



December 21, 2004

VIA EMAIL: ab1173@listserv.arb.ca.gov

Ms. Dorothy Shimer
Research Division
Air Resources Board
P.O. Box 2815
Sacramento, California 95812

Dear Ms. Shimer:

The American Chemistry Council Phthalate Esters Panel (Panel) submits these comments on the *Report to the California Legislature: Indoor Air Pollution in California* (draft for Peer Review, November 2004) (hereinafter, November draft report).¹ The Panel consists of the major domestic manufacturers and some users of phthalate esters.²

The Panel submitted comments in August of this year on the prior June draft of the report. A copy of those comments is attached. In response, the California Air Resources Board (CARB) appropriately has corrected the International Agency for Cancer Research (IARC) classification of di(2-ethylhexyl) phthalate (DEHP) in the November draft report. However, CARB has ignored several other of the Panel's comments, and has even added some additional misleading statements about phthalates to the November draft. These comments request that CARB revise the final report to more accurately and fairly convey information on phthalates. The Panel also recommends that CARB reconsider inclusion of phthalates in the final report at all, given the large gap between potential exposures from measured indoor air levels of phthalates and observed effects in animal studies.

1. The Final Report Should Fairly Present the Findings for DEHP that Tumors in Rodents Are Not Relevant for Humans

The Panel applauds CARB for correcting the report to show the current IARC classification for DEHP – Group 3 (not classifiable as to human carcinogenicity).

However, while the stated classification is correct, the report is then misleading in its summary of IARC's findings. The November draft report states (p. 94): "The International

¹ <http://www.arb.ca.gov/research/indoor/ab1173/report-11-04/report-11-04.htm>.

² The Panel members are BASF Corporation, Eastman Chemical Company, ExxonMobil Chemical Company, Ferro Corporation, and Teknor Apex Company.

Agency for Research on Cancer (IARC) has determined there is inadequate evidence for the carcinogenicity of di(2-ethylhexyl) phthalate (DEHP) in humans, yet sufficient evidence in experimental animals for carcinogenicity.” While technically accurate, this summary fails to present the heart of IARC’s conclusion – that “the mechanism by which di(2-ethylhexyl) phthalate increases the incidence of hepatocellular tumours in rats and mice is not relevant to humans” (IARC, 2000).

IARC had also found that there was inadequate data for humans and sufficient evidence in animals when it initially classified DEHP as Group 2B in 1982 (IARC 1982). The difference between 1982 and 2000 was the development of a large body of evidence that the mechanism by which DEHP causes the tumors seen in rodents is not relevant for humans.

As discussed in the Panel’s attached comments on the June draft (pp. 6-7), IARC shares a great deal of company in its conclusion. That the tumors seen in rodents are not relevant for human risk assessment of DEHP has been affirmed by a workshop sponsored by the International Life Sciences Institute (ILSI), by Health Canada, by Doull et al. and, most recently, by the California courts.

The report’s statement that IARC found inadequate evidence in humans and “yet” sufficient evidence in animals could be interpreted by readers to mean that DEHP may indeed pose a risk of cancer to humans because of the evidence in animals. But the gist of the IARC finding is that the evidence in animals is inapplicable to humans. Therefore, so as not to be misleading as to the state of the evidence and the import of the IARC findings, the report should be revised as follows:

The International Agency for Research on Cancer (IARC) has determined there is inadequate evidence for the carcinogenicity of di(2-ethylhexyl) phthalate (DEHP) in humans, and sufficient evidence in experimental animals for carcinogenicity, but that the mechanism by which DEHP increases the incidence of liver tumors in rats and mice is not relevant to humans. Other agencies have likewise found that the liver tumors seen in rodents exposed to DEHP are not relevant for human risk assessment.

2. The Final Report Should Not Indicate that Other Phthalates Are Carcinogenic

In its comments on the June draft report (pp. 7-8), the Panel explained that the evidence indicates that other phthalates, like DEHP, are not likely to pose a risk of cancer to humans and that CARB should remove references to “other phthalates” from statements about other carcinogenic pollutants. These comments were ignored, and the current draft report continues to indicate that other phthalates are carcinogenic, as follows:

Page 39: “. . . the 1994 CCRP estimates did not include all known indoor carcinogenic pollutants (methylene chloride, other polycyclic aromatic hydrocarbons, and other phthalates were not included, for example)”

Page 99: The estimates of excess cancers from indoor exposures are conservative, “because they do not include . . . [t]he risk from many other carcinogens also found in indoor air and house dust, such as . . . phthalates other than DEHP.”

Page II-3: “**There are a number of additional carcinogens known to be emitted from indoor sources that were not included in the indicator** chemicals list for the Comp Risk Project due to a lack of sufficient indoor data to estimate an exposure level. For example, other PAHs and phthalates are carcinogenic and have been measured indoors and as emissions from products.” (bolding in original)

There simply is not a basis for stating or implying that other phthalates are known to be carcinogens. As explained in the Panel’s previous comments:

- No phthalate other than DEHP has ever been classified as a known or probable human carcinogen. (And, as discussed above, such classification for DEHP has now been changed by IARC to “not classifiable as to human carcinogenicity.”)
- EPA classified BBP in 1987 as a possible human carcinogen based on effects seen in one sex of one species, but in 1999, IARC determined that BBP should be classified as Group 3, “not classifiable as to human carcinogenicity” (IARC, 1999).
- High doses of DINP have produced tumors in rats and mice, but a panel of experts convened by the Consumer Product Safety Commission (CPSC) concluded that human doses of DINP are not plausibly associated with a significant increase in cancer risk (CHAP, 2001), and the CPSC staff have concluded that “DINP is not likely to present a cancer risk to humans” (CPSC, 2003).
- A two-year dermal toxicity study of diethyl phthalate (DEP) by the National Toxicology Program found no evidence of carcinogenic activity in rats and only equivocal evidence of carcinogenic activity in mice (NTP, 1995).

The Panel is unaware of any evidence of carcinogenicity in any other phthalates. It therefore is wholly inappropriate to indicate that phthalates other than DEHP are carcinogenic and would contribute to a cancer risk estimate. CARB should remove the references to phthalates in the three statements quoted above and should not otherwise include any indication in the final report that other phthalates are carcinogenic.

In light of the IARC reclassification of DEHP, it also would be appropriate to point out that the cancer risk estimates were made on the assumption that the liver tumors in

rodents treated with DEHP are applicable to humans, but that IARC has now determined those tumors are not relevant to humans.

3. The Final Report Should Fairly Reflect the Data Concerning Phthalates and Endocrine Disruption

On page 94, the November draft report states: “Phthalates are another group of chemicals with many isomers that have been implicated as endocrine disruptors.” The Panel believes this is a gross misrepresentation of what the data support and that this sentence should be removed from the final report.

The November draft report (p. 24) defines “endocrine disruptor” as follows:

Endocrine disruptors are substances that alter the normal function(s) of the endocrine systems of animals and humans and adversely affect growth, development or reproduction. They can act like a natural hormone, bind to a receptor and prevent a normal response, or interfere with the way natural hormones and receptors are synthesized or controlled. Public attention has been drawn to endocrine disruptors that mimic or block the natural effects of female sex hormones (estrogens), but they can also affect male sex hormones, development and behavior.

As explained in the Panel’s comments on the June draft report (p. 4): The weight of the evidence demonstrates that phthalates neither mimic nor interfere with estrogen and androgen; some, *but not all*, phthalates have been shown to cause lowered testosterone levels when administered to rodents at very high doses;³ the mechanism for the lowered testosterone levels is unknown, but does not involve phthalates acting as either androgen mimics or as anti-androgens; and male reproductive tract developmental effects seen after administration of phthalates to rodents occur at high levels – far in excess of likely human exposures.

Therefore, the Panel believes it is highly misleading to state that phthalates have been implicated as endocrine disruptors. At the most, the data show that some (but not all) phthalates affect testosterone levels, with associated effects on male reproductive tract development, when administered in high doses to rodents. The final report should be corrected accordingly.

³ The title of a key paper is “Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP or DOTP, alters sexual differentiation of the male rat.” (Gray et al., 2000).

4. Measured Levels of Phthalates in Indoor Air Are Far Before Animal Effect Levels

In CARB's response to comments document (p. 9),⁴ the Panel's comments on the June draft are summarized as follows:

Comment: Phthalates in indoor air do not pose a substantial health risk or cancer risk and should be removed from the report. Di-2-ethylhexylphthalate is currently not classified as to its carcinogenicity.

The response given is as follows:

Response: Table 2.4 was revised to reflect the current IARC status and status as a TAC. However, there was not ample time for a full toxicological review of the many phthalate isomers in indoor air. Phthalates remain in the report in Sections 2.1.2 and 2.3.11. A complete evaluation of their prevalence in indoor air and any health impacts would be undertaken prior to any recommendations regarding these chemicals.

This cursory summary of the Panel's comment and response ignores the data provided by the Panel showing that potential human exposures to phthalates from indoor air are orders of magnitude below effect levels in animal studies. (See pages 1-3 and 7 of the Panel's August comments.)

The Panel agrees that, if phthalates remain in the report, a complete evaluation should be undertaken prior to any recommendations being made. However, the Panel believes that even a brief review of the data demonstrates that phthalates should be a low priority with respect to evaluation of potential health effects from indoor air. Comparison of measured indoor air levels of phthalates to effect levels identified for phthalates in sources such as EPA's IRIS database,⁵ the reviews of the National Toxicological Program Center for the Evaluation of Risks to Human Reproduction,⁶ and the Agency for Toxic Substances and Disease Registry toxicological profiles⁷ quickly shows that exposures from indoor air levels of phthalates are highly unlikely to cause health effects in humans.

The Panel therefore believes that CARB should reconsider inclusion of phthalates in the final report, as there is no reason to believe the expenditure of resources to do detailed

⁴ Summary of Public Comments and ARB Responses on the June 2004 Draft Report for AB1173 – Indoor Air Pollution in California,
<http://www.arb.ca.gov/research/indoor/ab1173/comments0604/responses06-04.pdf>.

⁵ <http://www.epa.gov/iris>

⁶ <http://cerhr.niehs.nih.gov/news/phthalates/index.html>

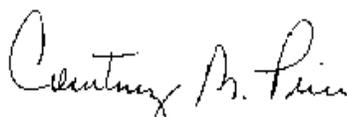
⁷ <http://www.atsdr.cdc.gov/toxpro2.html>

evaluations on these chemicals would indicate an indoor air concern. However, if phthalates continue to be included in the report, the statements about phthalates should be corrected as discussed above.

* * * * *

If you have any questions, please call Marian K. Stanley, Senior Director and Manager of the Phthalate Esters Panel, at (703) 741-5623, or email her at marian_stanley@americanchemistry.com.

Sincerely yours,



Courtney M. Price
Vice-President, CHEMSTAR

References

CPSC (2003). Response to Additional Questions from Commissioner Moore on Petition HP99-1 to Ban Polyvinyl Chloride in Toys and Other Products, Feb. 13, 2003, U.S. Consumer Product Safety Commission, Bethesda, MD, <http://www.cpsc.gov/library/foia/foia03/brief/response.pdf>

Gray, L.; Ostby, J.; Furr, J.; Price, M.; Verramachaneni, D.; Parks, L. (2000). Toxicol. Sci. 58:350-365.

IARC (2000). Di(2-ethylhexyl) phthalate. IARC monographs on the evaluation of carcinogenic risks to humans. Some Industrial Chemicals. Vol. 77, p. 41. International Agency for Research on Cancer, Lyon, France (summary available at <http://www-cie.iarc.fr/htdocs/monographs/vol77/77-01.html>).

IARC (1999). Butyl benzyl phthalate. IARC monographs on the evaluation of carcinogenic risks to humans. Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances. 73:115. International Agency for Research on Cancer, Lyon, France.

IARC (1982). Di(2-ethylhexyl) phthalate. IARC monographs on the evaluation of carcinogenic risks to humans. Some Industrial Chemicals and Dyestuffs. Vol. 29, p. 269. International Agency for Research on Cancer, Lyon, France (summary available at [http://www-cie.iarc.fr/htdocs/monographs/vol29/di\(2-ethylhexyl\)phthalate.html](http://www-cie.iarc.fr/htdocs/monographs/vol29/di(2-ethylhexyl)phthalate.html)).

Ms. Dorothy Shimer

December 21, 2004

Page 7

NTP (1995). Toxicology and Carcinogenesis Studies of Diethylphthalate (CAS No. 84-66-2) in F344/N Rats and B6C3F₁ Mice (Dermal Studies) with Dermal Initiation/ Promotion Study of Diethylphthalate and Dimethylphthalate (CAS No. 131-11-3) in Male Swiss (CD-1®) Mice. TR 429, National Toxicology Program, Research Triangle Park, NC.

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR



August 25, 2004

VIA EMAIL: ab1173@listserv.arb.ca.gov

Ms. Dorothy Shimer
Research Division, 5th floor
California Air Resources Board
P.O. Box 2815
1001 I Street
Sacramento, CA 95812

Dear Ms. Shimmer:

The American Chemistry Council Phthalate Esters Panel (Panel) submits these comments on the draft *Report on Indoor Air Pollution in California* (AB 1173, Keeley). The Panel consists of the major domestic manufacturers and some users of phthalate esters. These comments pertain to statements about phthalates in the draft Indoor Air Quality Report (draft IAQ Report).

The draft IAQ Report includes phthalates among substances it states pose substantial health risks in indoor air. However, the data strongly indicate that phthalates in indoor air do *not* pose substantial health risks. The Panel urges the California Air Resources Board (CARB) to remove phthalates from the Indoor Air Quality Report altogether, lest resources be diverted to control substances that evidence indicates pose no substantial health risk. If CARB continues to include phthalates in the IAQ Report, it should revise its statements about phthalates in accordance with these comments, and should provide readers with perspective on the very low risk posed by phthalates in indoor air.

If you have any questions, please call Marian K. Stanley, Senior Director and Manager of the Phthalate Esters Panel, at (703) 741-5623, or email her at marian_stanley@americanchemistry.com.

Sincerely yours,

A handwritten signature in black ink that reads "Courtney M. Price". The signature is written in a cursive style.



**Before the
California Air Resources Board**

**COMMENTS OF THE
PHTHALATE ESTERS PANEL OF THE AMERICAN CHEMISTRY COUNCIL
ON A DRAFT REPORT ON INDOOR AIR POLLUTION
MANDATED BY AB 1173 (KEELEY, 2002)**

AB 1173 Indoor Air Quality Report)
<http://www.arb.ca.gov/research/indoor/ab1173/ab1173.htm>)

Courtney M. Price
Vice President
CHEMSTAR

Dell E. Perelman, Esq.
Vice President and
General Counsel

Marian K. Stanley
Manager, Phthalate Esters Panel

Karyn M. Schmidt, Esq.
Theodore R. Waugh, Esq.
Counsel, CHEMSTAR

Of Counsel:
William K. Rawson, Esq.
Ann Claassen, Esq.
Latham & Watkins
555 Eleventh Street N.W.
Suite 1000
Washington, D.C. 20004

August 25, 2004

AMERICAN CHEMISTRY COUNCIL
1300 Wilson Blvd.
Arlington, VA 22209
(703) 741-5000

EXECUTIVE SUMMARY

The American Chemistry Council Phthalate Esters Panel (Panel) submits these comments on the draft *Report on Indoor Air Pollution in California* (AB 1173, Keeley). The Panel consists of the major domestic manufacturers and some users of phthalate esters. These comments pertain to statements about phthalates in the draft Indoor Air Quality Report (draft IAQ Report).

The draft IAQ Report includes phthalates among substances it states pose substantial health risks in indoor air. However, the data strongly indicate that phthalates in indoor air do *not* pose substantial health risks. These comments make the following points:

- Although phthalates are frequently detected in indoor by the highly-sensitive techniques of modern chemistry, their concentrations are extremely low (they are reported in nanograms per cubic meter). The exposures that could potentially result from these very low concentrations air are well below benchmarks that have been established for the protection of human health.
- The weight of evidence shows that phthalates do not mimic or block estrogen or androgen hormones. Some (but not all) phthalates cause decreased levels of testosterone when given to rodents in very high doses, but human exposures from reported indoor air concentrations would be far below such levels. Some phthalates influence male reproductive development in rodents, but do not do so in primates even at very high doses, indicating the rodent studies may not be relevant to humans. And, for these effects also, human exposures from reported indoor air concentrations would be far below the effect levels in rodents.
- There is not reliable evidence that phthalates cause or worsen asthma. Studies that report an association between phthalates and asthma have not controlled for potential confounders; most importantly, they cannot distinguish between phthalates causing or worsening asthma, versus persons with asthma selecting phthalate-containing products (e.g., vinyl flooring) to reduce dust concentrations in their homes. In studies in mice, phthalates did not stimulate the production of cellular products in the mice that are associated with the types of allergic reactions in the lung that typically lead to an asthma attack.
- Contrary to the statement in the draft IAQ report, di(2-ethylhexyl) phthalate (DEHP) is currently classified by the International Agency for Research on Cancer (IARC) as Group 3, “not classifiable as to human carcinogenicity,” on the basis that the mechanism by which DEHP increases the incidence of tumors in rodents is not relevant to humans. Other recent reviews and the California courts have likewise found that DEHP does not pose a risk of cancer to humans. However, even assuming that DEHP could be a human carcinogen, exposures from reported indoor air concentrations would be well below California’s No Significant Risk Level for DEHP.

- The scientific evidence does not support the draft IAQ Report statements that other phthalates are known indoor air carcinogens. To the contrary, the evidence suggests that, like DEHP, other phthalates are not likely to pose a risk of cancer to humans. The statements indicating other phthalates are known carcinogens should therefore be removed from the report.

For these reasons, the Panel urges the California Air Resources Board (CARB) to remove phthalates from the Indoor Air Quality Report altogether, lest resources be diverted to control substances that evidence indicates pose no substantial health risk. If CARB continues to include phthalates in the IAQ Report, it should revise its statements about phthalates in accordance with these comments, and should provide readers with perspective on the very low health risk posed by phthalates in indoor air.

TABLE OF CONTENTS

	<u>Page</u>
EXECUTIVE SUMMARY	i
INTRODUCTION	1
I. The Evidence Strongly Indicates that Phthalates in Indoor Air Do Not Pose Substantial Health Risks.....	1
A. Reported Indoor Air Concentrations of Phthalates Are Extremely Low – Well Below Health Benchmarks	1
B. The Weight of Evidence Is that Phthalates Do Not Mimic or Block Hormones.....	4
C. There Is Not Reliable Evidence that Phthalates Worsen Asthma.....	4
II. The Weight of Evidence Is that Phthalates in Indoor Air Do Not Pose a Cancer Risk.....	5
A. IARC No Longer Classifies DEHP as a Possible Human Carcinogen	6
B. There is a Strong Consensus Among Reviewing Scientists that DEHP Does Not Pose a Risk of Cancer to Humans	6
C. Exposures to Indoor Air Concentrations of DEHP Are Far Below the California No Significant Risk Level.....	7
D. Other Phthalates Are Not “Known Indoor Air Carcinogenic Pollutants”	7
CONCLUSION.....	8

INTRODUCTION

The American Chemistry Council Phthalate Esters Panel (Panel) submits these comments on the draft *Report on Indoor Air Pollution in California* (AB 1173, Keeley). The Panel consists of the major domestic manufacturers and some users of phthalate esters.¹ These comments pertain to statements about phthalates in the draft Indoor Air Quality Report (draft IAQ Report).

The draft IAQ Report includes phthalates among substances it states pose substantial health risks in indoor air. However, the data strongly indicate that phthalates in indoor air do *not* pose substantial health risks. Exposures from reported indoor air concentrations of phthalates are well below health benchmarks established to be protective of human health. The Panel therefore believes it would be appropriate for the California Air Resources Board (CARB) to remove all discussion of phthalates from the IAQ Report. Their inclusion in the Report may cause unwarranted concern and may lead to resources being misdirected toward control of substances that evidence indicates do not pose substantial health concerns.

If CARB nevertheless continues to include phthalates in the IAQ Report, then it should provide readers perspective on the very low risks posed by these substances in indoor air, as discussed below. It also should correct inaccurate statements about phthalates in accordance with these comments.

I. THE EVIDENCE STRONGLY INDICATES THAT PHTHALATES IN INDOOR AIR DO NOT POSE SUBSTANTIAL HEALTH RISKS

The draft IAQ Report states: “Available scientific information indicates that indoor air pollution poses substantial health risks in many indoor environments” (p. 1). It then includes phthalates in a table on “Sources and Potential Health Effects of Major Indoor Air Pollutants” (Table ES-1, p. 3 and Table 2.1, p. 28).² The implication is that phthalates are major indoor air pollutants that pose substantial health risks. However, the scientific evidence clearly establishes that this is not the case.

A. Reported Indoor Air Concentrations of Phthalates Are Extremely Low – Well Below Health Benchmarks

Phthalates are detected in indoor air samples, but at extremely low levels – generally well less than 1 microgram per cubic meter (ug/m³). Clark et al. (2003) have summarized indoor air concentrations for phthalates from a comprehensive review of the

¹ The Panel members are BASF Corporation, Eastman Chemical Company, ExxonMobil Chemical Company, Ferro Corporation, and Teknor Apex Company.

² Phthalates are included in the category of organic chemicals, for which potential health effects are listed as “Cancer; eye, nose, throat irritation; possible worsening of asthma; headaches; at high levels; loss of coordination; damage to liver, kidney and brain.” They are also included in the category of endocrine disruptors, with potential health effects listed as “Mimic or block natural effects of hormones (estrogen and others); developmental abnormalities.”

literature. Their data is provided in Table 1, along with health benchmarks for comparison. Table 1 demonstrates that the levels of phthalates detected in indoor air are far below levels established for the protection of health.

Table 1. Indoor Air Concentrations of Phthalate Esters

Phthalate and Region ^a	Indoor Air Concentrations in nanograms per cubic meter (ng/m ³) ^b				Chronic REL ^c ng/m ³	Exposure as ug/kg/day ^d	EPA RfD ug/kg/day ^e
	Median	Mean	Min	Max			
Dimethyl							
Europe	10	20.2	<1	129	--	0.037	--
Diethyl							
USA	340	NA	NA	NA	--	0.097	800
Europe	171	621	25	3234		0.92	
Dibutyl							
USA	NA	0.2	0.2	420	--	0.12	100
Canada	NA	2.9	NA	NA		0.00083	
Europe	551	1032	<3	9445		2.7	
Butylbenzyl							
USA	35	NA	NA	140	--	0.040	200
Europe	13	35	<3	465		0.13	
Di(2-ethylhexyl)							
USA	55	109	20	240	70,000	0.069	20
Canada	NA	NA	<500	3100		0.89	
Europe	111	245	18	1046		0.30	

NA = not available

- If a region is not included for a given phthalate, there were no data available for that region.
- From Clark, C., Cousins, I., Mackay, D., and Yamada, K. (2003). Observed concentrations in the environment. In: Phthalate Esters, The Handbook of Environmental Chemistry. 3Q. C. Staples, ed., Springer, New York, pp. 125-177.
- The noncancer chronic reference exposure level established by the California Air Resources Board and the California Office of Environmental Health Hazard Assessment.
- The exposure of a 70 kg person who breathes 20 cubic meters of air a day, containing phthalate at the maximum reported concentration, and assuming that all measured phthalate is bioavailable and absorbed by the blood stream. Based on the maximum value reported by Clark et al. (2003).
- The reference dose established by the U.S. Environmental Protection Agency, from the Integrated Risk Information System (IRIS) database Agency (www.epa.gov/ngispgm3/iris).

For di(2-ethylhexyl) phthalate (DEHP), CARB and the Office of Environmental Health Hazard Assessment (OEHHA) have established a chronic reference exposure level (REL) of 70 micrograms per cubic meter (ug/m³), or 70,000 nanograms per cubic meter (ng/m³).³ The

³ The REL is for noncancer endpoints. Cancer is discussed in Part II, below.

highest indoor level reported for DEHP is over 20-fold below that and the mean value for the United States is over 600 times lower.⁴

CARB and OEHHA have not established RELs for other phthalates. However, the U.S. Environmental Protection Agency (EPA) has developed oral reference doses (RfDs) for several phthalates. “The RfD is a numerical estimate of a daily oral exposure to the human population, including sensitive subgroups such as children, that is not likely to cause harmful effects during a lifetime.”⁵ If one conservatively assumes that all phthalate measured in the air is bioavailable and is absorbed into the bloodstream, then the air concentration can be converted to an equivalent oral concentration and compared to the RfD. This is a conservative approach, because absorption of inhaled chemicals is usually less than 100%, because some of the phthalate may be bound in a PVC matrix and not bioavailable, and because phthalates appear to be less toxic by parenteral routes (such as inhalation) than by the oral route (FDA, 2001). Nevertheless, as shown in Table 1, exposure even from the maximum reported air concentrations of phthalates would be well below EPA’s RfDs.

The RfDs are themselves set at values well below doses required to cause effects in rodents. The RfDs for phthalates are three or more orders of magnitude below even the most sensitive, reliable LOAELs (lowest observed adverse effect levels) reported for rodent studies. Yet primate studies indicate that humans are likely far less sensitive to phthalates than are rodents. For example, slight histopathological testicular effects have been reported in rodents dosed with 38 mg DEHP/kg/day for 90 days (Poon et al.), but no such effects were seen in a study of monkeys receiving up to 2500 mg DEHP/kg/day for about 455 days (Tominari et al., 2003). Thus, it is likely humans can be exposed to levels well in excess of the RfDs without experiencing adverse health effects. Since these reported indoor air levels of phthalates represent exposures far below the RfDs, they should not pose a substantial health risk.

The draft IAQ Report mentions that in a study by Rudel et al. (2003), “[t]he most abundant compounds in [indoor] air included bis(2-ethylhexyl) phthalates (DEHP) . . . [and other compounds]” (p. 78). CARB should not confuse frequency of detection with “abundance.” Nor do concentrations above some other measured chemicals necessarily indicate a risk. Phthalates are used in a wide variety of products, and, when looked for with modern, highly-sensitive analytical techniques, they are frequently detected. But, again, the levels detected are extremely low. The concentrations reported by Rudel et al. (2003) are similar to those summarized in Table 1, and represent exposures several orders of magnitude below levels that have caused health effects in animal studies. In this sense, the studies reflect that phthalates are not at all abundant in indoor air, but rather sparse. Certainly the science does not support making phthalates a focal point of concern for indoor air quality.

⁴ In 1999, OEHHA proposed a chronic REL of 10 ug/m³ (10,000 ng/m³) for DEHP. The Panel submitted comments explaining its belief that the science did not support that low an REL. Even if that were the REL, reported levels of DEHP are well below that level.

⁵ Definition of “Reference Dose (RfD)” at <http://www.epa.gov/glossary>.

B. The Weight of Evidence Is that Phthalates Do Not Mimic or Block Hormones

The draft IAQ Report includes phthalates in the category of endocrine disruptors, with potential health effects listed as “Mimic or block natural effects of hormones (estrogen and others); developmental abnormalities” (Table ES-1, p. 3 and Table 2.1, p. 28). However, the weight of the evidence is that phthalates do *not* mimic or block hormones.

The weight of evidence indicates that phthalates do not react with the estrogen receptor in live animals. Harris et al. (1997) reported that several phthalates weakly interacted with the estrogen receptor in screening tests under *in vitro* conditions, but that many – including di(2-ethylhexyl) phthalate (DEHP) – did not. Harris et al. also reported that monoesters, the phthalate metabolites that are present *in vivo*, were estrogenically inactive. A subsequent *in vivo* study by Zacharewski et al. (1998) showed that phthalates were not estrogenically active when tested in rats. More recent studies in rodents provide additional evidence that phthalates do not affect processes under estrogenic control (Gray et al., 1999; Moore et al., 2001). The current view is that, although some phthalates may interact with estrogen receptors under *in vitro* conditions, they are not estrogenic *in vivo*, at least in part because they are metabolized to inactive forms before absorption (Foster et al. 2000; Moore, 2000; Parks et al., 2000).

With respect to testosterone-mediated effects, some phthalates (*but not all*) have produced effects on male reproductive development in rats (Gray et al., 1999; 2000; Mylchreest et al., 1998; 1999; 2000). Researchers have determined that this process does not involve androgen receptor-mediated interactions – that is, phthalates neither mimic nor block androgen – although there is evidence of an effect on testosterone synthesis, due to some other as yet unknown mechanism (Gray et al., 1999; 2000; Parks et al., 2000). The effects on testosterone levels are observed at very high doses – doses far above exposures that would occur from reported indoor air concentrations of phthalates.

As just indicated, phthalates do cause developmental abnormalities, *in rodents* and at high doses. The studies in primates discussed in Section I.A. indicate that the effects in rodents may not be relevant to humans. Even assuming human relevance, however, the levels of potential exposure from reported indoor air concentrations are far below levels that produce developmental effects in rodents, as discussed in Section I.A., above.

C. There Is Not Reliable Evidence that Phthalates Cause or Worsen Asthma

Among the potential health effects listed for organic chemicals, in which category the draft IAQ Report includes phthalates, is “possible worsening of asthma” (Table ES-1, p. 3 and Table 2.1, p. 28). There have been some studies which have reported an association between phthalates and asthma prevalence; however, those studies are subject to a number of flaws and in no manner can be considered reliable evidence that phthalates cause or promote asthma.

Most importantly, an association is not proof of causation. In the case of asthma, patients are commonly advised to remove sources of dust from their homes, such as carpets. Thus, such homes are more likely to have phthalate-plasticized vinyl flooring. The studies published to date cannot distinguish whether the association of phthalates and asthma is because

the phthalates contributed to asthma, or because the occurrence of asthma led to greater use of phthalate-containing products.

The draft IAQ Report discusses a report by the National Academy Institute of Medicine (IOM, 2000), which “examined the scientific literature relating indoor air pollutants and other factors to asthma” (p. 29). The draft IAQ Report lists “plasticizers” as substances identified by the IOM as possibly associated with exacerbation or development of asthma (Tables 2.2 and 2.3, pp. 29-30). What the IOM report actually concluded about plasticizers (such as phthalates) was: “While the reports described above have attracted some interest in the research and building trades communities, there is inadequate or insufficient evidence to determine whether or not an association exists between nonoccupational exposure to plasticizers and the development or exacerbation of asthma.” (IOM, 2000).

Subsequent to that report, studies have been undertaken to investigate the potential for phthalates to cause respiratory sensitization. Butala et al. (2004) tested four common PVC phthalate plasticizers – di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), di-isoheptyl phthalate (DIHP) and butyl benzyl phthalate (BBP) – in a mouse model. The phthalate applications did not stimulate the production of cellular products in the mice (IgE, IL-4, and IL-13) that are associated with the types of allergic reactions in the lung that typically lead to an asthma attack. These results indicate that DEHP, DINP, DIHP, and BBP are not likely to produce asthma.

Questions have also been raised as to whether some phthalates could act as adjuvants, i.e., whether they might exacerbate the effects of other allergens (Larsen et al., 2001a; 2001b; 2002; 2003). These novel studies exhibited some variability, and did not show clear dose-response relationships. Larsen et al. (2002) concluded that some phthalates were adjuvants based on elevated levels of IgG1 and IgE. The authors considered that IgG1 and IgE were good markers for Type 1 allergy in human, and that they were co-regulated in mice via the Th2/IL-4 pathway. However, as summarized above, Butala et al. (2004) found phthalates to have no effect on IgE or IL-4 levels. To investigate this further, a research program has been undertaken with two aims: to determine if the results of Larsen and associates could be replicated in an independent laboratory, and to define the underlying mechanism(s). Participants in the program include the developers of the murine respiratory sensitizer model used by Butala et al. and the initial investigators of the Larsen et al. studies. Initial work from this program has not repeated the original findings of Larsen et al. Work continues to explore many possible variables to explain this difference. At the present time, however, the weight of evidence is insufficient to support a link between phthalates and asthma.

II. THE WEIGHT OF EVIDENCE IS THAT PHTHALATES IN INDOOR AIR DO NOT POSE A CANCER RISK

To quantify potential health risks from indoor air pollutants, the draft IAQ Report relies primarily on risk estimates from the 1994 California Comparative Risks Project. DEHP was one of the chemicals included in that project. The draft IAQ inaccurately indicates that DEHP is classified by the International Agency for Research on Cancer (IARC) as a possible human carcinogen, when IARC in fact classifies DEHP as “not classifiable as to human carcinogenicity” because IARC found the tumors seen in rodents treated with DEHP to not be

relevant to humans. Other recent reviews and the California courts have likewise found that DEHP does not pose a risk of cancer to humans. However, even assuming that DEHP could be a human carcinogen, potential exposures from reported indoor air concentrations are well below California's No Significant Risk Level for DEHP. The scientific evidence does not support the draft IAQ Report statements that other phthalates are known indoor air carcinogens. Therefore, the Panel believes that CARB should eliminate phthalates from any discussion of carcinogenic risk of indoor air pollutants.

A. IARC No Longer Classifies DEHP as a "Possible Human Carcinogen"

On page 32, the draft IAQ Report includes DEHP in a table of "Common Carcinogenic Indoor Air Pollutants" (Table 2.4). The table shows the U.S. EPA classification of DEHP to be Group B2, probable human carcinogen, and then indicates in parenthesis "IARC classification 2B, possible human carcinogen." This is inaccurate.

In 2000, IARC reviewed the extensive data that had been generated on DEHP carcinogenicity since IARC had classified it in the early 1980's. IARC determined that DEHP should be reclassified to Group 3, "not classifiable as to human carcinogenicity," on the basis that "the mechanism by which di(2-ethylhexyl) phthalate increases the incidence of hepatocellular tumours in rats and mice is not relevant to humans" (IARC, 2000). CARB should correct the IAQ Report to correctly reflect the current IARC classification of DEHP.

B. There is a Strong Consensus Among Reviewing Scientists that DEHP Does Not Pose a Risk of Cancer to Humans

Other recent reviews agree with the conclusion of IARC.

- *ILSI Workshop*. The International Life Sciences Institute (ILSI) Risk Science Institute formed a workgroup in 2001 to review information on the mechanisms by which peroxisome proliferating chemicals produce carcinogenic responses in rats and mice. The report of the workgroup was published in late 2003 (Klaunig et al., 2003). For peroxisome proliferators in general, the workgroup concluded: "In summary, the weight of evidence overall currently suggests that the rodent [mode of action] for liver tumors is not likely to occur in humans, taking kinetic and dynamic factors into account" (Klaunig et al., 2003, p. 693).⁶ DEHP was included as a case study by the group, with the following outcome: "The data lead to a conclusion that a carcinogenic response induced via the [modes of action] for liver tumorigenesis in the rodent is not likely to occur in humans following exposure to DEHP" (Klaunig et al., 2003, p. 704).

⁶ On the basis of the ILSI workgroup conclusions, the U.S. Environmental Protection Agency (EPA) has proposed a science policy: "When liver tumors are observed in long term studies in rats and mice, and 1) the data are sufficient to establish that the liver tumors are a result of a PPAR α agonist MOA and 2) other potential MOAs have been evaluated and found not operative, the evidence of liver tumor formation in rodents should not be used to characterize potential human hazard" (EPA, 2003, p. 15).

- *Health Canada Assessment.* As part of an evaluation of the use of DEHP in vinyl medical devices, Health Canada reviewed the cancer data and accepted the conclusions of IARC (2000) that DEHP is not classifiable as to its carcinogenicity to humans (Health Canada, 2002).
- *Doull et al. Assessment.* In 1998, a panel of scientific experts, chaired by Dr. John Doull, reviewed the data for DEHP in light of EPA's draft cancer risk assessment guidelines. The panel concluded: "DEHP should be classified as unlikely to be a human carcinogen under any known conditions of human exposure" (Doull et al., 1999, p. 352).

Thus, the consensus of a large number of scientific experts is that DEHP is not reasonably anticipated to be a human carcinogen.

Further, the California courts have found this to be the case. In *Baxter Healthcare Corporation v. Denton*, No. 99CS00868, (Sacramento Co. Super. Ct. 2002), the Superior Court of Sacramento found that DEHP poses no significant risk of cancer to humans. The California Court of Appeal recently upheld this finding. *Baxter Healthcare Corporation v. Denton*, 120 Cal. App. 4th 333; 15 Cal. Rptr. 3d 430; 2004 Cal. App. LEXIS 1054; 2004 Daily Journal DAR 8099; 34 ELR 20042 (Cal. App. 3d Dist. 2004)).

In light of the strong scientific consensus of these reviewers and the findings by the California courts, the Panel believes it would be appropriate for the IAQ Report to remove any reference to DEHP as a possible or probable human carcinogen.

C. Exposures to Indoor Air Concentrations of DEHP Are Far Below the California No Significant Risk Level

Even assuming that DEHP could be a human carcinogen, potential exposures from reported indoor air concentrations would not pose a significant risk of cancer.

OEHHA has recently reviewed the carcinogenicity data for DEHP and revised the No Significant Risk Level (NSRL) to 310 ug/day.⁷ Table 1 shows a maximum reported indoor air concentration for DEHP of 3100 ng/m³, or 3.1 ug/m³. For a person breathing 20 m³ a day, the exposure would be 62 ug/day, well under California's NSRL. Therefore, under California standards, DEHP in indoor air cannot be considered to pose a significant cancer risk.

D. Other Phthalates Are Not "Known Indoor Air Carcinogenic Pollutants"

The draft IAQ Report notes that the 1994 California Comparative Risks Project estimates "did not include all known indoor carcinogenic pollutants (. . . other phthalates were not included, for example)" (p. 33, *see also* pp. 82 and II-3). There is not justification for indicating that other phthalates are known indoor carcinogenic pollutants. The Panel strongly

⁷ See Notice of Modifications to Text of Regulations Title 22, California Code of Regulations Sections 12705 and 12805 (08/24/02), at http://www.oehha.org/prop65/CRNR_notices/FSR12705_82302.html.

believes that the references to “other phthalates” should be removed from the statements about other carcinogenic pollutants in the final IAQ Report.

No phthalate other than DEHP has been classified as a known or probable human carcinogen. EPA classified BBP in 1987 as a possible human carcinogen based on effects seen in one sex of one species, but in 1999, IARC determined that BBP should be classified as Group 3, “not classifiable as to human carcinogenicity” (IARC, 1999). High doses of DINP have produced tumors in rats and mice, but a panel of experts convened by the Consumer Product Safety Commission (CPSC) concluded that human doses of DINP are not plausibly associated with a significant increase in cancer risk (CHAP, 2001), and the CPSC staff have concluded that “DINP is not likely to present a cancer risk to humans” (CPSC, 2003). A two-year dermal toxicity study of diethyl phthalate by the National Toxicology Program found no evidence of carcinogenic activity in rats and only equivocal evidence of carcinogenic activity in mice (NTP, 1995).

Thus, there is not an adequate basis for stating that other phthalates are known to be carcinogenic indoor air pollutants. To the contrary, the evidence suggests that, like DEHP, other phthalates are not likely to pose a risk of cancer to humans.

CONCLUSION

For the reasons discussed herein, the science does not support an assertion that phthalates in indoor air pose a substantial risk to human health. To the contrary, reported concentrations of phthalates in indoor air would result in exposures far below health benchmarks designed to be protective of human health. The Panel therefore urges CARB to remove phthalates from the Indoor Air Quality Report altogether, lest resources be diverted to control substances that evidence indicates pose no substantial health risk. If CARB continues to include phthalates in the IAQ Report, it should revise its statements about phthalates in accordance with these comments, and should provide readers with perspective on the very low risk posed by phthalates in indoor air.

References:

- Butala, J., David, R., Gans, G., McKee, R., Guo, T., Peachee, V., and White, K. (2004). Phthalate treatment does not influence levels of IgE or TH2 cytokines in B6C3F1 mice. *Toxicology* 201:77-85.
- CHAP (2001). Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP), <http://www.cpsc.gov/LIBRARY/FOIA/Foia01/os/dinp.pdf>.
- Clark, C., Cousins, I., Mackay, D., and Yamada, K. (2003). Observed concentrations in the environment. In: *Phthalate Esters, The Handbook of Environmental Chemistry*. 3Q. C. Staples, ed., Springer, New York, pp. 125-177.
- CPSC (2003). Response to Additional Questions from Commissioner Moore on Petition HP99-1 to Ban Polyvinyl Chloride in Toys and Other Products, Feb. 13, 2003, U.S. Consumer Product Safety Commission, Bethesda, MD, <http://www.cpsc.gov/library/foia/foia03/brief/response.pdf>
- Doull J, Cattley R, Elcombe C, Lake B, Swenberg J, Wilkinson C, Williams G, van Gemert M (1999). A cancer risk assessment of di(2-ethylhexyl)phthalate: Application of the new U.S. EPA risk assessment guidelines. *Reg. Toxicol. Pharmacol.* 29:327-357.
- EPA (2003). Proposed science policy: PPAR- α agonist-mediated hepatocarcinogenesis in rodents and relevance to human health risk assessment. Office of Prevention, Pesticides & Toxic Substances, U.S. Environmental Protection Agency. <http://www.epa.gov/oscpmont/sap/2003/december9/peroxisomeproliferatorssciencepolicypaper.pdf>
- FDA (2001). Safety assessment of di(2-ethylhexyl)phthalate (DEHP) released from PVC medical devices. Center for Devices and Radiological Health, U.S. Food and Drug Administration, Rockville, MD. <http://www.fda.gov/cdrh/ost/dehp-pvc.pdf>.
- Foster, P.; Cattley, R.; Mylchreest, E. (2000). *Food Chem. Toxicol.* 38:S97-S99.
- Gray, L.; Wolf, C.; Lambright, C.; Mann, P.; Price, M.; Cooper, R.; Ostby (1999). *J. Toxicol. Indust. Health* 15:94-118.
- Gray, L.; Ostby, J.; Furr, J.; Price, M.; Verramachaneni, D.; Parks, L. (2000). *Toxicol. Sci.* 58:350-365.
- Harris, C.; Henttu, P.; Parker, M.; Sumpter, J. (1997). *Environ. Health Perspect.* 105:802-811.
- Health Canada (2002). DEHP in medical devices: an exposure and toxicity assessment. Medical Devices Bureau, Therapeutic Products Directorate, Health Products & Foods Branch, Health Canada. http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/advcomm_eapdehp.html

IARC (2000). Di(2-ethylhexyl) phthalate. IARC monographs on the evaluation of carcinogenic risks to humans. Some Industrial Chemicals. 77 ,15-22. International Agency for Research on Cancer, Lyon, France.

IARC (1999). Butyl benzyl phthalate. IARC monographs on the evaluation of carcinogenic risks to humans. Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances. 73:115. International Agency for Research on Cancer, Lyon, France.

IOM (2000). Clearing the Air: Asthma and Indoor Air Exposures. Institute of Medicine, Division of Health Promotion and Disease Prevention, Committee on the Assessment of Asthma and Indoor Air. National Academy Press, Washington, DC, 2000, page 251 (available at <http://books.nap.edu/books/0309064961/html>).

Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, DeLuca JG, Lai DY, McKee RH, Peters JM, Roberts RA, Fenner-Crisp PA (2003). PPARalpha agonist-induced rodent tumors: modes of action and human relevance. *Crit. Rev. Toxicol.* 33:655-780. <http://www.epa.gov/oscpmont/sap/2003/december9/crittox33665578003.pdf>

Larsen, S., Hansen, J., Thygesen, P., Begtrup, M., Poulsen, O., and Nielsen, G. (2001a). Adjuvant and immuno-suppressive effect of six monophthalates in a subcutaneous injection model with BALB/c mice. *Toxicology* 169: 37-51.

Larsen, S., Lund, R., Nielsen, G., Thygesen, P., and Poulsen, O. (2001b). Di-(2-ethylhexyl) phthalate possesses an adjuvant effect in a subcutaneous injection model with BALB/c mice. *Toxicology Letters* 125: 11-18.

Larsen, S., Lund, R., Nielsen, G., Thygesen, P., and Poulsen, O. (2002). Adjuvant effect of di-n-butyl-, di-n-octyl-, di-iso-nonyl- and di-iso-decyl phthalate in a subcutaneous injection model using BALB/c mice. *Pharmacology and Toxicology* 91: 264-272.

Larsen, S., Lund, R., Thygesen, Poulsen, O., and Nielsen, G. (2003). Investigation of the adjuvant and immuno-suppressive effects of benzyl butyl phthalate, phthalic acid and benzyl alcohol in a murine injection model. *Food and Chemical Toxicology* 41: 439-446.

Moore, N. (2000). *Reproduct. Toxicol.* 14:183-192.

Moore, R.; Rudy, T.; Lin, T.-M.; Ko, K.; Peterson, R. (2001). , *Environ. Health Perspect.* 109:229-237.

Mylchreest, E.; Cattley, R.; Foster, P. (1998). *Toxicol. Sci.* 43:47-60.

Mylchreest, E.; Sar, M.; Cattley, R.; Foster, P. (1999). *Toxicol. Appl. Pharmacol.* 156:81-95.

Mylchreest, E.; Wallace, D.; Cattley, R.; Foster, P. (2000). *Toxicol. Sci.* 55:143-151.

NTP (1995). Toxicology and Carcinogenesis Studies of Diethylphthalate (CAS No. 84-66-2) in F344/N Rats and B6C3F₁ Mice (Dermal Studies) with Dermal Initiation/ Promotion Study of Diethylphthalate and Dimethylphthalate (CAS No. 131-11-3) in Male Swiss (CD-1®) Mice. TR 429, National Toxicology Program, Research Triangle Park, NC.

Parks, L.; Ostby, J.; Lambright, C.; Abbott, C.; Klinefelter, G.; Barlow, N.; Gray, L. (2000). *Toxicol. Sci.* 58:339-349.

Poon, R.; Lecavalier, P.; Mueller, R.; Valli, V.E.; Procter, B.G.; and Chu, I. (1997). Subchronic oral toxicity of di-n-Octyl Phthalate and di(2-Ethylhexyl) Phthalate in the Rat. *Food Chem. Toxicol.* 35:225-239.

Rudel, R., Camann, D., Spengler, J., Korn, L., and Brody, F. (2003). Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. *Environ. Sci. Technol.* 37(20):4543-4553.

Tomonari, Y.; Kurata, Y.; Kawasuso, T.; David, R. M.; Gans, G.; Katoh, M. (2003). Testicular toxicity study of di(2-ethylhexyl) phthalate (DEHP) in juvenile common marmoset. *The Toxicologist* 72:385.

Zacharewski, T.; Clemons, J.; Meek, M.; Wu, Z.; Fielden, M.; Matthews, J. (1998). *Toxicol. Sci.* 42:282-293.