State of California
AIR RESOURCES BOARD

Supplemental Analysis Regarding the Air Resources Board's
Proposed Airborne Toxic Control Measure for *Para*-dichlorobenzene

February 10, 2005

Introduction

On June 24, 2004, the Air Resources Board (ARB or Board) conducted a public hearing to consider a proposed Airborne Toxic Control Measure (ATCM) for *para*-dichlorobenzene ["PDCB"; also known as 1,4-dichlorobenzene, 1,4-dichlorobenzene(*p*-), and/or *p*-Dichlorobenzene]. The ARB received comments on the proposed ATCM both at the hearing and during the 45-day public comment period preceding the hearing. Some of the comments were from the Chlorobenzene Producers Association (CPA), who stated that numerous risk management agencies both in the United States and all over the world have declined to regulate PDCB on the basis of carcinogenicity. CPA observed that the Initial Statement of Reasons (ISOR) for the proposed ATCM does not mention any of the risk assessments conducted by these other agencies, and argued that because of this omission the ISOR does not comply with the requirements in Health and Safety Code section 39665 for the "report on the need and appropriate degree of regulation" for PDCB.

ARB staff does not agree with CPA's comment. Before adopting an ATCM for a toxic air contaminant (TAC), Health and Safety Code section 39665 requires the ARB to prepare a report on the "need and appropriate degree of regulation" for the TAC--commonly referred to as a "health risk and needs assessment." ARB staff did this for PDCB and included it in Chapter VII of the ISOR. California law does not require that the report discuss risk assessments conducted by other entities.

While not legally required to do so, staff nonetheless decided that it is appropriate to explain why the ARB staff does not agree with other entities that have declined to regulate *para*-dichlorobenzene. This document contains staff's analysis of this issue. This document is intended to ensure that the public has the opportunity to better understand why the ARB staff has reached a different conclusion than these other entities, and to provide the public with an opportunity to comment on the ARB's analysis. Consequently, this analysis is being made available for public comment during the supplemental 15-day comment period for the proposed ATCM. Since this analysis supplements the rulemaking record, only new references not already listed in the ISOR are listed as references at the end of this document.

Toxicity Review in California

1. Review by OEHHA

For the ARB's TAC identification and control program California law specifies that the Office of Environmental Health Hazard Assessment (OEHHA) will be the entity to conduct the health evaluations required for the program (previously, the California Department of Health Services performed this function). OEHHA is also responsible for establishing health risk assessment guidelines used in the State's Air Toxics Hot Spots Program. State law further requires that all health evaluations and the Air Toxics Hot Spots Program risk assessment guidelines (including any cancer or noncancer health values) developed by OEHHA undergo peer review by an independent scientific review panel. The Scientific Review Panel on Toxic Air Contaminants, established under the Toxic Air Contaminant program, was required by the Legislature to fulfill this peer review requirement.

2. Health-Protective Approach

When evaluating the toxicity of substances such as suspected carcinogens, California and OEHHA have historically taken a health-protective approach. A substance is determined to be a carcinogen in California if either animal data or human data show carcinogenicity. While human data on carcinogenicity provides greater certainty and is used preferentially where available, definitive human data may be extremely difficult to obtain due to practical, legal, and ethical reasons (OEHHA, 2001). Most human chemical carcinogenesis data is obtained from occupational epidemiology studies. Logistical constraints often hamper the ability to study occupational exposures, particularly where a large occupational cohort can not be defined. The sample sizes in these smaller studies render the studies insensitive. Additionally, many occupational studies must contend with confounders including mixed chemical exposures. Thus, human studies are limited. The health-protective approach is to consider animal data as pertinent to humans, unless the animal data are clearly shown to be not relevant to humans. The majority of chemicals that are carcinogenic to experimental animals are also carcinogenic to humans.

For *para*-dichlorobenzene, human data are lacking, but animal data have shown carcinogenicity. Laboratory tests conducted by the National Toxicology Program (NTP) in 1987 clearly show liver tumors in mice and kidney tumors in rats. Additionally, NTP noted 1) a significant increase in male rat mononuclear cell leukemia incidence at the high dose of PDCB; 2) a significant positive dose-response in the incidence of female mouse thyroid follicular cell adenomas; and 3) a significant positive dose-response in the incidence of male mouse adrenal gland pheochromocytomas, with the incidence in the high-dose mice being significantly greater than that of controls. Thus, in this NTP study PDCB caused a number of different types of cancers. NTP also noted an increase in male rat

kidney tumors. Some agencies, including OEHHA, have come to the conclusion that the rat kidney tumor data are not relevant to humans based on a plausible scientific explanation. However, recent data on the induction of deoxyribonucleic acid (DNA) damage and possible clastogenicity of *para*-dichlorobenzene in rat kidney cells (Robbiano *et al*., 1999) may require a reevaluation of this position.

Additionally, *para*-dichlorobenzene has been shown to bind to DNA and induce DNA and chromosome damage in human and rat cells. These data suggest that *para*-dichlorobenzene is a genotoxic carcinogen. In California, the mouse liver carcinogenicity data are considered relevant to humans, and as a result *para*-dichlorobenzene has been listed by the State of California under Proposition 65 as a chemical known to the state to cause cancer since January 1, 1989. Also, *para*-dichlorobenzene has been a California TAC since 1993. (Lattanzi *et al*., 1989; Oikawa and Kawanishi, 1996; Sasaki *et al*., 1997; Robbiano *et al*., 1999; Canonero *et al*., 1997; OEHHA, 2004a)

Based on the NTP data showing evidence of liver carcinogenicity in both male and female mice, OEHHA developed a cancer unit risk value for *para*-dichlorobenzene of 1.1×10^{-5} $(\mu g/m^3)^{-1}$, and an inhalation potency (slope factor) of 4.0×10^{-2} $(mg/kg\text{-}day)^{-1}$ (OEHHA, 2002). These cancer potency numbers, which are incorporated into the Air Toxics Hot Spots Program Risk Assessment Guidelines, were peer reviewed by the independent Scientific Review Panel on TACs as required by law (HSC 44360(b)(2)) on June 3rd, 1998. The nine member Scientific Review Panel on TACs is required to evaluate the Air Toxic Hot Spots Program health risk assessment guidelines and to recommend changes and additional criteria to reflect new scientific data or empirical studies.

The members of the Scientific Review Panel on TACs must be highly qualified and professionally active or engaged in the conduct of scientific research. The experts required by law to be represented on the Scientific Review Panel on TACs are a pathologist; an oncologist; an epidemiologist; an atmospheric scientist; a biostatistician; a physician or scientist specializing in occupational medicine; a toxicologist; a biochemist or molecular biologist; and a member with relevant scientific experience that is also experienced in the operation of scientific review or advisory bodies. Members of the Scientific Review Panel on TACs are appointed from a pool of nominees submitted to each appointing body (Secretary of Environmental Protection, Senate Committee on Rules, Speaker of the Assembly) by the President of the University of California. The pool must include, at a minimum, three nominees for each discipline represented on the Panel, and must include only individuals who hold, or have held, academic or equivalent appointments at universities and their affiliates in California.

The level of certainty associated with the health effects of *para*-dichlorobenzene is comparable to another California TAC, currently regulated by two ATCMs. Chlorinated dioxins (dioxins) is a family of compounds of which perhaps one of the most toxic is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). TCDD was

identified by the ARB as a Toxic Air Contaminant in 1986 (CDHS, 1986), and was listed as a Proposition 65 carcinogen in 1988 (OEHHA, 2004a). At the time of regulation, California considered available data to be inconclusive whether or not dioxins, as a group, are human carcinogens. However, National Toxicology Program (NTP) test data for TCDD showed rodent carcinogenicity, and California considers the animal data relevant to humans (CDHS, 1986; OEHHA, 2002, pp 167-187). Dioxins are created and emitted from the burning of various materials, such as waste containing certain plastics and other synthetic items. The ARB has applied the rodent carcinogenicity data in risk assessments for two ATCMs: "Dioxins Airborne Toxic Control Measure (ATCM) -- Medical Waste Incinerators," September 25, 1998 (ARB, 1998), and "Airborne Toxic Control Measure to Reduce Emissions of Toxic Air Contaminants from Outdoor Residential Waste Burning," February 3, 2003 (ARB, 2003). Note that the International Agency for Research on Cancer (IARC) now considers that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, the dioxin that has been studied the most, to be carcinogenic to humans.

The level of certainty associated with the health effects of *para*-dichlorbenzene is also comparable with methylene chloride (also called dichloromethane) and with trichloroethylene (also called TCE). Methylene chloride was identified by the ARB as a TAC in 1989 (CDHS, 1989), and was listed as a Proposition 65 carcinogen in 1988 (OEHHA, 2004a). Similarly, trichloroethylene was identified by the ARB as a TAC in 1990 (CDHS, 1990), and was listed as a Proposition 65 carcinogen in 1988 (OEHHA, 2004a). For both substances, California considers the available human data to be inadequate. However, test data for both substances show rodent carcinogenicity, and California therefore considers both to be carcinogens (CDHS, 1989; CDHS, 1990; OEHHA, 2002, pp 361-368, 522-530). The ARB has applied the rodent carcinogenicity data in the risk assessment for one ATCM: "Chlorinated Toxic Air Contaminants Airborne Toxic Control Measure (ATCM) -- Automotive Maintenance and Repair Activities," November 11, 2001 (ARB, 2001). This ATCM prohibits the use of methylene chloride, trichloroethylene, and perchloroethylene as well, in four automotive consumer products: brake cleaner, carburetor or fuel-injector air intake cleaner, engine degreaser, and general purpose degreaser.

The action taken by ARB on the *para*-dichlorobenzene ATCM is consistent historically with other actions related to this compound by the State of California. A Maximum Contaminant Level of 0.005 mg/L in drinking water for *para*-dichlorobenzene, based on liver tumor incidence in both male and female mice observed in the NTP study, was established by the California Department of Health Services (CDHS, currently OEHHA) in 1988. In 1994, OEHHA re-evaluated *para*-dichlorobenzene as a carcinogen based on the weight of overall evidence, and concluded there is still sufficient evidence to consider *para*-dichlorobenzene as a carcinogen. A Public Health Goal of 0.006 mg/L was developed for *para*-dichlorobenzene in drinking water by OEHHA in 1997, again,

based on the liver tumor incidence in male and female mice observed in the NTP 1987 study (OEHHA, 1997).

3. Consistency with Other Organizations

The State of California is not the only entity to consider *para*-dichlorobenzene as a carcinogen. The IARC concluded that there is sufficient evidence in experimental animals for the carcinogenicity of *para*-dichlorobenzene and that it is "possibly carcinogenic to humans" (Group 2B) in 1987. IARC re-evaluated this finding in 1999 and reaffirmed the classification (IARC, 1999).

In addition, the NTP has also made a formal finding regarding the carcinogenicity of *para*-dichlorobenzene. *Para*-dichlorobenzene was originally listed in NTP's Fifth Annual Report on Carcinogens in 1989 as a compound "reasonably anticipated" to be a carcinogen, and retains that listing in the current (Eleventh) Report on Carcinogens (NTP, 2005).

Toxicity Reviews Conducted by Other Bodies

1. Introduction

Organizations outside California may use different criteria before either considering a substance a carcinogen or before acting to control a substance. Some of these organizations use approaches that are less health-protective. For example, data from at least two animal species or human data may be needed to show carcinogenicity. Whether a particular mice strain used for testing is allegedly susceptible to tumor formation may also be a consideration. The organization may question the relevance of the mouse liver data to humans, even when there is no scientific explanation or consensus regarding the relevance or non-relevance of the data. In California, once a substance has been found to be carcinogenic in either animals or humans, the substance is considered a carcinogen unless it can be demonstrated that the data are not relevant to humans. For example, the argument that the strain of mice tested is susceptible to cancer formation does not show that the mouse liver data are not relevant to humans. It should be noted that NTP still uses the $B6C3F_1$ mouse strain for chemical carcinogenesis testing, and both NTP and IARC consider $B6C3F_1$ mouse liver tumor data to be relevant to human cancer risk determinations. Furthermore, susceptibility to cancers varies widely within the human population. Thus, the more sensitive animal strains are appropriate to consider.

Another difference in the approach organizations outside California take concerns the estimated *para*-dichlorobenzene exposure levels to human populations. Some reviews by other organizations estimated relatively low exposure levels, but did not consider more recent scientific data available after the reviews. Also, some methodologies employed by other organizations

seriously underestimated *para*-dichlorobenzene exposure risks, compared with the ISOR risk assessment for the ATCM.

2. Summary of Reviews

The Chlorobenzene Producers Association (CPA), representing *para*-dichlorobenzene chemical manufacturers, and manufacturers of *para*-dichlorobenzene solid air fresheners and toilet/urinal care products, has provided for the rulemaking record reviews prepared by some other organizations in the U.S. and in foreign countries concerning available toxicity data. Because of assertions that the ATCM and health risk assessment may not have a sound scientific basis, we are providing the following comments to explain why the ARB does not agree with the conclusions reached by some of these agencies.

> CPA Exhibit 1: 40 CFR parts 141 and 142 - "National Primary Drinking Water Regulations--Synthetic Organic Chemicals; Monitoring for Unregulated Contaminants; Final Rule." US EPA. July 8, 1987.

The United States Environmental Protection Agency (US EPA) position in this rulemaking differs from the California position, in which California considers the mouse liver carcinogenicity data relevant to humans. In the rulemaking US EPA considered the mouse liver data to be controversial. Instead of basing a standard on carcinogenicity, US EPA based the *para*-dichlorobenzene drinking water standard on chronic (non-cancer) health effects. At the time, US EPA decided against classifying PDCB in the "Group 2B" category (probable human carcinogen), and instead classified it in the "Group C" category (possible human carcinogen), while acknowledging that the downgrading is controversial. It should be noted that US EPA did not explicitly consider the other tumor findings from the NTP study: 1) a significant increase in male rat mononuclear cell leukemia incidence at the high dose of PDCB; 2) a significant positive dose-response in the incidence of female mouse thyroid follicular cell adenomas; and 3) a significant positive dose-response in the incidence of male mouse adrenal gland pheochromocytomas, with the incidence in the high-dose mice being significantly greater than that of controls. The NTP study therefore indicates that PDCB caused a number of different tumors in the experimental animals, not just kidney and liver tumors. Also, none of the more recent genotoxicity data (described above) was available to US EPA at the time this evaluation was performed. These data indicate that PDCB can damage DNA which is widely believed to be the first step in carcinogenesis. Please note that the US EPA rulemaking for drinking water in no way affected the US EPA listing of *para*-dichlorobenzene as a Hazardous Air Pollutant (HAP) under the federal Clean Air Act.

CPA Exhibit 2 - (document excerpts): "Briefing Package - Hazard Evaluation of Consumer Products Containing 1, 4-Dichlorobenzene." United States Consumer Product Safety Commission. October 30, 1991.

The Consumer Product Safety Commission (CPSC) position differs from the California position, in which California considers one animal study for *para*-dichlorobenzene sufficient to determine possible carcinogenicity to humans. In the evaluation, CPSC concluded the available data were not adequate to presume that PDCB presented a risk to humans as a carcinogen. CPSC believed more data were needed to make a determination, since there was only one study in which liver tumors were observed in one animal species (mice) at a single dose. The CPSC evaluation states that "the evidence for carcinogenicity is not considered sufficient by HS *[CPSC Health Sciences]* staff unless the substance has been found to cause a statistically significant dose-related increase in tumors: (a) in multiple species, strains, or independent sites or origin or in experiments using different routes of administration or dose levels; or (b) to an unusual degree in a single experiment (one species/strain/sex) with regard to tumor type, site, or early age at onset". The scientific judgment of the CPSC was that available data were not adequate at the time to support a finding that PDCB is "toxic" under the Federal Hazardous Substances Act by virtue of its carcinogenicity. However, similar to the US EPA 1987 evaluation, CPSC did not explicitly consider: 1) a significant increase in male rat mononuclear cell leukemia incidence at the high dose of PDCB; 2) a significant positive dose-response in the incidence of female mouse thyroid follicular cell adenomas; and 3) a significant positive dose-response in the incidence of male mouse adrenal gland pheochromocytomas, with the incidence in the high-dose mice being significantly greater than that of controls. The NTP study showed that PDCB caused a number of different tumors at different sites in the laboratory animals. CPSC also did not consider the elevated male mouse hepatoblastoma incidence in the 600 mg/kg dose group. Although these data were not statistically significant compared to controls, NTP noted that no hepatoblastomas had been observed in NTP corn oil gavage male mice (0/1,091) or in untreated control male mice (0/1,784) at that point in time. If these data had been considered by CPSC, they likely would have been sufficient to warrant the designation of *para*-dichlorobenzene as a carcinogen. Please note that the CPSC review in no way affected the US EPA listing of PDCB as a HAP under the federal Clean Air Act.

CPA Exhibit 3: Risk Assessment - 1,4-Dichlorobenzene. French Ministry of the Environment (FME) Final Report. May 2001.

The French Ministry of the Environment (FME) assumed that the mouse liver data were not relevant to humans, based on a lack of positive genotoxicity data at the time of the evaluation and a presumption that $B6C3F_1$ mice are susceptible to induction of liver tumors to a degree which makes them unsuitable as a model for human chemical carcinogenesis risk. This differs from the California position,

in which the mouse liver data are considered relevant to humans. However, FME did acknowledge that the mouse liver data have not been actually demonstrated to be irrelevant to humans. As noted above, NTP still uses the $B6C3F_1$ mouse strain for chemical carcinogenesis testing, and both NTP and IARC consider $B6C3F_1$ mouse liver tumor data to be relevant to human cancer risk determinations. We believe that the exclusion of the NTP mouse liver tumor data was inappropriate. Additionally, the evaluation of the applicability of the mouse liver tumor data to human cancer risk assessment, which was in large part based on a determination that *para*-dichlorobenzene is not genotoxic (capable of damaging DNA), was performed before the availability of the *para*-dichlorobenzene genotoxicity data described above. FME also concluded that the margin-of-safeties are insufficient, that there is a need for limiting the risks by control measures, and that there may be carcinogenicity and reproductive toxicity due to repeated-dose exposure mainly by inhalation.

> CPA Exhibit 4 - (document excerpts): Chlorobenzenes Other Than Hexachlorobenzene - Environmental Health Criteria 128. International Programme on Chemical Safety. World Health Organization. 1991.

The International Programme on Chemical Safety (IPCS) of the World Health Organization is consistent with the California position when considering the relevance of the mouse liver data to humans. The main difference between IPCS and California concerns estimated population exposure levels. IPCS believed, at the time of the review, that the general population was exposed to low levels of *para*-dichlorobenzene that were of little concern. ARB does not agree since the ATCM risk assessment shows adverse exposures and risks, based on our more recent review of the data.

The IPCS concluded that the general population appears to be exposed to low levels of *para*-dichlorobenzene. This was based on ambient air comparisons with an IPCS toxicity estimate using an experimental "no-observed-effect level" (NOEL) from long-term, chronic teratogenicity (developmental malformations), and developmental reproductive toxicity studies on experimental animals. The NOEL applied (*para*-dichlorobenzene concentration of 450 mg/m^3, equivalent to 450,000 $\mu g/m^3$, for inhalation) did not pertain to carcinogenicity. In the IPCS toxicity estimate, the NOEL was adjusted by dividing with an assumed "uncertainty factor" of 500 to derive a "tolerable daily intake" (TDI) level. With *para*-dichlorobenzene, which IPCS states may be a carcinogen in rodent liver, the carcinogenic effect was taken into consideration subjectively within the "uncertainty factor." The TDI was then used for comparison with ambient (outdoor) *para*-dichlorobenzene concentration data, which were considerably lower than the TDI. The full text of the IPCS document is available from the Internet (IPCS, 1991).

There are several shortcomings with the IPCS TDI and general population exposure estimate. In the IPCS review, carcinogenicity was included in the

analysis via the non-cancer NOEL, along with an "uncertainty factor" based on a subjective assumption rather than any actual experimental carcinogenicity data. Carcinogenic risk assessment as routinely practiced in California assumes that in the absence of evidence to the contrary, carcinogens are considered to have no threshold of action. Therefore, there is no “safe” level of exposure to carcinogens, and the quantitative risk assessment methodology used by IPCS would be considered inappropriate. IPCS also speculated that *para*-dichlorobenzene might be a nongenotoxic carcinogen. However, this assessment was performed before the availability of the *para*-dichlorobenzene genotoxicity data described above. Additionally, the *para*-dichlorobenzene air concentration data for comparison were based on average ambient (typical outdoor) levels, which are known to be considerably lower than indoor levels and those outdoor levels in the vicinity of wastewater treatment plants. Since the IPCS review was released, several important studies have been completed to better assess indoor concentrations and the associated health risks. Therefore, the IPCS review is partly outdated and differs substantially from the ATCM risk assessment, which uses better, more recent data, and more refined analyses, as presented in the ISOR.

The ATCM evaluation used risk calculation methods based on cancer potency factors, as recommended by OEHHA with review by the Scientific Review Panel on TACs. The ATCM included health risk calculations for specific population groups exposed to considerably higher air concentrations of *para*-dichloro-benzene -- people indoors and people living in the vicinity of wastewater treatment plants. The ATCM risk assessment also used up-to-date computer modeling methods, in accordance with US EPA modeling algorithms and guidelines, to relate air emissions to air exposure concentrations. (OEHHA, 2000; 2002; 2003). Therefore, results from the ATCM risk assessment, which calculated an increased excess cancer risk of 242 in a million based on an indoor *para*-dichlorobenzene level of 22 µg/m^3, 24-hour average, differs substantially with the IPCS results.

> CPA Exhibit 5 - (document excerpts): "Toxic Air Contaminant List (35 Ill. Adm. Code 232) - R90-1 (Rulemaking)." Illinois Pollution Control Board. September 26, 1991.

Exhibit 5 is out-of-date, and Illinois is presently consistent with California.

In 1991, the Illinois Pollution Control Board (IPCB) decided to agree with a US EPA evaluation at the time, concerning uncertainty with *para*-dichlorobenzene carcinogenicity data. Using the US EPA uncertainty as a basis, along with a regulation change at the time, IPCB de-listed the substance from the Illinois TAC list. However, a subsequent rule change has since re-listed the substance as an Illinois TAC. In the current IPCB regulations, all federal HAPs (including *para*-dichlorobenzene) are listed as Illinois TACs. Therefore,

Illinois is entirely consistent with California, in which the ARB lists all federal HAPs as California TACs.

The current IPCB rule, Title 35 IIlinois Administrative Code - Part 232 "Toxic Air Contaminants," is available from the Internet (IPCB, 2004).

> CPA Exhibit 6: 1,4-Dichlorobenzene - Priority Substance List Assessment Report. Environment Canada/Health Canada (EC/HC). 1993.

Canada concluded in 1993 that PDCB was not entering the environment in Canada in quantities or under conditions that may constitute a danger to the environment on which human life depends, or to human life or health. This differs with the current ATCM risk assessment showing adverse exposures and health risks.

In 1993, Canada used a "tolerable daily intake" (TDI) estimate for comparison with available air concentration data and estimated population intake levels of *para*-dichlorobenzene. The TDI method was very similar to that in the IPCS review (CPA Exhibit 4, discussed above). As with the IPCS review, ARB staff considers the Canadian review to have many shortcomings and did not consider more recently available data. Again, there was no actual carcinogenicity data used, instead a non-cancer chronic effect level ("no-observed-effect-level" or NOEL) was used. This level was divided by an "uncertainty factor" of 500 (x 10 for inter-species variation; x 10 for intra-species variation; and x 5 for evidence of carcinogenicity, considered not observed in the review). In the review, comparison with the estimated total daily intake of PDCB for various age groups in the Canadian population showed levels well below the TDI.

While the Canadian review attempted to account for indoor exposure, indoor levels were estimated by multiplying Canadian outdoor data with a scale-up factor. Other data show that the Canadian-derived scale-up factor was low and considerably underestimated indoor air exposure levels. The Canadian evaluation estimated Canadian indoor concentrations to be in the range 0.4 to 5.3 $\mu g/m^3$, after using a scale-up factor of 1.8 derived from a 1988 U.S. study. A study in 1991 in the U.S. showed measured 24-hour average concentrations of 22 $\mu g/m^3$ indoors, while outdoor air averaged 0.6 $\mu g/m^3$ (Wallace, 1991), as was discussed in the ISOR. The low Canadian exposure estimate, as well as the use of a NOEL non-cancer chronic effect level of 450 mg/m^3 (equivalent to 450,000 $\mu g/m^3$) applied before dividing by the "uncertainty factor" of 500, suggested to Canadian reviewers that *para*-dichlorobenzene "is not entering the environment in quantities or under conditions that may constitute a danger in Canada to human life or health."

The Canadian result differs substantially from the ATCM risk assessment, which uses better, more recent data, and more refined analyses, as presented in the ISOR, and which calculated an increased excess cancer risk of 242 in a million,

based on an indoor *para*-dichlorobenzene level of 22 µg/m^3, 24-hour average. The ATCM evaluation used calculation methods based on cancer potency data, as recommended by OEHHA with review by the Scientific Review Panel on TACs. The ATCM evaluation included health risk calculations for people in the vicinity of wastewater treatment plants, and for people indoors exposed to considerably higher air concentrations of *para*-dichlorobenzene compared with the Canadian evaluation. The ATCM risk assessment also used up-to-date computer modeling methods, in accordance with US EPA modeling algorithms and guidelines, to relate air emissions to air exposure concentrations (OEHHA, 2000; 2002; 2003). It should be noted that the Environment Canada/Health Canada assessment states that a compound demonstrating adequate evidence of carcinogenicity in two species would be classified in Group II (probably carcinogenic to humans). However, the decision to classify *para*-dichlorobenzene as a Group III carcinogen (possibly carcinogenic to humans), which led to the use of a threshold-based risk assessment, did not account for the NTP (1987) male rat mononuclear cell leukemia data. Lack of positive genotoxicity data was used as supporting evidence for the decision to assign *para*-dichlorobenzene to Group III, but the assessment was completed prior to the availability of the positive genotoxicity data described above.

> CPA Exhibit 7: *para*-dichlorobenzene - Priority Existing Chemical Assessment Report No. 13. National Industrial Chemicals Notification and Assessment Scheme, Australia. December 2000.

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) used criteria that excluded the NTP (1987) mouse liver tumor data, which OEHHA considers relevant to humans. Therefore, NICNAS concluded that *para*-dichlorobenzene did not pose a carcinogenicity risk to humans.

The NICNAS criteria for classifying a substance as a carcinogen excludes test data from concern for humans, if any one of the following conditions is met:

1. the tumor formation mechanism is clearly identified with good evidence that the data can not be extrapolated to humans;

2. the only available tumor data are liver tumors in certain sensitive strains of mice; or

3. the only available tumor data are from animal strains and their organs that tend to have a high incidence of spontaneous tumors.

NICNAS concluded that there are substantial differences in liver metabolism between mice and humans, the only available carcinogenicity data showed liver tumors in mice, and the mice were sensitive strains that tend to spontaneously develop tumors.

In contrast, carcinogenic risk assessment, as routinely practiced in California, is that once a substance has been found to be carcinogenic in either animals or humans, the substance is considered a carcinogen unless it can be demonstrated that the data are not relevant to humans. For example, the argument that the strain of mouse tested is susceptible to cancer formation does not show that the mouse liver data are not relevant to humans. As discussed above, it should be noted that NTP still uses the $B6C3F_1$ mouse strain for chemical carcinogenesis testing, and both NTP and IARC consider $B6C3F_1$ mouse liver tumor data to be relevant to human cancer risk determinations. This approach is more health-protective than that of NICNAS.

Additionally, NICNAS did not explicitly consider: 1) a significant increase in male rat mononuclear cell leukemia incidence at the high dose of PDCB; 2) a significant positive trend in the incidence of female mouse thyroid follicular cell adenomas; and 3) a significant positive dose-response in the incidence of male mouse adrenal gland pheochromocytomas, with the incidence in the high-dose mice being significantly greater than that of controls. These NTP data show that PDCB caused tumors in a number of sites in the experimental animals.

It should also be noted that one element in the decision of NICNAS to discount the NTP mouse liver tumor data was the claimed lack of positive genotoxicity data for *para*-dichlorobenzene. However, NICNAS did not include a report by Robbiano *et al*. (1999) which described induction of both DNA fragmentation and micronuclei in rat and human kidney cells, and generally discounted a number of positive genotoxicity assays described above.

> CPA Exhibit 8: Alpha$_{2U}$-Globulin: Association with Chemically Induced Renal Toxicity and Neoplastia in the Male Rat. EPA/625/3-91/019F. US EPA. September 1991.

The US EPA review did not discuss nor address the outstanding issue of the mouse liver carcinogenicity data, which OEHHA considers relevant to humans.

> CPA Exhibit 9 (document excerpts): Integrated Critieria Document Chlorobenzenes Effects. Appendix to Report no. 710401015. National Institute of Public Health and Environmental Protection. Bilthoven, The Netherlands. October 1991.

Exhibit 9, which consists of excerpts from an appendix to a report from The Netherlands, suggests a "maximal acceptable daily intake" of 0.2 mg/kg-body-weight, in the document's Section 5.1 for "RISK ASSESSMENT FOR MAN." It is not clear whether this intake level is based on carcinogenicity or on chronic non-cancer effects (change in weight of liver and kidneys of experimental rats). This approach differs with the OEHHA approach, which assumes for carcinogens there is no safe exposure level. If the suggested intake level is based on experimental rat data, this would indicate that the 1987 NTP mouse liver data

and associated carcinogenicity were not incorporated into the suggested intake level for The Netherlands. ARB staff was not able to obtain a complete copy of the appendix or a copy of the main report.

Summary and Conclusion

The proposed ATCM for *para*-dichlorobenzene is a rulemaking for emission control purposes. The rulemaking and associated risk assessment are not intended to address the identification, designation, or listing of *para*-dichlorobenzene as a TAC. The purpose of the risk assessment is to quantify the current health risks and the risk benefits to be expected from the ATCM. *Para*-dichlorobenzene is already listed as a federal HAP, is a California TAC, is regulated in California's Drinking Water Program as a carcinogen, and is a California Proposition 65 substance known to cause cancer. The IARC of the World Health Organization has determined that there is "sufficient evidence" in animals for carcinogenicity, and *para*-dichlorobenzene is "possibly carcinogenic to humans (Group 2B)." The NTP lists *para*-dichlorobenzene as "reasonably anticipated" to be a human carcinogen.

California takes a health-protective approach. The ARB relies on the scientific expertise and recommendations of OEHHA, with peer review by the independent Scientific Review Panel on TACs, for evaluation of toxicity data, including carcinogenicity data. OEHHA has considered the mouse liver carcinogenicity data to be relevant to humans since 1989, and has extrapolated the mouse liver data to derive risk factors for humans (OEHHA, 2002, pp 243-246), which the ARB has used to calculate health risks. A health risk assessment using these factors is included in the ISOR released for public review on May 7, 2004. Organizations in the U.S. and in foreign countries may differ from ARB when evaluating the carcinogenicity of *para*-dichlorobenzene. Some organizations may assume that the mouse liver carcinogenicity data are not relevant to humans, choose to totally exclude the mouse liver data, or wait for additional carcinogenicity data before supporting a carcinogenic determination. CPA has not provided any convincing scientific information, either in its own comments or in the submitted review documents (Exhibits 1 through 9), to either invalidate the mouse liver carcinogenicity data, or to show the mouse liver data are not relevant to humans.

ARB uses the latest recommended risk assessment methodologies from OEHHA, with peer review by the Scientific Review Panel on TACs, and, for air exposure determinations, the latest computer modeling techniques in accordance with US EPA-approved algorithms and modeling guidelines. The ATCM risk assessment for *para*-dichlorobenzene included more recent data which were not available for review in several of the outdated documents submitted by CPA. Carcinogens are widely considered to have no safe level of exposure and hence no minimum safe threshold level. Any control measure less stringent than a total prohibition of PDCB would mean higher exposure risks. The ARB has not

received any oral testimony or written comments with any convincing scientific information to invalidate the fundamental basis of the ATCM risk assessment.

While OEHHA and ARB consider and value the efforts and opinions of other organizations in the U.S. and in foreign countries, ARB is responsible to conduct its own reviews and draw its own conclusions with expert help on health effects from OEHHA, whose work is also peer reviewed by the independent Scientific Review Panel on TACs.

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