Your Comments on Chlorinated Dioxins and Dibenzofurans

Your letter of July 11, 1985, concerning Report to the Scientific Review Panel on Chlorinated Dioxins and Dibenzofurans, Part B has been forwarded to the Department of Health Services. They will prepare responses to your comments, which we will include along with your letter in Part C of the revised report. Dow Chemical will receive the revised report when it is submitted to the Scientific Review Panel.

Thank you for your comments.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: P. Venturini, ARB
R. Neutra, DHS

CHEMICAL MANUFACTURERS ASSOCIATION

July 12, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Attention: Dioxin
Air Resources Board
P.O. Box 2815
Sacramento, Ca. 95812

Dear Mr. Loscutoff:

On behalf of the Chemical Manufacturers Association's Dibenzofurans/Dibenzodioxins Program Panel, I am pleased to submit comments on the Chlorinated Dioxins and Dibenzofurans reports. A complete review of the reports was not possible in the short time provided. Given the importance of obtaining external review of critical regulatory support documents, CMA believes the Air Resources Board (ARB) should allow additional opportunity for review. Nevertheless, there are several important points that we would like to bring to your attention at this time.

The report specifies that the Department of Health Services (DHS) has concluded that all dioxin and dibenzofuran isomers substituted in at least the 2,3,7,8 position are potential human carcinogens. The treatment of all such isomers, especially the hepta isomer, as potential human carcinogens is not generally accepted. The available toxicological evidence indicates that the hepta isomer is considerably less toxic than the tetra-, penta-, and hexa-substituted isomers. This viewpoint is supported by the Federal Environmental Protection Agency. In a recent response to a petition filed by the Environmental Defense Fund and the National Wildlife Federation, EPA concluded that the hepta isomer would not be pursued for regulatory purposes. The Panel believes that the California Air Resources Board should adopt a similar approach and drop the hepta isomer from regulatory consideration.

The Panel is also concerned about treating all of the 2,3,7,8 substituted isomers as toxicologically equivalent as outlined in Scenarios 1 and 2 (See pages 10-20 thru 10-22). Such an approach ignores the available toxicological evidence which suggests that the different isomers have significant variation in toxicological properties. The Panel believes that the ARB should rely on the type of approach outlined in Scenario 3 when estimating risk from

exposure to a mixture of dioxin and furan isomers. This approach, that of assigning relative potencies to the various isomers, makes use of the available toxicological information and is consistent with the procedure recently recommended by EPA's Chlorinated Dioxin Workgroup. A copy of EPA's Interim Risk Assessment Procedures for Mixtures of Chlorinated Dioxins and Dibenzofurans is enclosed. The Panel believes that the approach outlined in Scenario 3 and suggested by EPA is not only a better approximation of the true risk but also provides the necessary public health protection that is desired.

Lastly, the Panel is concerned about the recommendation that dioxin and dibenzofurans be treated as substances without a carcinogenic threshold. There is considerable evidence which suggests that 2,3,7,8-TCDD is a promoter. TCDD has not been found to bind to DNA or to stimulate unscheduled DNA synthesis when tested in rat hepatocytes or in a human cell line. Overall, all of the mechanistic studies including the results from the lifetime bioassay supports the concept of a nongenetic mechanism of carcinogenesis for TCDD.

I hope that these comments are useful. Please contact me at 202-887-1189 for any further information.

Sincerely,

Robert J. Fensterheim
Manager
Dibenzofurans/
Dibenzodioxins Program

STATE OF CALIFORNIA
GEORGE DEUKMEJIAN, Governor

AIR RESOURCES BOARD
1102 Q STREET
P.O. BOX 2815
SACRAMENTO, CA 95812

August 9, 1985

Mr. Robert J. Fensterheim
Manager, Dibenzofuran/Dibenzodioxin Program
Chemical Manufacturers Association
2501 M. Street NW
Washington, DC 20037

Dear Mr. Fensterheim:

Subject: Your Comments on Chlorinated Dioxins and Dibenzofurans

Your letter of July 12, 1985, concerning Report to the Scientific Review Panel on Chlorinated Dioxins and Dibenzofurans, Part B has been forwarded to the Department of Health Services. They will prepare responses to your comments, which we will include along with your letter in Part C of the revised report. CMA will receive the revised report when it is submitted to the Scientific Review Panel.

Thank you for your comments.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: P. Venturini, ARB
R. Neutra, DHS

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CORPORATE ENGINEERING & ENVIRONMENTAL
TECHNICAL SERVICES DIVISION

July 17, 1985

Mr. Wm. V. Loscutoff
Chief
Toxic Pollutants Branch
Attention: Dioxin Comments
Air Resources Board
1102 Q Street
Sacramento, CA 95814

Dear Mr. Loscutoff:

In your letter to the general public of June 12, 1984, you requested comments on the April and June, 1985 documents prepared by the Department of Health Services ("DHS") entitled "Health Effects of 2,3,7,8-Tetrachlorodibenzo -p-dioxin and Related Compounds," which concerns the chlorinated dioxins and the dibenzofurans. We appreciate the opportunity to comment on this important report, as well as on other related reports published by DHS.

In view of the vast amount of information reviewed and evaluated in these documents and the technical complexity of the issues, we would have preferred having a longer comment period.* Given the time constraints, we have chosen to use a brief outline format for submitting our comments. For those ideas

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*As it turned out, we received your letter of June 12th on June 17th. My request for the documents was submitted on the 18th and we received the assessments from your office on June 27th. This left us with only two work-weeks (which includes one holiday) for comment. We requested a short extension on the comment period of three work days, and Mr. Dale Shimp of your office has kindly assured us that if our comments reached your office by July 17, 1985, they would receive the same consideration as if they had arrived by July 12, 1985, the original due date.

which you believe deserve further discussion, perhaps we could, at your request, develop these more thoroughly over the ensuing weeks.

The following are our thoughts on 2,3,7,8-Tetrachlorodibenzo-p-dioxin ("TCDD") as discussed in the April and June reports and the related documents.

A. Science vs. Policy: Our primary difficulty with the documents, as presented, is that there appears to be commingling of purely departmental policy positions with conclusions which DHS avers to be based strictly on scientific data. Undeniably, much hard work has gone into the process of assembling the relevant background data, and the document is very thorough in that respect. However, the analysis of the data is heavily colored by the policy perspective from which DHS is operating.

The lack of distinction between conclusions based on science and conclusions based on policy gives readers of the document the impression that all of the conclusions are based on science and are widely held in the scientific community, when in fact they frequently are not. For example, on page 7 of the document entitled REPORT TO THE SCIENTIFIC REVIEW PANEL ON CHLORINATED DIOXINS AND DIBENZOFURANS, dated June, 1985, the DHS states:

> "Based on its review of all available scientific data, the DHS concludes that 1) 2,3,7,8 TCDD and the hexachloro dioxins are carcinogenic in animals; 2) dioxins and dibenzofurans chlorinated in the 2,3,7 and 8 positions which contain 4,5,6 or 7 chlorine atoms are potential human carcinogens; 3) chlorinated dioxins and dibenzofurans should be treated as substances without a carcinogenic threshold; 4) health effects other than cancer are not expected to occur at current ambient levels; and 5) the maximum likelihood estimate of lifetime excess cancers is 240 per million for continuous exposure to 2,3,7,8 TCDD at an airborne concentration of 10 pg/m^3 and 6 per million for comparable exposure to H6CDD."

These conclusions, which are worded in such a way as to give the mistaken impression that they represent the majority of scientific thought, appear to be influenced by the Department's a priori assumptions regarding carcinogens. For example, the following conclusions which are more strongly supported by the weight of scientific evidence (much of which was presented in the DHS documents) could also have been stated:

1) 2,3,7,8 TCDD and the hexachloro dioxins are carcinogenic in animals;

2) dioxins and dibenzofurans chlorinated in the 2,3,7 and 8 positions which contain 4,5,6 or 7 chlorine atoms are suspected potential human carcinogens;

3) these chemicals most likely have a threshold since the bulk of the animal and human data suggest that if TCDD is a human carcinogen at all, it is only a promoter, rather than an initiator, and promoters have been shown, and would be expected, to have a threshold;

4) health effects other than cancer are not expected to occur at current ambient levels;

5) epidemiological data show TCDD has not produced an increased cancer risk in persons who have been exposed to doses greater than that which result from breathing the maximum ambient concentrations predicted for the state of California. Such data indicate that a "de minimus" cancer risk would exist at the anticipated ambient levels (0.5-3.0 pg/m^3).

We submit that the conclusions expressed by the DHS diverge from the above conclusions by reason of department policy rather than science. In fact, as will be discussed, many of the conclusions drawn by DHS are contrary to the weight of scientific evidence which they have reviewed in their documents.

Further, several of the positions taken by DHS in their April and June, 1985 reports are similar to those taken in the carcinogen policy proposed by DHS in 1982. It is our understanding that because the 1982

carcinogen policy was not formally accepted by the State, the principles described in that policy are not tenable and were not to be implemented. It seems that this has occurred because their conclusions are not always consistent with the scientific data reviewed by the DHS in their document. Instead, the conclusions appear to be based on the current DHS policy (as described in the section which reviews their assumptions, p. 10-3) on how they feel carcinogens should be assessed and regulated.

Mr. Robert C. Barnard, a respected observer of how risk assessment is practiced in the Federal government and a Rhodes Scholar, has studied the issue of the roles of Science and Policy in the assessment process. In his chapter in Diesler's text, Reducing the Carcinogenic Risks in Industry (Dekker Pub., 1984), Mr. Barnard made the following statements:

> The National Academy of Sciences (NAS) report (on risk assessment) speaks of "policy" in the context of both scientific risk assessment and risk management.... The NAS report points out that the scientific analysis will involve analytic choices by the scientist in the assessment process. These choices, the NAS concluded, involve both scientific and "policy" considerations.
>
> To explain what scientific policy considerations are, the NAS Report analyzes the steps in a scientific risk assessment and describes some of the option choices in each step. For example, in evaluating epidemiologic data the scientists must decide what weight should be given studies with different results. Another example is the degree of confirmation of a positive animal study and the relevance of comparative metabolic data in evaluating the results. Choices among the analytic options involve science policy, which is different in character from the social policy used in making regulatory decisions.
>
> The fact that science policy determinations are made in the course of a scientific evaluation, however, should not be an excuse to inject economic and social policies into the scientific analysis. Neither economic or political judgments nor a scientist's personal value

judgments should affect or constrain the scientific evaluation. The scientific evaluation should be unbiased, objective, and free of constraints imposed by management policy dictates.

It is sometimes said that the scientific evaluation of risk should be "conservative" because it deals with human health. But this puts "conservatism" in the wrong place in the regulatory structure. It is the function of the regulator to apply the social criteria of cost, safety, reasonableness, and acceptability. It is in making these decisions that "conservatism" may play a role. If a scientific evaluation is constrained in the name of "conservatism" by social values or management policy, the result will be biased in unobvious ways. Such an evaluation does not provide a sound basis for the difficult social/legal decisions a regulator must make.

EPA Administrator Ruckelshaus, in a recent major policy speech before the National Academy of Sciences, stressed the importance of an adequate science base for regulatory decisions. His speech contrasted regulatory decisions based on social policies with scientific evaluation which must be free of bias and be unconstrained by sociopolitical "policies":

> Scientists assess a risk to find out what the problems are. The process of deciding what to do about the problems is risk management.
>
> Despite these often conflicting pressures, risk assessment at EPA must be based on scientific evidence and scientific consensus only. Nothing will erode public confidence faster than the suspicion that policy considerations have been allowed to influence the assessment of risk. (Emphasis in the original text.)

A scientific assessment should be neither "conservative" nor "liberal." The assessment must be objective; science "policy" judgments should not be a device to inject social policy constraints.

B. Guidelines For Conducting A Risk Assessment: We wish specifically to encourage DHS to apply the most recently developed criteria and guidelines for conducting a risk assessment. Over the past 12 months several significant consensus documents and scientific publications including the proposed EPA guidelines and OSTP guidelines have been written. These are useful guides for evaluating any substance which may pose a carcinogenic hazard to man. Although the process of assessing the risk of exposure to low levels of carcinogens is a rapidly changing one, we believe that any valid risk assessment should be able to meet certain basic tests. These tests for validity have been distilled to a series of questions developed by Dr. Robert Sielken of Texas A & M University (Regulatory Toxicology and Pharmacology, 1985; in press), as follows:

> "All quantitative models for cancer risk are not equal. Nor are they all equally relevant or equally reflective of the available scientific information. There are several questions which the government regulator, industrial executive, or a staff member should ask in order to better ascertain the value of a particular quantitative cancer risk assessment. Several of these questions are stated here. A negative answer to almost any one of these questions can seriously diminish the relevance and value of the risk assessment [emphasis supplied].

1. Were all the events which are called a "carcinogenic response" of equal severity or consequence?

2. Does the quantitative model reflect the time the carcinogenic response occurs?

3. If a time-to-response model has been used, is the stated probability of a carcinogenic response inflated by ignoring competing routes?

4. Does the family of curves represented by the dose response model contain enough curves of differing shapes to reflect the observed curvature in the experimental data?

5. Has the dose level been expressed on a biologically relevant scale?

6. Are the experimental data at the high doses relevant to the low dose behavior?

7. Are the animals used for experimentation and the carcinogenic responses observed in these animals relevant to humans?

8. Are the experimental data consistent across the animals which are considered relevant to humans?

9. If animal to human extrapolation is to be used for cancer risk assessment, then have the relevant biological differences in the species been identified and incorporated into the risk assessment?

10. Have any differences between the route of the experimental exposure and the route of human exposure been accounted for?

11. Are the exposure durations and patterns (once in a lifetime, intermittent, continuous, etc.) the same in the experimental data as they are in the human population at risk?

12. Are the inferences made from short-term tests consistent with the inferences made from long-term studies?

13. Are the inferences drawn from animal-based models consistent with those from human epidemiological data?

14. Have the human exposures been carefully identified with respect to routes, durations, dose levels, and patterns (continuous, intermittent, etc.)?

15. Has the statistical variability in the quantitative risk assessment, caused by the variability in the experiment, been characterized?

16. Have the assumptions, policy decisions, and value judgments incorporated into the quantitative risk assessment been clearly stated and the impact on the quantitative risk assessment been evaluated and recorded?

17. Are the risks characterized in understandable and appropriate terms?

18. Are the stated risks actually estimates of the risks as opposed to upper bounds or lower bounds of the risks?

19. If the uncertainty of the risk estimate is described in terms of bounds on the risk, then have both upper and lower bounds been recorded as well as their method of determination, including the assumptions made in that determination and their impact?

20. Have the quantitative risk assessments been based on outdated guidelines or procedures?"

It would appear that many of the criteria which Dr. Sielken advances are not fully addressed in the DHS document. We recommend strongly that DHS carefully review these questions as they pertain to TCDD and attempt to address them wherever possible in its risk assessment.

C. Nongenotoxicity of TCDD: DHS's discussion of the question of TCDD genotoxicity appears to be another example of the commingling of DHS's policy, as outlined in the 1982 proposed Cal. Cancer Policy, dictating conclusions drawn in the risk assessment. Foremost scientists in dioxin research have stated that there is virtually no scientifically acceptable evidence to suggest that TCDD should be classified as an initiator (Pitot, et. al., Cancer Research, 40:3616-3620, 1980). Among the prominent scientists who have studied the dioxins and who feel strongly that public health standards for TCDD and the furans do not need to be assessed solely through use of low dose extrapolation approaches are Dr. Perry Gehring, Dr. Richard Kociba, Dr. Alan Poland, Dr. Jim Byard, Dr. Robert Neal, and Dr. Gary Williams. Since this list contains many of the well-regarded scientists who have studied the molecule or nongenotoxic mechanisms of cancer, we submit that this question merits a more thorough evaluation than DHS has given it. Instead, DHS has summarily treated the issue as follows, at p. 10-2:

> "There are arguments for use of a threshold approach when the compound produces cancer through an indirect, i.e., epigenetic mechanism. TCDD has been shown to be a promoter of tumorigenesis, an epigenetic mechanism, in two separate systems, the two-stage mouseskin model and the two-stage rat liver model. A number of studies have indicated that TCDD did not directly damage DNA. However, there are other studies which suggest that TCDD is a mutagen and possibly a clastogen (chromosome-breaking agent). Therefore, even though TCDD is a promoter, it may also induce direct genetic damage that leads to the

> observed carcinogenic effect. Because of doubt about the carcinogenic mechanism of TCDD, the staff of DHS feels that the appropriate method for risk assessment of TCDD is based on a no-threshold approach."

We submit that the "conclusion" reached is not consistent with the available data. It does not necessarily follow that because TCDD may be a clastogen in tests like the sister chromatid exchange (SCE) assay and because science doesn't fully understand "how" TCDD acts, it should, by definition, be treated as an initiator in the risk assessment process. First, the meaning of the SCE and related tests continues to be unclear to both mutageneticists and regulators. For example, even within the EPA, the results of clastogen assays receive little attention when more classic in-vitro test results are available. Second, our lack of understanding of the mechanism of TCDD is not an appropriate rationale for choosing to use the multi-stage or any other modeling approach. Numerous researchers have suggested that a safety factor approach, modified safety factor approach (Gaylor-Kodell), or a non-threshold model which allows for responsiveness to the biologic data are equally credible approaches to assessing promoters.

It is critically important to the risk assessment that DHS distinguishes among chemicals which are clearly initiators, versus those which have minimal or no initiator capability, versus those which are solely promoters. Specifically, we would recommend that each of the studies on genotoxicity be critically reviewed and that the weight of evidence approach should be used to classify TCDD. The existing discussion in section 7-1 of the April document seems to treat all of the studies equally when, in fact, some are clearly superior to others. It is inappropriate to allow the results of 2 or 3

studies which suggest TCDD may be marginally genotoxic to overrule the conclusions drawn in 10 or more studies which suggest that it is not. Further, several high quality papers which discuss "how" promoters are likely to be involved in the cancer process were not discussed. Specifically, work by Dr. T.J. Slaga, Dr. H.C. Pitot, Dr. Gary Williams, and Dr. Al Poland should be informative. Even DHS's review of the data suggests that if they had no general departmental policy on carcinogens, the data would argue that the majority of the scientific community would regard TCDD as nongenotoxic. The work of Poland and Knutson (Ann Rev Pharmacol Toxicol, 22:517(1982)), Pitot, et. al. (Cancer Res, 40:3616-3620, (1980)), Poland and Glover (Cancer Res, 39(9):3341-3344 (1979)), Althaus, et. al. (1982), Poland et. al. (Nature 300:271-273, (1982)), and Bartsch, H. et. al. (in Mutagenicity, New Horizons in Genetic Toxicology (1982)) would appear sufficient to support that position.

Several lines of evidence explain why the aforementioned researchers and others have chosen not to classify TCDD as an initiator. First, TCDD does not appear to have mutagenic power when tested in a broad array of in-vitro tests. Second, the majority of metabolic pathways which have been proposed for TCDD do not include a step which would generate a reactive moiety such as an epoxide or a free radical. Third, little binding of TCDD to DNA has been observed, especially when compared to nearly any of the classic carcinogens which are often three to six orders of magnitude more active. Fourth, based on its structure activity relationship and its analogy to other heavily chlorinated molecules, it is unlikely that it has initiator capability. To many researchers, these data are so compelling that they consider it a serious injustice to let a small number of reports, which suggest that TCDD may be a

weak mutagen, cloud the issue to the extent that regulatory agencies should be driven to adopt cancer models which were intended only for genotoxic chemicals. Comments to this effect have been made by such premier researchers as Dr. Alan Poland of the University of Wisconsin, Dr. Robert Neal, formerly of Vanderbilt University, and now at CIIT, and Dr. Al Young, Senior Policy Analyst at the Office of Science and Technology Policy.

DHS is apparently aware of these data, since page 9-4 of the DHS document published on April 19, 1985 notes that:

> "There is only limited evidence that TCDD is an initiator of carcinogenesis. Initiators are believed to act directly with DNA and produce genotoxicity such as binding to DNA in such a way as to cause a mistake during replication. Although there is evidence that TCDD is metabolized to a potentially reactive compound through epoxide formation, and that strong protein binding occurs after metabolic activation, good evidence that TCDD binds to DNA is lacking since only one study showed little if any binding. Other evidence that may indicate TCDD is genotoxic is ambiguous in that some studies indicate TCDD is mutagenic or co-carcinogenic while others indicate it is not.
>
> "Based on this discussion, no mechanism of action can be associated with the carcinogenic effect observed when animals are treated with TCDD. There is stronger evidence that TCDD acts as a co-carcinogen or promoter than as an initiator. However, the action as an initiator cannot be discounted based on current knowledge [emphasis supplied]."

In the final analysis, the DHS seems to have chosen to accept the conclusions of a few "less-than-widely accepted" studies over the weight of evidence provided by researchers whose data indicate that TCDD is almost certainly not an initiator. The agency, consistent with its proposed cancer policy, has chosen to take a position which is not always based on the bulk of scientific evidence. Rather, it has chosen to base its decision on selected

evidence which suggests that TCDD may have some initiator capability. Apparently, as discussed in their 1982 policy, unless there are compelling arguments to the contrary, such chemicals will be treated as initiators. We would suggest that by that "standard" the data which DHS claims it would need to conclude that a chemical is not an initiator will almost never be available or sufficiently compelling. We recognize that DHS is attempting to "err on the side of safety" in adhering to this standard. However, the potential hazard with such an approach is that by requiring such compelling data the DHS will be unable to distinguish the true public health threats from those that present only "de minimus" risk.

Once the decision is made to classify TCDD as an initiator, a number of other assumptions, which are implicit in current thoughts on the assessment of risks posed by tumor initiators, are unavoidable, i.e., the use of low dose extrapolation models which assume no threshold, are linear at low doses and are almost entirely insensitive to the biological data since the "bounding" procedures used in the models essentially neglect the information gained at the low doses, etc. (Sielken; The Capabilitites, Pitfalls and Future of Quantitative Risk Assessment, University of Waterloo, 1985).

We submit that the agency should acknowledge that, in fact, the bulk of data suggest that if TCDD is carcinogenic at all, it is as a promoter rather than an initiator, and that they should explore the effect of such an acknowledgement on the risk assessment approach and on the risk estimates. If an appropriate safety factor was applied to the NOEL or the predicted 1% incidence level, I think the DHS would find that the results are much different than the "acceptable level" identified by the multi-stage model. By

choosing its current "policy driven" approach, DHS produces a risk assessment which may describe TCDD as a potential problem which is much more serious than the majority of the data would suggest.

D. Estimating Human Risks: The importance of identifying TCDD as a promoter rather than an initiator may seem to be a relatively insignificant one to the DHS, but it can have a profound impact on the assessment. For example, several members of the DHS staff have stated that promoters should be treated much like initiators in a regulatory sense since it is their position that the scientific community cannot, without question, rule out the possibility that some humans abound with initiated cells. Presumably, these cells, when exposed to low levels of a promoter, proceed through the various stages in the carcinogenic process. One difficulty we have with this interesting hypothesis is that it is not widely held to be accurate. More importantly, it is always difficult, if not impossible, to prove the negative. In general, however, when scientists are faced with these dilemmas, they rely on their good judgment and the weight of evidence to make their decisions.

We believe that the weight of the evidence strongly suggests that this "initiated cell" theory is not valid. Studies wherein promoters were administered to tumor-prone animals (e.g., those which develop an increase in tumors when exposed to changes in temperature, light cycle, and bedding) for a portion of their lifetime demonstrate that even these animals did not have an increased number of tumors compared to those which were not exposed to the promoter (the controls). Such studies suggest that if exposure to promoters does increase the likelihood that persons will develop tumors due to the

existence of a background number of initiated cells, the risk is certainly not linear at low doses or additive as assumed in the current cancer models. The weight of information on nongenotoxic carcinogens indicate that risks are likely to be insignificant or nonexistent at low doses.

One of the characteristics of a promoter is that the dose of the promoter must be sufficiently great at the site of initiation to "push" the cell to the next stage. This carries with it the thought that a "threshold" dose must be reached. Also, the processes involved in getting the promoter to the DNA within the initiated cell are basically non-linear...absorption, distribution, metabolism, and elimination. In short, none of the characteristics of promoter or the biological aspects suggest that they should be interpreted using classic risk models which were intended for use in analyzing the risks posed by radiation...a physical challenge which is clearly mutagenic, has a linear rather than a non-linear dose delivery system, and which has a good chance of having low dose linearity.

Surely, given the information gained from animal studies, the lack of genotoxicity, the fact that promoters have, at the least, a practical threshold, we should be able to extrapolate from the animal data on TCDD to determine a dose at which humans would be expected to be at a "de minimus" level of risk.

If such an "acceptable" or "virtually safe" daily dose were determined using this approach, the regulator and the public would <u>not</u> be as likely to be misled as they currently are by the mathematical models which claim that a certain number of cases of cancer per million exposed persons can be expected. These models have not been validated for initiators and it is

likely that their use for nongenotoxic chemicals is even less appropriate. For example, we know that when exposure to promoters is terminated, carcinogenesis is reversible (except where late stage cancer development has been reached). Second, promoters differ from initiators in that intermittent exposure to promoters does not necessarily yield and often has not yielded an effective cumulative dose with corresponding additive risk, as assumed by the low dose extrapolation cancer models. Support for this position can be found in animal studies which demonstrate that when exposure to a promoter is terminated early in the study, no additional tumors develop. There are many reasons why promoters should be regulated differently from classic initiators, and these have been discussed in several published manuscripts which we could send to you at your request.

E. Human Epidemiology Data: Section 8.2 of the April document contains a rather complete review of the human experience. A shortcoming of the proposed report is the absence of a discussion that man is apparently much more resistant than animals to the carcinogenic hazard and acute toxicity of TCDD. It is, of course, noted in the document that there is a wide range of susceptibility among various animal species to the toxicity of TCDD; but what is not acknowledged is that there are many incidences of rather significant human exposure wherein neither death nor even chloracne was noted in the exposed population. For example, the epidemiology studies of veterans of Vietnam and, more importantly, studies of workers at the Nitro plant in West Virginia indicate that even people who were chronically exposed to TCDD,

including those who developed chloracne, do not appear to be at increased risk of cancer or of any increased mortality or morbidity.*

Some have said that these studies are inconclusive because insufficient time has elapsed for the true effects to be manifested and that they lack statistical power. However, epidemiologists at NIOSH and elsewhere have indicated that sufficient time has passed to give us some assurances that TCDD certainly does not have the carcinogenic potency in humans that was once anticipated based on animal data. This conclusion is supported by epidemiological studies which found no increase in cancer incidence in employees at the Nitro plant in West Virginia who were exposed to TCDD 30 years ago and who still had chloracne symptoms. Further, we know that for more potent carcinogens the time-to-tumor-onset in animals is shorter than for less potent carcinogens. Consequently, the absence of tumors in TCDD exposed persons supports the conclusion that TCDD is a carcinogen in man at all, it is neither a potent carcinogen nor an initiator. In short, if TCDD were a potent carcinogen in humans, some indication of its tumorigenicity would have been seen by this time. As DHS correctly noted, Dr. Hardell's studies have been reviewed on numerous occasions and they have been found to be too wrought with problems to be very useful. Due to the issues we have raised here, we believe that it would be

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*The dioxin epidemiology studies were reviewed in detail recently by United States District Court Judge Jack B. Weinstein in dismissing the claims of certain "Agent Orange" plaintiffs. Judge Weinstein found, based on his exhaustive review of the literature and affidavits submitted by plaintiffs experts, that the plaintiffs could not demonstrate any recoverable injury resulting from dioxin exposure. See In re "Agent Orange" Product Liability Litigation, Civ. No. 81-662 et. al. (E.D. N.Y. May 8, 1985).

useful for DHS document to explain to the public some of the serious difficulties and uncertainties in extrapolating TCDD data obtained in animals to the human situation. The conclusions reached by DHS which predict a certain number of human cancers indicates a certainty that is quite likely to be inaccurate given the human experience.

F. Difficulties in Scale-Up: The DHS document gives the impression that by adjusting the animals doses, where it purportedly corrects for inhalation and surface area differences between man and rodents, that it has corrected for virtually all important biologic differences between species. From this "scale-up", DHS confidently predicts certain increases in the human cancer rate based on the rodent bioassays. As DHS is aware, the scale-up process is more complicated than this. Whenever possible, corrections need to be made for the differences in the metabolic rate constant, Vmax, quantity of adipose tissue, uptake and elimination rates, mode of action, as well as many other factors (Ramsey and Andersen, 73, 159-175, Toxicol Appl Pharm, 1984).

The uncertainties in scale-up for TCDD are especially great given the wide array of toxic responses which have been observed in animals compared with the rather narrow description of adverse effects seen in exposed humans. Further, the human epidemiology data (chloracne, morbidity, and mortality) suggest that, for TCDD, scale-up may not be possible. We strongly recommend that DHS provide readers of its report with some sense of the many uncertainties and assumptions inherent in the scale-up approach they have selected. Such an acknowledgement would help put any attempt at quantification of human risk into its proper perspective. Lastly, given these difficulties and uncertainties, we would suggest that DHS use the FDA terminology of "virtually

safe" or "acceptable" levels of exposure rather than offer estimates of excess human deaths.

G. Inappropriateness of Predicting Human Cancer: In view of the scientific evidence that man is less susceptible than animals to the acute and chronic hazards of TCDD, and in view of TCDD's lack of genotoxic activity, it would appear that a mathematical extrapolation of rodent bioassay data using only the results of the multi-stage model, or for that matter any model, are likely to be misleading. Basically, the assessment process used by DHS is similar to that which has been applied by other regulatory agencies for potent initiators such as radiation, benzpyrene, and aflatoxin; chemicals for which there are strong scientific data that support the argument that they act through a carcinogenic mechanism different from TCDD's. Further, it is especially troublesome that DHS would choose to describe the risks associated with a given exposure with such certainty in light of the human epidemiology data, the lack of TCDD genotoxicity, differences in pharmocokinetic behavior between species, and the possible differences in metabolism between species.

DHS, in its conclusions (page 7 of the Report to the Scientific Review Board (June 15)), notes that "the maximum likelihood estimate of lifetime excess cancers is 240 per million for continuous exposure all day long to airborne concentration of 10 pg/m^3." It strikes us that the expression of a cancer risk with this certainty is likely to be incorrect. For example, Dr. Crouch and Dr. Wilson, of Harvard (Wilson, Tech Review, February 1979, p. 41-46), have indicated that if one were to express the hazard of eating eight peanut butter sandwiches (40 tablespoons of peanut butter) in one lifetime, in comparable terms, the risk of developing cancer from that

exposure to aflatoxin is about 1 per one million exposed persons. Because data like this have never been taken seriously by regulators, at least to the extent of suggesting the ban of peanut butter or to discourage its consumption, we are inclined to think that the Federal Regulatory agencies have given tacit agreement that one should not blindly adhere to the information gained from models nor unnecessarily alarm the public to a danger that, in all probability, does not exist. Actually, for aflatoxin, the modeling data are on firmer ground since aflatoxin has, at least, been shown to be capable of causing tumors in man. As an aside, we know of no environmental or occupational health standard (limit) which has been based solely, or even primarily, on the risk estimates derived from one of the cancer models.

H. Critique of DHS "Generic Assumptions" on Cancers: As is appropriate, DHS has acknowledged the assumptions it has used in the risk assessment [p. 10-3, April 1985]. Regrettably, our current lack of understanding about mechanisms of cancer and man's ability to cope with low levels of exposure to all toxicants, including carcinogens, require that assumptions like these be made for many toxicants.

However, in spite of our current lack of scientific knowledge about the overall mechanism of cancer, we do know a good deal about TCDD. Dr. Al Young of the Office of Science and Technology Policy has stated that we need not know a good deal more about dioxin in order to manage its risks. By reason of our current level of knowledge, we submit that some of the "generic" assumptions listed on p. 10-3 need not be made.

The assumption, for instance, that "animal data are applicable to humans" is, in general, necessary and widely accepted, but only when there are insufficient human data. In the case of dioxin, at least three epidemiology studies have found that no cancer excess has been noted in exposed human populations. In fact, no epidemiological study has demonstrated that low level exposure to TCDD causes an increased incidence of any disease in man other than chloracne, which is rarely seen at very low doses.

Further, evidence that man is certainly not as susceptible as the most sensitive animal species; i.e., the guinea pig, is reflected by the lack of even one documented human death following acute exposure, although dozens of people have been exposed to fairly high doses in several industrial accidents and many have been repeatedly exposed to much lesser doses due to inadvertent contact with herbicides contaminated with TCDD.

In view of this information, it seems inappropriate to apply classic mathematical models which are linear at low doses, lack a threshold, and are insensitive to low dose animal tumor incidence data. Certainly, it appears to be alarmist for DHS to predict the number of human deaths caused by inhalation exposure to TCDD based solely on bioassays in which rats exposed to TCDD developed tumors at doses at least 1,000 fold greater than that to which DHS has predicted Californians would be exposed via ambient air.

To claim that use of this modeling procedure is "appropriate" because both Dr. Kimbrough of CDC and the EPA used it in their reports on dioxin is not dispositive of anything. Many assumptions made in those assessments are open to criticism, and neither meets all of the criteria described in the most recently proposed EPA guidelines for evaluating carcinogens (Nov. 1984). As

noted in the EPA Guidelines and in the OSTP Guidelines, many considerations influence the selection of the appropriate model for estimating a cancer incidence rate from animal bioassay data. As noted by the EPA Science Advisory Board, when there is only weak evidence that a chemical is likely to be a carcinogenic hazard to man, predictions of human cancer incidence rates based on the results of modeling of bioassay should not be developed.

The assumption that "high dose bioassays are appropriate for determining low dose responses" is only appropriate when pharmacokinetic data are lacking or when there is evidence for linearity over a broad range of doses for the reasons which have been discussed by Hoel and Andersen (Science, 1983); and Starr and Buck (Fund Appl Toxicol, 1984). Lastly, linearity is not likely at low doses, especially for dioxin. Since at least four kinetic studies on TCDD have been conducted, these should be reviewed by DHS and their significance to the assessment explained.

As the DHS is also aware, there is a growing sentiment within the scientific community that very low doses of carcinogens are probably not likely to pose a significant hazard to humans because of biologic protective mechanisms which exist in the body, as well as naturally occurring anticarcinogens which humans ingest (Ames, B.N. Science, 221:1256-1263). Dr. Bruce Ames has noted that the existence of these mechanisms is not surprising given the presence of carcinogenic substances in our "natural diet" over the millenia. The research is now quite clear that both antioxidants and glutathione, as well as a host of other chemicals, can play a critical role in protecting cells and the cellular DNA against even potent initiators, depending on dose. Consequently, it seems too simplistic for DHS to continue

to "assume" that exposure to low doses elicits the kind of biologic response seen following exposure to high doses, let alone assume that such exposures are quantitatively related.

We are not advocating that nothing be done but rather that all of the available data be assessed in producing a consensus judgment as to the degree of risk associated with a given level of human exposure. The overall decision about the acceptability of a particular degree of exposure must be based on a melding of all the relevant information. Even though the DHS has clearly done a commendable job of reviewing all the available TCDD literature, the "bottom line" DHS estimate of risk is still based on the rodent data extrapolated 2-4 orders of magnitude away from the observable range without incorporation of the human data, pharmacokinetic data, or genotoxicity data.

The assumption that "lifetime cumulative average daily dose is the appropriate dose to use for dose-response assessments" may be appropriate for situations which involve both continuous exposure (such as seen in ambient air) and chemicals which are initiators. However, for TCDD, which is not an initiator, it is not justified. Since the bulk of the data suggest that if TCDD is carcinogenic at all, it is only a promoter, a cumulative model would overestimate the hazard.

As discussed previously, the assumption that "a threshold for the observed carcinogenic effect does not exist" is not justified for TCDD.

The assumption that "benign and malignant tumors may be combined for dose-response assessment" has been debated within the scientific community for at least 10 years. The inclusion of benign tumors in the math modeling aspect of the risk assessment is a policy decision, not a scientific one. Strong

arguments have been made that this is not scientifically appropriate. Rather, the type of benign tumor should dictate whether it should be placed in that category of tumors which possess the capability for becoming malignant.

The assumption that "doses on a surface area basis are equivalent between species" is a rather simplistic view that has been losing support in the scientific community. For TCDD, it is unlikely that the surface area conversion is meaningful because of the wide differences in various biologic responses (e.g., acute toxicity and AHH induction) between species, the difference between rat and mouse data in the bioassays, the human epidemiology data, and the data which suggest it is the parent compound (TCDD) which is the toxic moiety (rather than the metabolite). The surface area correction is generally applicable only when a metabolite is the biologically active moiety responsible for binding to the DNA or the receptor.

Summary

The toxicological aspects of the dioxins and the dibenzofurans are among the most interesting of any group of chemicals. The DHS has done a commendable job of assembling the pertinent data and has attempted conscientiously to build a risk assessment based on its departmental guidelines. However, because the dioxins are distinctly atypical of many toxins, and because we have a fairly in-depth understanding of what effects they do not elicit in humans exposed to low doses, we believe that blind adherence to these guidelines is likely to paint a false picture of its true hazard to man. In order for the DHS report to be as accurate as possible, the DHS should:

(a) reevaluate the genotoxicity issue and make decisions based on the weight of evidence derived from widely accepted studies;

(b) alter the risk assessment approach if the data indicate that TCDD is, in all likelihood, acting through a nongenotoxic mechanism;

(c) attempt to incorporate into the assessment the favorable human experience with TCDD.*

(d) modify, or at least qualify, the conclusions on human cancer risk. In light of the lack of evidence for any chronic effects in humans, it seems inappropriate to predict with such certitude the incidence of cancer in humans for a given exposure scenario.

Once again, we appreciate the opportunity to comment on this issue. We hope that you find the comments useful.

Sincerely,

Dennis J. Paustenbach, Ph.D.
Manager, Industrial and
Environmental Toxicology

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*The attempt to do this by comparing the results of the model to Ott's human study is not convincing given the wide range of the 95% confidence limits and the low incidence rate observed in Ott's study. Given his limited database, we would expect agreement.

STATE OF CALIFORNIA

GEORGE DEUKMEJIAN, Governor

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August 9, 1985

Mr. Dennis J. Paustenbach, Ph.D.
Manager, Industrial and Environmental
Toxicology
SYNTEX, Inc.
PO Box 10650
Palo Alto, CA. 94303

Dear Mr. Paustenbach:

Subject: Your Comments on Chlorinated Dioxins and Dibenzofurans

Your letter of July 17, 1985, concerning Report to the Scientific Review Panel on Chlorinated Dioxins and Dibenzofurans, Part B has been forwarded to the Department of Health Services. They will prepare responses to your comments, which we will include along with your letter in Part C of the revised report. SYNTEX, Inc. will receive the revised report when it is submitted to the Scientific Review Panel.

Thank you for your comments.

Sincerely,

William V. Loscutoff

William V. Loscutoff, Chief
Toxic Pollutants Branch
Stationary Source Division

cc: P. Venturini, ARB
R. Neutra, DHS