

FINAL STATEMENT OF REASONS
22 CALIFORNIA CODE OF REGULATIONS

SECTIONS 12705(b) and 12705(d). SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

SECTION 12805. SPECIFIC REGULATORY LEVELS: REPRODUCTIVE TOXICANTS

This is the Final Statement of Reasons for specific regulatory levels for 22 chemicals listed as known to the State to cause cancer or reproductive toxicity under the Safe Drinking Water and Toxic Enforcement Act of 1986 (hereinafter the Act or Proposition 65), popularly known as “Proposition 65.” On June 8, 2001, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt regulatory levels for 23 chemicals listed pursuant to the Act as known to the State to cause cancer or reproductive toxicity. The Notice set forth proposed regulatory levels for adoption in Title 22, California Code of Regulations, Section 12705 (22 CCR §12705) for 19 chemicals listed as known to the State to cause cancer in Title 22, California Code of Regulations, Section 12000. These chemicals are: chloroethane, di(2-ethylhexyl)phthalate (DEHP), lead, lead acetate, lead phosphate, lead subacetate, methylhydrazine, methylhydrazine sulfate, 5-morpholinomethyl-3[(5-nitrofurfurylidene)-amino]-2-oxazolidinone, MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone), phenylhydrazine, phenylhydrazine hydrochloride, polygeenan, carbazole, MeIQ (2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline), MeIQ_x (2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline), methyl carbamate, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone, and trimethyl phosphate. In addition, the Notice announced proposed regulatory levels for adoption in Title 22, California Code of Regulations, Section 12805 (22 CCR §12805) for four chemicals listed as known to the State to cause reproductive toxicity in Title 22, California Code of Regulations, Section 12000. These chemicals are: arsenic (inorganic oxides), benzene, cadmium, and quizalofop ethyl. (Unless otherwise indicated, all further section references are to Title 22, California Code of Regulations.) The Initial Statement of Reasons set forth the grounds for the proposed regulation.

Pursuant to the Notice of Proposed Rulemaking, a public comment period was held between June 8, 2001 and July 23, 2001, and a public hearing was held on July 23, 2001. Written comments were received regarding the proposed regulatory levels for eight chemicals: arsenic (inorganic oxides), benzene, cadmium, DEHP, lead, lead acetate, lead phosphate and lead subacetate. Oral comments were made at the public hearing regarding DEHP and benzene. The comments received were such that on February 11, 2002, OEHHA issued a 15-Day Notice of Modifications to the Proposed Regulations. The 15-Day Notice indicated that OEHHA was removing eight of the chemicals from the rulemaking package to review and resolve substantive comments regarding these chemicals. OEHHA has since resolved the substantive comments for all but one (arsenic [inorganic oxides]) of these eight chemicals. On March 29, 2002, OEHHA issued an additional 15-Day Notice of Modifications to the Proposed Regulations. This second 15 Day-Notice announced that OEHHA proposed to adopt safe harbor levels for seven of the

eight chemicals previously withdrawn, namely, benzene, cadmium, DEHP, lead, lead acetate, lead phosphate, and lead subacetate. The Notice provided the proposed safe harbor levels, which, for one chemical (DEHP) differed from that originally proposed on June 8, 2001.

The regulation here adopts regulatory levels for 22 of the 23 chemicals included in the Notice of Proposed Rulemaking. Comments for arsenic (inorganic oxides) were of a nature that precludes the adoption of a regulatory level for this chemical at this time. OEHHA intends to promulgate a regulatory level for arsenic (inorganic oxides) at a later date.

This Final Statement of Reasons provides the following: 1) an update of the information contained in the Initial Statement of Reasons released on June 8, 2001, 2) a determination whether the regulation imposes a mandate on local agencies or school districts, 3) a summary of each objection or recommendation made regarding the proposed rule, together with an explanation of how the proposed action has been changed to accommodate the objections or recommendations, or the reasons for making no change, 4) a determination that no alternative considered would be more effective in furthering the aims of the regulation or would be as effective and less burdensome to affected private persons than the adopted regulation, and 5) an explanation setting forth the reasons for rejecting any proposed alternative that would lessen the adverse economic impact on small businesses.

UPDATE OF INITIAL STATEMENT OF REASONS

UPDATE OF TECHNICAL INFORMATION IN THE INITIAL STATEMENT OF REASONS

All data, studies, reports, or other documents relied on for this regulation were identified in the Initial Statement of Reasons of June 8, 2001. Because regulations are not being adopted here for one of the 23 chemicals proposed on June 8 (i.e., arsenic [inorganic oxides]), the Initial Statement of Reasons contains information not relied on for this adoption.

The document supporting the NSRL for DEHP will be modified. Modifications to the text of the DEHP support document will not have any impact on the calculation of the NSRL. This document is referred to in the Initial Statement of Reasons as OEHHA (2001b). For completeness, a brief description of two additional reports following-up the epidemiological studies reported by Oliver *et al.* (1978) of clofibrate (an agent, which, like DEHP, is in a class of chemicals called “peroxisome proliferators”) will be added to the NSRL document along with their appropriate citations in the References section. These studies do not affect the interpretation of the epidemiological evidence nor do they influence the calculation of the NSRL.

Upon internal review of the NSRL document for DEHP cited in the Initial Statement of Reasons (OEHHA, 2001b), OEHHA discovered a calculation error. This occurred in the

dose estimates used to derive the cancer potencies, and consequently the NSRL, from the animal studies. This error was a transposition between the sexes of each species of the default assumptions of the fraction of body weight that rats and mice consume as food. The corrected values have been inserted in the document. This revision results in a slight change in the calculated NSRL for DEHP, from 300 micrograms per day to 310 micrograms per day.

REASONABLE ALTERNATIVES TO THE REGULATION AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES

At the time the Notice of Proposed Rulemaking and Initial Statement of Reasons were made available on June 8, 2001, OEHHA was not aware of any alternatives to the proposed regulatory action. Alternatives were suggested during the 45-day public comment period and the two post hearing comment periods. These are addressed within the summary and response to comments section of this document.

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

The proposed regulatory action will not adversely impact small business. The proposed regulation identifies levels below which businesses are exempt from Proposition 65 warning requirements and the discharge prohibition. It does not impose any requirement upon any business, including small business.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

As noted in the Notice of proposed rulemaking, OEHHA made an initial determination that the adoption of the regulation will not have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states. The regulation identifies levels below which businesses are exempt from Proposition 65 warning requirements and the discharge prohibition. No costs or expenses are incurred by businesses to comply with the proposed regulation. There is no significant adverse economic impact on any business. In fact, the proposed regulatory action makes it easier for affected businesses to comply with Proposition 65.

DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

SUMMARY OF AND RESPONSE TO OBJECTIONS AND RECOMMENDATIONS

Comments received are summarized below and responses to these comments provided. Comments received have been numbered and compiled, and page numbers assigned to the compiled comments, as indicated in the table below. Comments C-1 through C-9a were received during the initial 45-day comment period; PH1-1 through PH1-3 during the first 15-day post hearing comment period corresponding to the first modification in proposed rulemaking, and PH2-1 through PH2-3 during the second 15-day post hearing comment period.

Comment No.	Commenter	Subject of comments	Compiled comments page numbers
C-1	Western States Petroleum Association (WSPA)	Proposed benzene MADL	6 - 20
C-1a	Supplemental comments submitted by WSPA	Proposed benzene MADL	22 - 43
C-2	Alise Cappel, Center for Environmental Health & Health Care Without Harm	Proposed DEHP NSRL	45 - 51
C-3	Lead Industries Association, Inc. (King and Spalding)	Proposed Lead, Lead Acetate, Lead Phosphate Lead Subacetate NSRLs	53 - 55
C-4	Courtney Price, CHEMSTAR / American Chemistry Council	Proposed DEHP NSRL	57 - 119
C-5	Health Risk Consultants, Inc.	Proposed lead, Lead Acetate, Lead Phosphate Lead Subacetate NSRLs	212 - 129
C-6	International Lead Zinc Research Organization, Inc. (ILZRO)	Proposed lead, Lead Acetate, Lead Phosphate Lead Subacetate NSRLs	131 - 147
C-7	Gary Whitmyre, risksciences, LLC	Proposed lead, Lead Acetate, Lead Phosphate Lead Subacetate NSRLs	149 - 153
C-8	Battery Council International	Proposed lead, Lead Acetate, Lead Phosphate Lead Subacetate NSRLs	155 - 156

Comment No.	Commenter	Subject of comments	Compiled comments page numbers
C-9	American Environmental Safety Institute (July 23, 2001)	Proposed cadmium MADL	158 - 161
C-9a	Roger Carrick on behalf of the American Environmental Safety Institute (March 11, 2002)	Proposed cadmium MADL	163 - 178
PH1-1	National Food Processors Association	1 st modification to proposed regulation - cadmium	183 - 187
PH1-2	Coalition For Safe Ceramicware	1 st modification to proposed regulation - cadmium	189 - 195
PH1-3	Michelle Corash, Morrison & Foerster LLP.	1 st modification to proposed regulation - cadmium	196 - 203
PH2-1	Alliance of Automobile Manufacturers	2 nd modification to proposed regulation – proposed benzene MADL	206 - 223
PH2-2	Center for Ethics and Toxics	2 nd modification to proposed regulation – proposed cadmium MADL	225 - 228
PH2-3	Roger Carrick on behalf of the American Environmental Safety Institute (April 12, 2002 and April 16, 2002)	2 nd modification to proposed regulation – proposed cadmium MADL	240 – 296
PH2-4	American Chemistry Council	2 nd modification to proposed regulation – proposed DEHP NSRL	298-299

SUMMARY AND RESPONSE TO COMMENTS RECEIVED DURING THE INITIAL 45-DAY COMMENT PERIOD OF JUNE 8, 2001 THROUGH JULY 23, 2001.

BENZENE

C-1 = Western States Petroleum Association (WSPA), technical comments prepared by Dr. Jay Murray

C-1a = Supplemental comments submitted by WSPA

Commenter C-1 submitted comments on July 20, 2001, in response to the proposed rulemaking. The commenter requested a meeting with OEHHA, which occurred on November 26, 2001, and also asked to submit additional comments. OEHHA agreed to

consider supplemental comments, which were submitted on January 18, 2002. Objections raised in the initial and final comments are provided below.

In the first set of comments, the commenter objected to the selection of the 1988 study by researchers Keller and Snyder (1988) [Mice exposed in utero to 20 ppm benzene exhibit altered numbers of recognizable hematopoietic cells up to seven weeks after exposure. *Fund Appl Toxicol* 10: 224-232.] and a hematopoietic effect, in this case reduced relative number of nucleated red blood cells in animals exposed in utero, for the calculation of the maximum allowable dose level (MADL). Four main objections were raised in this regard, and the commenter proposed a different study and endpoint for MADL development. The supplemental comments elaborated on the objections and submitted new material to support the objections.

COMMENT NO. 1: The first objection raised was that the proposed MADL is not based on evidence and standards of comparable scientific validity to the evidence and standards which formed the basis for listing benzene as known to the state to cause reproductive toxicity, as required by 22 CCR §12801(a) and §12803(a). (see Comments, C-1, pp.8, 10-13, 20; C-1a, p.26). Two main points were raised in this regard. First, that the proposed MADL is not based on an endpoint of developmental toxicity as defined by the Developmental and Reproductive Toxicant (DART) Identification Committee's listing criteria. Second, that the basis for the DART Committee's recommendation to list benzene as a developmental toxicant was not a reduction in the relative number of early nucleated red cells in neonates.

Response: With respect to the first point, the DART Committee provides the following definition of developmental toxicity in its Criteria for Recommending Chemicals for Listing as "known to the state to cause reproductive toxicity"

“Developmental toxicity is defined to include adverse effects on the products of conception (i.e. the conceptus), including but not limited to:
-Embryo fetal mortality (including resorption, miscarriage/spontaneous abortion, or stillbirth), malformations, structural abnormalities and variation, altered fetal growth, and change in gestational age at delivery.
-Postnatal parameters including growth and development, physiological deficits and delay, neurological, neurobehavioral and psychological deficits, altered sex ratio, abnormal sexual development or function, and morbidity or mortality,
-Transplacental carcinogenesis,
-Somatic or genetic (germ cell) mutations in the conceptus.“

As discussed in more detail below, the endpoint “early nucleated red blood cells” is consistent with the broad definition provided by the DART Committee's criteria. A paragraph from earlier in the criteria notes that:

“These criteria are intended to give the DART Identification Committee maximal flexibility in evaluating all pertinent scientific information in

determining whether a chemical is known to the State to cause reproductive toxicity. These criteria are not intended to limit the scope of the Committee' consideration of appropriate scientific information, nor to limit its use of best scientific judgment.”

The DART Committee chose not to list each developing system that might be a target for a developmental toxicant. The phrases “malformation”, “growth and development” and “physiological deficits or delays” apply to the various developing systems (e.g., kidney, GI tract, thyroid, cardiovascular) which the DART Committee chose not to enumerate. In this case, the developing system selected for a developmental toxicity investigation by Keller and Snyder (1988, as cited above), and used by OEHHA for MADL derivation, was the hematopoietic (i.e., blood cell-producing) system.

The fact that abnormalities such as those in the hematopoietic system are not specifically mentioned in the DART Committee criteria does not exclude them for consideration in hazard identification or MADL development. In fact, the endpoints proposed for use by the commenter for benzene MADL development, decreased fetal body weight and delayed ossification, are also not specifically mentioned in the DART Committee listing criteria. Their appropriateness would need to be inferred from the language of the criteria just as is the case for reduced early nucleated red blood cells.

The second point was that the basis for the DART Committee's recommendation to list benzene as a developmental toxicant was not a reduction in the relative number of early nucleated red cells in neonates.

The DART Committee did not state which endpoints served as a basis for its decision to add benzene to the list of chemicals known to the State to cause reproductive toxicity (See transcript, Proposition 65 Developmental and Reproductive Toxicant (DART) Identification Committee, Public Meeting, Tuesday, December 9, 1997, Held at: Department of Health Services, 744 P Street, Sacramento, CA), nor is the DART Committee requested or required to do so. The DART Committee uses a “weight of evidence” approach to hazard identification as described in their criteria:

“in evaluating the sufficiency of data, a “weight-of-evidence” approach shall be used to evaluate the body of information available for a given chemical”.

The only statement the members of the DART Committee specifically made regarding their deliberations is their member-by-member vote in response to the question “has benzene been clearly shown through scientifically valid testing, according to generally-accepted principles to cause developmental toxicity?”

The DART Committee did discuss the hematopoietic endpoint at its meeting and did not exclude it as irrelevant. It was mentioned by most members as a factor contributing to their decision, as indicated in the quotes from the transcript.

In the quote provided by the commenter, Dr. Burke mentions fetal growth retardation and delayed ossifications, genotoxicity and hematopoietic toxicity, and asks other DART Committee members for their thoughts on growth retardation and the other endpoints.

Some other quotes from the transcript are provided below:

Dr. Hendrickx: “I would comment that I think there’s sufficient experimental evidence to implicate benzene as a developmental toxicant essentially due to the same factors that you emphasized in your overview.” (referring to Dr. Burke’s prior comments which included mention of decreased fetal weight, delayed ossification, genotoxicity and hematopoietic toxicity)

Dr. Miller: “I think there is good animal evidence in particular to support that benzene has adverse effects on fetal growth and potentially disrupts the fetal hematopoietic system which carries on into postnatal events and postnatal changes. ... I think the strength of the animal data is sufficient to list it as a developmental toxicant.”

Dr. Jones: “I agree completely with you I think there is evidence – at least it looks to me as though there’s evidence that there is a long-term effect, at least on the hematopoietic cells.”

Dr. Samuels: (during discussion of a study of childhood leukemia) “in that case it sounds like a fairly substantial study which would then probably relate it to the effects on the blood cells, so I think that’s consistent.”

As recorded in the transcript, DART Committee members voiced concern about the developmental effects of benzene on the hematopoietic system. The committee did not explicitly identify which developmental endpoints served as the basis for listing, nor were they required to do so. This does not preclude the use of hematopoietic or other developmental endpoints for calculation of the MADL.

COMMENT NO. 2: The second major objection raised by C-1 was that the proposed MADL is based on an endpoint that represents an adaptive hematopoietic response, not an adverse reproductive effect, as required by 22 CCR §12801(c) (see Comments, C-1, pp.9, 13-15; C-1a, p.26).

Response: The proposed MADL is based on changes in the relative number of early nucleated red blood cells (early nRBCs). Further description of the relevance of this endpoint may be valuable.

Differential cell counts have long been a cornerstone of hematological diagnosis. Differentials can be used to diagnose anemia (reduced red blood cells (RBCs)), and leukemia (increased white blood cells (WBCs)). Differentials can also be used to determine whether hematopoiesis - the production of blood cells- is proceeding normally. For this purpose, immature blood cell populations, precursors of the mature RBCs and WBCs, are studied.

The cells in the blood, both RBCs and WBCs, come from progenitor cells which proliferate and differentiate into precursor cells. In the case of RBCs, the precursor cells are the nucleated RBCs (nRBCs). The nRBCs lose their nucleus when they mature into fully functional RBCs. Early nRBCs can be distinguished from late nRBCs because they do not yet contain hemoglobin, the oxygen-carrying molecule of the mature RBCs, but they do still contain endoplasmic reticulum that is synthesizing proteins under direction of the nucleus. In order to understand whether the production of blood cells is normal, hematologists look at the relative number of different populations of nucleated cells (lymphocytes, granulocytes, and nRBCs). They expect that the relative numbers of these populations will be the same in all individuals with normal production of blood cells.

In their 1988 paper, Keller and Snyder (1988, as cited above) cited previous studies showing that benzene produces anemia and leukemia in adults and is toxic to bone marrow, where the production of blood cells occurs in adults. Thus they undertook to study the production of blood cells in infant mice who were exposed to benzene *in utero* by using differential cell counts. They found that both early nRBCs and late nRBCs were reduced in a dose-dependent manner. In two-day old mice, the group difference from control was statistically significant for late nRBCs at 20 ppm benzene in air. In addition, early nRBCs were significantly reduced at 5 and 10 ppm benzene in air. Thus, reduction in early nRBCs in the two-day old mice with exposure to 5 ppm benzene was the most sensitive indicator of benzene developmental hematopoietic toxicity in mice exposed in the womb.

The issue of reduction in early nRBCs as an adaptive response is addressed in the discussion section of the Keller and Snyder paper as follows: “depressions in erythroid precursor cells did not affect the levels of circulating red cells in these animals. The erythron has a large capacity to deal with an erythropoietic insult. It is known, for example that during phases of acute anemia, the cell cycle time of recognizable erythroid precursor cells shortens (Hanna et al., 1969) [Shortening of the cell-cycle time of erythroid precursors in response to anaemia. *Brit J Haemat* 16: 381-7]. This can lead to a lower steady-state number of erythroid precursors while at the same time producing normal or near normal numbers of mature functioning red cells. Such a compensatory mechanism may be in effect among the *in utero* benzene-exposed mice in this study.”

The key phrase for the issue under consideration here is “for example.” The authors are attempting to explain the presence of normal numbers of mature RBCs in the presence of a reduced population of nRBCs. Thus, the authors were suggesting that a compensatory change *occurs in response to* the reduced population of precursors in order to maintain normal circulating levels of RBCs. They do not specify what this compensatory response might be, but mention the change in cell cycle length in response to anemia as an example of a compensatory response in the hematopoietic system. This does not negate the primary effect of benzene on nRBCs.

Some further information may be valuable. The study of cell cycle shortening in anemia (Hanna et al., 1969, as cited above) did not measure the population of early nRBCs, but

just the length of the cell cycle. Keller and Snyder's statements about changes in RBC precursor populations are used to extend their example of a compensatory mechanism. Another article (Suda et al., 1978) [Erythroblast kinetics in pernicious anaemia, erythroleukaemia and sideroblastic anaemia. *Scand J Haematol* 20: 117-28], did measure changes in precursor cell populations in response to pernicious anemia in humans. The percentage of early nRBCs (of total precursors) was actually greater in the anemic subjects than in controls ($p < 0.025$), while the percent of late nRBCs and total nRBCs did not differ from controls. The absolute number of nRBCs is also known to *increase* in order to compensate for increased oxygen carrying demand in neonates (Korst et al., 1996) [Nucleated red blood cells: an update on the marker for fetal asphyxia. *Am J Obstet Gynecol* 175 (4 Pt 1), 843-6]; (Dollberg et al., 2000) [Effects of passive smoking in pregnancy on neonatal nucleated red blood cells. *Pediatrics* 106, E34].

If the commenter's interpretation were to be accepted (that the reduced number of early nRBCs is due to reduced cell cycle time in response to anemia), one would have to infer that benzene caused anemia in this study. In the paper cited by Keller and Snyder (Hanna et al., 1969, as cited above), anemia was induced by bleeding rats of 1/3 of their blood volume. If it is the case that lower nRBCs are a marker of benzene-induced anemia of this magnitude, and this anemia persisted in fetuses seven days after discontinuation of benzene exposure, the nRBC endpoint takes on even greater importance.

The commenter also suggested that benzene-induced reduction in nRBCs could be due to accelerated maturation of the immune system. However, the data from the Keller and Snyder paper do not indicate accelerated maturation of production of blood cells (hematopoiesis). As the hematopoietic system matures, the number of immature granulocytes and erythrocytes in peripheral blood decreases and the number of lymphocytes increases (as a proportion of all nucleated cells) as the site of production of blood cells shifts to the bone marrow. Benzene led to a decrease in the nRBCs, but no corresponding decrease in granulocytes or increase in lymphocytes. In fact the number of immature granulocytes *increased* in mice exposed to 20 ppm benzene.

The commenter also indicated that the results of a study by Murray et al. (Murray et al., 1979) [Embryotoxicity of inhaled benzene in mice and rabbits. *Amer Industr Hyg Assoc J* 40: 993-98] suggested that the hematopoietic alterations seen in the Keller and Snyder (1988, as cited above) study were a compensatory change, not a sign of or a trigger for developmental toxicity. However, the two studies are very different in design and it is difficult to draw inferences from one to the other. In the Murray et al. study (1979, as cited above), mice were exposed to either 0 or 500 ppm benzene for seven hours/day on gestational days 6-15. Decreased fetal body weight and delayed ossification were observed in the treated fetuses. This study therefore provided no opportunity to observe whether effects would occur at an exposure to 5 ppm benzene; it provided no information on the shape of the dose-response curve between 0 and 500 ppm that would indicate that a 100-fold difference in exposure meant that no effects would occur at 5 ppm exposure; and the Murray et al. study (Murray et al., 1979, as cited above) assessed different endpoints of toxicity from those assessed by Keller and Snyder.

COMMENT NO. 3: The third major objection is that Proposition 65 regulates chemicals known to the state to cause cancer or reproductive toxicity, not hematopoietic effects. (see Comments, C-1, pp.9, 13, 15-16, 20; C-1a, pp.26-27).

Response: Reproductive effects and hematopoietic effects are not mutually exclusive categories. Toxicity to any system that is incurred during development qualifies as developmental, and hence reproductive, toxicity. The following definition of developmental toxicity was provided by the United States Environmental Protection Agency (U.S. EPA) in its Guidelines for Developmental Toxicity Risk Assessment (*Fed Reg* 56: 63798-63826, 1991).

“The study of adverse effects on the developing organisms that may result from exposure prior to conception (either parent), during prenatal development or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.”

Additionally, functional developmental toxicology is described as follows:

“the study of alterations or delays in the physiological and /or biochemical competence of an organism or an organ system following exposure to an agent during critical periods of development pre- and /or postnatally.”

The commenter reiterates several times his opinion that the MADL endpoint (hematopoietic effects) is not a developmental toxicity endpoint. (see response to COMMENT NO. 1).

“in fact the proposed MADL is not even based on an endpoint of developmental toxicity, as that term is defined by the DART Committee’s listing criteria”.

“A reduction in the relative number of early nucleated red cells in a sample of nucleated cells from the peripheral blood of neonates is not an endpoint of developmental toxicity...”

“A reduction in the relative number of early nucleated red cells is not a relevant endpoint since it is not a relevant endpoint of developmental toxicity.”

The use of the endpoint is said to be inconsistent with “usual” and “traditional” developmental toxicology studies. Developmental toxicology is a broad area of study, containing findings produced by industry, government and university laboratories. In addition to “traditional” guideline studies that are submitted by industry to government agencies, the scientific literature each year contains thousands of studies on specific aspects of developmental toxicity. With regards to incorporating the findings of such studies into risk assessment, the U.S. EPA guidelines cited above state:

“Although not as well-studied, data indicate that the cardiovascular, respiratory, immune, endocrine, reproductive, and digestive systems also are subject to alterations in functional competence following exposure during development. Currently there are no standard testing procedures for these functional systems; however, when data are encountered on a chemical under review they are considered in the risk assessment process.”

In the case of benzene, studies on developmental hematopoietic effects were initiated by academic toxicologists because benzene is a well-known hematopoietic toxicant in adults and there was concern about effects on this system during development. This is described by Keller and Snyder (1988, as cited above) as follows:

“Surprisingly, although benzene is a potent hematotoxicant, there have been very few studies concerning the effects of benzene on the developmental hematopoietic system (Pollini et al. 1965, Koizumi and Suzuki 1966, Murray et al 1979, Mizens 1982). Benzene may be particularly toxic to fetal hematopoietic cells since the populations of these cells are actively expanding (Paul et al 1969) and since benzene is particularly toxic to actively replicating cells (Snyder 1987).”

These investigator-initiated studies were encountered by OEHHA during the review for MADL development and considered for use. Because the exposure levels were lower than in other developmental toxicity studies, the Keller and Snyder (1988, as cited above) study was selected for MADL development, in accordance with 22 CCR §12803(a)(4).

Finally, it should be noted that the DART Committee discussed hematopoietic endpoints as “toxicity” (see quotations above). There is no indication that they distinguished between this endpoint and others in terms of whether they considered the effect to be adverse or adaptive.

COMMENT NO. 4: In his fourth major objection, the commenter states that the Keller and Snyder (1988, as cited above) study is not “of sufficient quality” as required by 22 CCR §12803(a)(4) and it does not meet generally accepted scientific principles as required by 22 CCR §12803(a)(3). (see Comments, C-1, pp.9, 16-18, 20; C-1a, pp.25-26).

Response: In support of the objections, the commenter raised issues regarding the study’s group size, number of pups in each litter examined, different analytical methods to measure different concentrations of benzene in the chambers, and what the commenter considered “confusing and conflicting” results concerning other endpoints measured in other studies by these authors.

The group size in the Keller and Snyder (1988, as cited above) study was five (dams exposed). Larger group sizes are typical in studies conducted according to guidelines such as those for the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The

purpose of this is to ensure that the study is sufficiently sensitive; that is, to avoid false negative findings. If a study demonstrates an effect with a smaller group size, as did Keller and Snyder, the finding is not negative, and there is no problem with false negatives.

The Snyder laboratory at New York University Medical Center had conducted previous studies on benzene developmental hematotoxicity and thus had experience with effect size to understand how large a group size would be necessary to demonstrate effects of interest. It was preferable for them to use this group size rather than the larger “traditional” group size in order to be consistent with the principle of minimizing distress to experimental animals.

The Keller and Snyder (1988, as cited above) study used “litter-based” statistics, which is the most appropriate approach to developmental toxicology studies. Two alternative ways to obtain litter based statistics are to evaluate all the animals in the group and get a litter mean, or to evaluate randomly selected animals to represent the group and use these values. Thus, the approach taken by Keller and Snyder, to use one animal per litter per sex, was appropriate and is indeed widely used in studies with postnatal evaluations.

The use of two different analytical methods to confirm benzene concentrations, depending on the dose, appears to raise a concern about the quality of the study in the mind of the commenter because of “a question about whether controls and all dose levels were run at the same time.” There are probably a number of different explanations for the use of two different analytical methods, including their sensitivity range and their availability in relation to the number of chambers that were simultaneously monitored. There is no information available to choose between the various possible explanations.

As an additional approach to inferring poor study quality, the commenter provided an extensive discussion of results obtained from the Snyder laboratory on a different endpoint, the progenitor cell endpoint (colony forming units (CFUs)) in a different study (Keller and Snyder, 1986) [Mice exposed in utero to low concentrations of benzene exhibit enduring changes in their colony forming hematopoietic cells. *Toxicology* 42: 171-81]). OEHHA did not use this endpoint or this study for MADL development. Thus, these comments are not directly relevant to the development of the MADL for benzene. The commenter found the studies had “somewhat confusing and conflicting results.” This was taken by the commenter to reflect a generally poor quality of the work done by this group of investigators.

The Snyder group has produced a number of studies of benzene developmental hematopoietic toxicity with support from the National Institute for Occupational Safety and Health, the March of Dimes, and the National Institutes of Health. The series of studies refined and solidified the picture of benzene developmental toxicity at low doses.

The inconsistency noted by the commenter was in whether benzene increased, decreased or did not change the number of red blood cell CFUs (CFU-E), depending on the dose, sex and age of the mouse offspring. However, it should be noted that there is extensive

feedback on progenitor cell proliferation and benzene can both increase and decrease the number of CFUs in adult mice depending on the dose and duration of treatment (Farris et al., 1997) [Benzene-induced hematotoxicity and bone marrow compensation in B6C3F1 mice. *Fund Appl Toxicol* 36: 119-29]. Gender differences in benzene effects are also well known. The results of Keller and Snyder concerning CFU-E cannot be considered conflicting in the context of all the data on benzene hematopoietic actions.

COMMENT NO. 5: Finally, the commenter states that alternative studies are appropriate for establishing a MADL for benzene. (see Comments, C-1, pp.9-10, 18-20).

Response: The Proposition 65 regulations contain the following directives for dose-response assessment (i.e., setting a MADL).

“Where multiple reproductive effects provide the basis for the determination that a chemical is known to the state to cause reproductive toxicity, the reproductive effect for which studies produce the lowest NOEL shall be utilized for the determination of the NOEL [No Observable Effect Level]. ... The NOEL shall be based on the most sensitive study deemed to be of sufficient quality. ... When data do not allow the determination of a NOEL, the lowest observable effects level (LOEL) shall be divided by 10 to establish a NOEL for purposes of assessment.” (22 CCR §12803(a)).

The commenter proposes another study (Coate et al., 1982) [citation not provided by commenter and not found by OEHHA] for MADL development. The NOEL from this study is cited by the commenter to be 40 ppm, 8 times higher than the LOEL from the Keller and Snyder (1988, as cited above) study (5 ppm), and 80 times higher than the NOEL (0.5 ppm) derived from Keller and Snyder’s LOEL. The commenter indicates that no effects were observed in the Coate et al. study at levels twice as great as the highest air concentration in the Keller and Snyder study (20 ppm), which produced more extensive and long-lasting effects on the production of blood cells than the 5 ppm air concentration. The Coate et al. study does not address the hematopoietic toxicity of benzene to which the fetus is particularly sensitive. Use of the Coate et al. study would not comply with 22 CCR §12803(a)(4) for selecting a NOEL for MADL development, which requires the selection of the most sensitive study deemed to be of sufficient quality.

COMMENT NO. 6: Additional comments were submitted on January 18, 2002 (dated January 17, 2002; see Comments, C-1a, pp. 22-23). These comments were prepared by Dr. F. Jay Murray, as were the previous comments (C-1) discussed above. The additional comments were based on the report “Analysis of the underlying biological basis for using neonatal hematology measurements in risk assessments of the developmental toxicity of benzene” by Dr. Richard D. Irons which was appended to the introductory materials prepared by Dr. Murray.

Dr. Murray’s comments selected and summarized points from Dr. Irons’ document, and suggested that it was important to note that his and Dr. Irons’ assessments independently reached the conclusion that it would be highly inappropriate to use the study by Keller

and Snyder (1988, as cited above) as a basis for a quantitative risk assessment. (see Comments, C-1a, p.9).

Response: It is important to note at the outset that there is no indication that Dr. Irons intended his report to respond to the OEHHA document on MADL development. He had developed the report at the request of the Aromatic Producers Association of the Council of the European Chemical Industry, but the purpose of the document is not specified. Most of Dr. Irons' report discusses proliferation of hematopoietic (i.e., blood-producing) progenitor cells, a topic addressed in a study by Keller and Snyder (1986, as cited above) and a topic on which Dr. Irons has conducted considerable basic research in conjunction with benzene-induced leukemia. Proliferation of hematopoietic progenitor cells was not studied in the paper used for MADL development (Keller and Snyder, 1988, as cited above). There is limited text in Dr. Irons' report (see Comments, C-1a, pp.37-38), concerning the Keller and Snyder (1988, as cited above) article, which is the basis of the MADL. As discussed below in more detail, Dr. Irons based his conclusions largely on the earlier study by the same investigators, and expressed concerns primarily about the validity of the methodology used in that 1986 study, not the 1988 study relied upon by OEHHA for establishing a MADL. As discussed above in the response to his original submittal, Dr. Murray based his conclusion that the study by Keller and Snyder (1988, as cited above) should not be used primarily on the assumption that the observed effect was not an adverse developmental effect, but rather was adaptive. Thus, although the conclusions drawn in the two assessments are superficially similar, the bases on which they are drawn differ markedly.

COMMENT NO. 7: The comments indicate that the Keller and Snyder (1986, as cited above) study does not represent a scientifically valid test by today's standards because it relied on the use of conditioned media without defined growth factors. This is considered an unsatisfactory approach for purposes of quantification. Also, this study applied methodology to developmental hematology which then and now is unprecedented. The biological significance of the findings is unknown. (see Comments, C-1a, p.25).

Response: The Keller and Snyder (1986, as cited above) study was not used for purposes of MADL development. Thus, any methodological deficiencies in the study are not applicable to MADL development.

COMMENT NO. 8: With regard to the issue of biological significance of effects seen in the Keller and Snyder (1988, as cited above) article, Dr. Irons provides several descriptive sentences listing the parameters that were not affected. Also, with regard to the correlation with adverse health findings Dr. Irons noted, the mice did not demonstrate the types of effects seen in response to severe insults, such as anemia or infection, during the fetal period of production of blood cells. (see Comments, C-1a, pp.36-37).

Response: These statements seem to imply that all parameters must be affected to demonstrate developmental hematotoxicity of a toxicant. This is contrary to conventional interpretation of multi-endpoint developmental toxicity studies. In the absence of any support for this premise, OEHHA relies on the data as published. Dr. Irons also noted

that the benzene effect could be secondary to damage to the liver, rather than effects on the bone marrow. This consideration is not relevant for MADL development. Manifestation of developmental toxicity is a valid basis for LOEL and NOEL determination regardless of what organ system is initially damaged in producing the effect. Further, many of Dr. Irons' comments are directed at the hepatic phase of fetal erythropoiesis, whereas the benzene exposure in the Keller and Snyder (1988, as cited above) paper was during organogenesis, which precedes the hepatic phase of erythropoiesis. The effect of this low-level benzene exposure would not be expected to resemble the consequences of severe anemia or infection. Also, as stated above, the exposures in Keller and Snyder (1988, as cited above) occurred during the period of organogenesis, rather than during the fetal period.

COMMENT NO. 9: Regarding the Keller and Snyder (1988, as cited above) study, the analysis of peripheral blood indices was apparently conducted at different times, because each dose is compared to a different set of controls that differ one from the other. (see Comments, C-1a, p.37).

Response: The occurrence of different sets of controls was based on the random process used to select individual offspring to represent litters. Litter-based statistics are preferable to offspring based statistics, because the litter is the more appropriate unit of analysis. To obtain litter-based statistics, either the entire litter can be evaluated and a mean value obtained, or animals representing the litter can be randomly selected and evaluated. Keller and Snyder chose the random selection approach. Because they randomly selected offspring from each treated litter, they decided to randomly select offspring from a control litter for comparison to each treated litter. This is a more statistically conservative approach than randomly selecting one set of controls.

This process is described as follows in the methods section of the article:

“Peripheral and organ blood cell counts were determined on the four animals (two males and two females) randomly selected from each litter. Cell counts from animals randomly selected from matched air control litters were determined each time cell counts were determined from a benzene-treated litter. Thus each benzene-exposed animal had its own age-matched air control.”

There is nothing in the methods section of the article to suggest that the analysis was conducted at different times for the different *dose groups*; rather each treated litter was matched with a control litter at the time the slides were read.

COMMENT NO. 10: Although an apparent decrease in early nucleated red cells was reported among 2-day neonates this effect was not evident in 16 day fetuses or 6-week adults. . . . No biologically significant effects or dose-response is observed for the effects of benzene on peripheral blood differential counts in 6-week adults. (see Comments, C-1a, p.30).

Response: Careful examination of the data tables suggests that there was a dose-dependent effect of benzene on this cell population at all ages. Table 2 in the Keller and Snyder (1988, as cited above) article shows that there was a dose-dependent pattern of decrease in early nRBCs in the 16-day fetus, although none of the group comparisons reaches significance. As regards adult values, as demonstrated in Table 2, this cell population is not found in the peripheral blood of adults, but is located instead in the bone marrow. Table 3 in the Keller and Snyder (1988, as cited above) article demonstrates a dose-dependent decrease in the early nRBCs in the bone marrow of 6-week old adults, with the high dose group (20 ppm) statistically different from controls.

COMMENT NO. 11: No decline in circulating red blood cells was noted in any age group at any dose level. . . . The biological significance of the endpoints measured has not been established. . . . None of the reported findings correlate with significant adverse health effects. (see Comments, C-1a, pp.37-38).

Response: There is no empirical evidence on whether or not the reported findings in mice correlate with effects at the clinical level, such as reduced ability to respond to anemia or hypoxia, because this has not been examined experimentally. The data as a whole indicate that the benzene effect is not limited to the erythroid cell lines. Because the early nRBC results are from differentials, a corresponding increase in other nucleated cell populations must be occurring. The data from Tables 2 and 3 in the Keller and Snyder (1988, as cited above) article suggest that granulocytes are proportionally increased in numbers. The implications of this change for immune system function and susceptibility to leukemia are also not known. In the absence of empirical evidence to the contrary, it is health conservative to assume that permanent alteration of a system such as the production of blood cells should be taken seriously in the risk assessment process.

It is important to note that the RBC counts in Table 1 in the Keller and Snyder (1988, as cited above) article are a concentration measure (RBCs per mL of blood) of non-nucleated cells in the blood, while the early nRBC counts in Table 2 are from differential cell counts of nucleated cells. Differential cell counts determine the representation of different blood cell types in a fixed population of cells, in this case 100 nucleated cells. The absolute number of cells in peripheral blood could vary with a variety of factors, such as plasma volume. The differentials provide information on whether the hematopoietic process is disturbed, independent of the concentration of cells in the blood. Thus the two measures are not readily compared to determine a consistency of toxicant action.

It is also important to keep in mind that early nRBCs population are a critical index of regulation of developmental erythropoiesis (production of red blood cells). This is the population that responds to erythropoietin, the hepatic protein hormone which is produced first under regulation of retinoic acid during *in utero* life and then in response to hypoxia after birth. Because of the responsiveness of early nRBCs to hypoxia, elevated numbers of early nRBCs are often used clinically as an index of fetal distress. Thus the lower numbers of early nRBCs can be seen as reflecting impairment at an

important step in regulation of red blood cell production. That this impairment persists into adulthood after a brief (10 day) in utero exposure is a significant finding.

Thus, to briefly summarize these responses, the issues raised by Dr. Murray based on Dr. Irons review of the Keller and Snyder (1988, as cited above) paper were not found to require revision of the MADL upon careful consideration by OEHHA staff.

CADMIUM

C-9 = American Environmental Safety Institute (July 23, 2001)

C-9a = Roger Carrick on behalf of the American Environmental Safety Institute (March 11, 2002)

COMMENT NO. 12: One party submitted two sets of written comments (C-9 and C-9a) objecting to the proposed MADL for cadmium. In a discussion under the heading “Proposed Standard on Cadmium is Too High,” commenter C-9 stated that OEHHA has already determined that cadmium is a reproductive toxicant pursuant to Proposition 65, and has set a “safe harbor” exposure level of 0.05 µg/day for a cadmium inhalation exposure. (see Comments, C-9, p.159).

Response: Both individual statements are correct, but as a matter of clarification, cadmium is also listed under Proposition 65 as a chemical known to cause cancer. The 0.05 µg/day inhalation “safe harbor level” in regulation is a “no significant risk level” specified in Title 22, California Code of Regulations, § 12705 (22 CCR § 12705) for the cancer endpoint only and is explicitly further limited to the inhalation route of exposure. As such, it applies to neither reproductive toxicity endpoints (the subject of MADLs) nor to oral exposures. As a further note of clarification, the MADL for oral exposure to cadmium proposed for adoption in 22 CCR §12805 applies to reproductive toxicity only and is not relevant to evaluation of the potential cancer risks from cadmium exposure by the route of ingestion, which is currently addressed in 22 CCR § 12707.

COMMENT NO. 13: Commenter C-9 noted that the Agency for Toxic Substances and Disease Registry (ATSDR) in its “Toxicological Profile for Cadmium, 1999 Update” sets a “minimum risk level” of 0.0002 mg/kg/day for cadmium ingestion, based upon that heavy metal's toxic effects on the human kidney, and that the proposed MADL of 4.1 µg/day “would subject every person so exposed on a daily basis to massive kidney damage, according to the ATSDR.” (see Comments, C-9, p.159).

Response: Although potential damage to the kidney is an important public health concern, it is not addressed by Proposition 65. That is, the only hazards posed by chemicals that are subject to Proposition 65 are cancer and reproductive toxicity. Additionally, OEHHA believes this statement to be factually in error, and notes that it may reflect a misunderstanding of the units in which the MADL and ATSDR values are given. The MADL is expressed as a microgram per day amount, whereas the ATSDR level is expressed as milligrams per kilogram body weight per day. To directly compare the ATSDR level with the MADL, the ATSDR level must be multiplied by bodyweight

to convert to milligrams and then further multiplied by 1,000 to convert to micrograms. Body weight in this case would be 58 kilograms (as specified in 22 CCR §12803(b) for a woman with conceptus). The ATSDR minimum risk value is therefore equivalent to 11.6 µg/day, more than twice the proposed MADL.

COMMENT NO. 14: Commenter C-9 also cited the ATSDR Toxicological Profile for Cadmium and noted that on page 118 [the section “Developmental Effects”] that document states: “The most sensitive indicator of developmental toxicity appears to be neurobehavioral development.” The commenter also compared the absence of discussion of the Ali et al. study with the “extensive discussion” of the Baranski et al. study in the subsequent section “Relevance to Public Health” of the ATSDR Toxicological Profile. The commenter also stated that according to the Initial Statement of Reasons for the proposed MADL for cadmium, “OEHHA apparently relies on the ATSDR Cadmium Profile’s recitation of the study by [Ali et al.] ... OEHHA appears to rely upon citation of this study in ... Table 2-2....” (see Comments, C-9, p.160).

Response: OEHHA did not rely upon the ATSDR Toxicological Profile for Cadmium [ATSDR, Toxicological Profile for Cadmium; Update 1999] in developing the MADL. Rather, in the course of reviewing the available data on cadmium, OEHHA evaluated the original publications authored by Baranski et al. (1983) [Effects of oral, subchronic cadmium administration of fertility, prenatal and postnatal progeny development in rats. *Archives of Toxicology* 54: 297-302] and by Ali et al. (1986) [Developmental and long term neurobehavioral toxicity of low level in utero cadmium exposure in rats. *Neurobehavioral Toxicology and Teratology* 8: 463-468], in addition to original publications by other researchers. The results of both the Baranski et al. (1983, as cited above) and the Ali et al. (1986, as cited above) papers are briefly described to approximately the same extent in the ATSDR document immediately following the passage quoted above by the commenter: “The most sensitive indicator of developmental toxicity appears to be neurobehavioral development.” In the later section of the document exactly the same statement is reiterated; the “extensive discussion” of the Baranski et al. (1983, as cited above) study referred to by the commenter consists of the following statement: “The lowest exposures shown to cause these effects in animals are 0.02 mg/m³, 5 hours a day, 5 days a week, by inhalation (Baranski 1985) and 0.04 mg/kg/day, 5 days a week orally (Baranski et al. 1983).” No evaluation of the quality of either the Baranski et al. (1983, as cited above) or the Ali et al. (1986, as cited above) paper is provided anywhere in the ATSDR document.

COMMENT NO. 15: Commenter C-9 contends that the oral MADL for cadmium should be 0.232 µg/day, and be derived from the study by Baranski et al. (1983, as cited above). The commenter further contends that since the Baranski study is the most sensitive study, by regulation (22 CCR §12803(a)(4)) it should provide the basis for the establishment of the MADL. Additional information in this regard is provided in Comment C-9a. (see Comments, C-9, pp.159-160 and Comments, C-9a, pp.163-180).

Response: While it is correct that the Baranski et al. (1983, as cited above) study reports an association between maternal oral exposure to cadmium and neurobehavioral effects

on offspring at doses which are lower than those reported by Ali et al. (1986, as cited above), the study used as the basis for the MADL must be “of sufficient quality”, as further specified in the same section of the regulation cited by the commenter (22 CCR §12803(a)(4)). The Baranski et al. (1983, as cited above) study was evaluated by OEHHA according to criteria provided in 22 CCR §12803(a)(3), and found unsuitable for quantitative risk assessment. For example, the paper did not specify the numbers of pregnant females exposed to cadmium. It appears that only eight offspring of each sex for each treatment group were assessed postnatally, although the presentation of the data is ambiguous and may only represent a total of eight offspring per treatment group. No indication of the number of litters represented was provided, nor was any information provided on whether the pups were randomly selected in a balanced fashion across litters or from a pool of all pups from all litters in each dose group. These omissions preclude a thorough evaluation of the reported results. Thus, the Baranski et al. (1983, as cited above) study, as published, was found not to be of sufficient quality for setting a MADL.

Subsequent to discussions between OEHHA and the commenter, the commenter provided to OEHHA additional, unpublished information pertaining to the 1983 Baranski study that was identified as having been obtained directly from Dr. Baranski. For reference, this submission is identified as C-9a (see Comments, C-9a, pp.163-180). There is no indication that the additional data provided have undergone any form of peer review, Good Laboratory Practice review or comparable validation. This additional information was also evaluated with respect to the requirements of 22 CCR §12803. Overall, the available procedural detail on the experiments reported in Baranski et al. (1983, as cited above) and in the additional materials provided do not describe a study of sufficient quality for the purpose of quantitative risk assessment.

The information provided indicates that there are no written records of certain basic toxicity parameters, and demonstrated that in at least one instance the text of the paper did not accurately reflect such data as were archived (i.e., the 1983 study report states that “the viability...ind[ex]...showed no significant differences between control and treatment groups”, while the additional data provided to OEHHA indicates a statistically significant ($p < 0.001$) increase in viability for the high-dose group, as compared to controls). With regard to the neurobehavioral effects that form the basis for the commenter’s contention that this is the most sensitive study, the additional information provided states that it “appeared” the technician conducting the neurobehavioral assessments selected eight litters per treatment group (which ranged in size from 12 – 17 litters) for testing. Although it is stated that the eight litters were randomly selected, this is expressed as a consequence of the decision by the technician to test only some of the litters rather than as a component of the study protocol. In the absence of an *a priori* rationale or protocol for selecting only a subset of available litters for testing, the possibility of a confounding bias in litter selection cannot be excluded.

Thus, the Baranski et al. (1983, as cited above) study does not meet the regulatory criteria in 22 CCR §12803 for sufficient quality, and the reported effects in this study cannot be considered reliable. In contrast, the Ali et al. (1986, as cited above) paper does present adequate details of the methods, results, and statistical analysis, and thus was deemed to

be the most “sensitive study of sufficient quality” for establishment of a MADL, as is required by 22 CCR §12803(a)(4).

DI(2-ETHYLHEXYL)PHTHALATE (DEHP)

C-2 = Alise Cappel, Center for Environmental Health & Health Care Without Harm

C-4 = Courtney Price, CHEMSTAR / American Chemistry Council

C-7 = Gary Whitmyre, risksciences, LLC

COMMENT NO. 16: Alise Cappel, Center for Environmental Health & Health Care Without Harm (see Comments, C-2, p.45 and Hearing Transcript, pp.7-9), supports OEHHA’s decision to set the No Significant Risk Level (NSRL) for DEHP at 300 micrograms per day, stating that the value is “entirely supportable” and that it is prudent to consider DEHP a human carcinogen. The commenter states that this decision is supported by a recent publication by Melnick (2001) in which he argues that there are still insufficient data to conclude that DEHP poses no cancer risk to humans [Is peroxisome proliferation an obligatory precursor step in the carcinogenicity of di(2-ethylhexyl)phthalate (DEHP)? *Environ Health Perspect* 109(5):437-4].

Response: Comment acknowledged.

COMMENT NO. 17: Courtney Price, CHEMSTAR / American Chemistry Council (see Comments, C-4, pp.57-61), “strongly agrees” with raising the NSRL for DEHP, “applauds” OEHHA for adjusting the potency, and “commends OEHHA for its use of mechanistic data for risk assessment purposes.” The commenter suggests that OEHHA should go further in applying science, consider the strong scientific consensus that humans are less sensitive and that the liver tumors in rodents are not relevant to humans. The commenter contends OEHHA should use a threshold model in the development of the NSRL. The commenter also states that OEHHA should consider removing DEHP from the list of substances known to cause cancer.

Response: In the development of the NSRL for DEHP, OEHHA considered the scientific evidence regarding what is known about the mechanism by which DEHP and the class of chemicals called peroxisome proliferators cause cancer. In recognition of evidence that humans are less sensitive to peroxisome proliferators than rats and mice at the cellular level, OEHHA has evaluated the available data comparing rodent and human cellular sensitivity, and has adjusted the cancer potency from which the NSRL for DEHP is derived based on this evaluation. OEHHA considered the application of both threshold and non-threshold models in the development of the NSRL for DEHP; however, for reasons detailed in the document and below, a non-threshold approach to the dose-response assessment was chosen.

OEHHA does not have the authority to remove DEHP from the Proposition 65 list of chemicals known to the State to cause cancer. DEHP was placed on the list, effective January 1, 1988, by the State’s Qualified Experts (then called the Scientific Advisory Panel), and only the current state’s qualified experts (now called the Carcinogen

Identification Committee of the OEHHA Science Advisory Board [22 CCR Section 12301]) have the authority to remove this chemical from the list.

COMMENT NO. 18: Courtney Price, CHEMSTAR / American Chemistry Council (see Comments, C-4, p.59), states that a summary statement in the NSRL document of the lack of epidemiological studies available on DEHP carcinogenicity should be amended to reflect the possibility that no carcinogenic effect is occurring in human populations.

Response: OEHHA has reviewed the statement in question and will modify it to highlight the uncertainty of the outcome of adequate epidemiological investigations. The statement will be modified to read: “Thus, numerous issues have limited the ability to detect a *possible* carcinogenic effect in certain highly DEHP exposed patient populations,” (emphasis added).

COMMENT NO. 19: Courtney Price, CHEMSTAR / American Chemistry Council (see Comments, C-4, pp.57-60), states that the data support a finding that liver tumors in rodents exposed to DEHP are not relevant to humans. The commenter cites the International Agency for Research on Cancer (IARC) review concluding that DEHP is “not classifiable as to carcinogenicity to humans” because the rodent tumors are not relevant to humans, a finding by the European Commission that DEHP is not carcinogenic, and a statement from Health Canada that DEHP is “unlikely to be carcinogenic to humans.” The commenter includes a statement from a publication by Fenner-Crisp (1996) that “If it is concluded that the observed rodent liver tumor was the consequence solely of hepatocellular proliferation accompanied by peroxisome proliferation, the dose-response should be modeled using a NOEL/UF or benchmark dose (threshold) approach.” The commenter states that the NSRL document should include a statement that there is a “strong possibility” that the actual carcinogenic potency of DEHP is zero because of these findings and those of other independent scientists.

Response: OEHHA disagrees with these agencies’ findings regarding the carcinogenic potential of DEHP to humans, particularly with the conclusion reached by IARC that the mechanism by which DEHP causes cancer does not operate in humans. OEHHA finds that the mechanism by which DEHP causes cancer is presently unknown, except that it is receptor-mediated. The responsible receptor, the peroxisome proliferator activated receptor-alpha, appears to be functional in both rodents and humans, although it is expressed at lower levels in humans compared to mice. Regarding the quote by Fenner-Crisp, OEHHA responds to this conditional statement with a conclusion that it has not been shown that hepatocellular proliferation accompanied by peroxisome proliferation is the cause of the liver tumors induced by DEHP. While these two phenomena have been hypothesized to be involved, there remain large uncertainties about what role, if any, each of these plays in the development of tumors. OEHHA recognizes that there are considerable uncertainties in the assessment of cancer risk in humans, particularly when they are based upon extrapolations from other species; however, a statement that there is a “strong possibility” that the carcinogenic potency of DEHP is zero is not warranted. Consistent with the use of the upper 95% confidence bound of the slope of the dose-

response curve as the cancer potency estimate, there is some confidence that the true carcinogenic potency may be below that used to calculate the NSRL for DEHP.

COMMENT NO. 20: Courtney Price, CHEMSTAR / American Chemistry Council (see Comments, C-4, p.60), states that receptor-mediated effects, such as those caused by DEHP, should use a threshold model, citing a publication by Poland (1997) [Reflections on risk assessment of receptor-acting xenobiotics. *Regul Toxicol Pharmacol* 26:41-3]. The commenter states that OEHHA's decision in using a non-threshold approach was based on the fact that the receptor may be normally nearly saturated with endogenous ligands, and therefore an additional xenobiotic, such as DEHP, would be additive to cancer risk. The commenter states that animal data for DEHP and diisononyl phthalate show evidence for a threshold for both liver tumors and liver changes indicative of peroxisome proliferation (citing David *et al.*, 1999, *Toxicol Sci*, 50 (2):195-205, and CPSC, 2001, Chronic Hazard Advisory Panel on Diisononyl Phthalate, Bethesda). The commenter states that OEHHA has ignored human and primate data showing a lack of responsiveness to DEHP.

Response: OEHHA does not find the commenter's contention that the carcinogenicity data for DEHP in rodents provide convincing evidence of a threshold response compelling. In the case of the DEHP studies in mice by David *et al.*, there is an increase in tumor incidence with each increasing dose among DEHP-treated mice relative to untreated control mice. Likewise, there is an increase in peroxisomal enzyme activity with increasing dose, although it should be noted that the role of peroxisomal enzyme activity, *per se*, in the etiology of liver cancer by DEHP is presently unclear. These findings are consistent with a non-threshold dose-response relationship. It is unclear how the commenter believes the differences in responsiveness which have been observed between rodents and primates (including humans) informs the dose-response relationship and whether or not a threshold exists for the cancer response. OEHHA has not ignored the differences in peroxisomal effects between rodents and non-rodent species. To the contrary, OEHHA has evaluated the merits of these largely *in vitro* studies and used a reasonable approach to interspecies scaling – the application of a scaling factor – as a result. The commenter has fairly captured the essence of OEHHA's rationale for using a non-threshold approach to the receptor-mediated carcinogenicity of DEHP. Two of the studies which the commenter asserts show a lack of effect on primate liver, Kurata *et al.* (1998, *Toxicol Sci*, 42 (1): 49-56) and Pugh *et al.* (2000, *Toxicol Sci*, 56 (1), 181-188), were only conducted for 13 and 2 weeks, respectively. The short duration of these studies precludes judgment as to whether the animals in these studies were at increased risk of cancer. It should be noted that liver effects were observed in the Kurata *et al.* studies in marmosets, with increases in hepatic microsomal enzyme content and an increase in peroxisomal volume observed, although other parameters such as peroxisomal number and volume density were not increased.

COMMENT NO. 21: Courtney Price, CHEMSTAR / American Chemistry Council (see Comments, C-4, p.60), asserts that there are basic physiological differences between rodents and humans regarding the blood levels of natural ligands such as fatty acids, citing a publication by Vamecq and Latruffe (1999) [Medical significance of peroxisome

proliferator-activated receptors. *Lancet* 354:141-8]. Further, the commenter states that human hepatocytes do not increase metabolism of fatty acids to the extent that rodents do, and certainly not using enzyme systems associated with oxidative stress, tumorigenesis, or tumor promotion, citing studies in primates which used corn oil as a vehicle control [Short *et al.*, 1987, *Toxicol Ind Health*, 3 (2): 185-195; Kurata *et al.*, 1998].

Response: Few data exist regarding the levels of peroxisome proliferator activated receptors and their level of occupancy by endogenous ligands under normal physiological conditions in the human body. The review by Vamecq and Latruffe sheds little additional light on this. Still fewer data exist which evaluate peroxisome proliferator activated receptor status during different conditions such as fasting, among diabetics, between sexes, and at different ages. The commenter's assertion that human hepatocytes do not respond to the same degree as rodent hepatocytes to DEHP has been recognized in the NSRL document. The difference forms part of the basis for the application of a ten-fold interspecies scaling factor to the carcinogenic potency for DEHP in converting from mouse to human cancer potency. The commenter's assertion that the enzymes associated with oxidative stress, tumorigenesis, and tumor promotion are not induced in humans is questionable. Beyond the activation of the peroxisome proliferator activated receptor-alpha, the genes (whose expressions are controlled by this receptor) which are responsible for increasing a cell's susceptibility to transformation to a cancer cell are presently unknown. Since these genes and the proteins and enzymes they produce are unknown, it is not possible to determine whether or not they have been shown to be induced in human cells or not.

COMMENT NO. 22: Courtney Price, CHEMSTAR / American Chemistry Council (see Comments, C-4, p.60), cites a publication by Willhite (2001) which suggests that the mode of action of peroxisome proliferator activated receptor-alpha ligands is a sigmoidal dose-response curve and there is no justification for applying a "radiomimetic linear regulatory model" [Weight-of-evidence versus strength-of-evidence in toxicologic hazard identification: Di(2-ethylhexyl)phthalate (DEHP). *Toxicol* 160:219-226].

Response: OEHHA determined that there was a reasonable basis for assuming that the receptor-mediated carcinogenic response to DEHP does not have a threshold (see response to comment 20 above). The justification was outlined in the NSRL document. The multistage polynomial which was generated using the tumor response data provides a useful mathematical expression of the relationship between dose and cancer risk in the observable range. This expression was extrapolated to low-dose to provide an estimate of the dose associated with an increased risk of one in 100,000, as required by 22 CCR§ 12703 (b).

COMMENT NO. 23: Courtney Price, CHEMSTAR / American Chemistry Council (see Comments, C-4, p.61), states that the solubility and vapor pressure data for DEHP in the NSRL document should be changed.

Response: OEHHA has reviewed the solubility and vapor pressure data which was contained in the draft NSRL document and in the materials submitted by the commenter [Staples *et al.* (1997) The environmental fate of phthalate esters: A literature review. *Chemosphere* 35(4):667-749]. OEHHA agrees that a room temperature vapor pressure value is more appropriate to include, so the vapor pressure statement will be modified according to the commenter's referenced suggestion. The solubility data reviewed in this same paper differ considerably from the theoretical solubility value recommended by the publication's author. OEHHA agrees that water solubility of DEHP is quite low; however, the experimentally measured values reported in Staples *et al.* were generally near that reported in the NSRL document. The few that were calculated on a theoretical basis were considerably lower in magnitude. A solubility for DEHP reported by a manufacturer in Material Safety Data Sheets is 0.34 mg/L, a value very close to that reported in the NSRL document. OEHHA prefers to report a value in the range of those which have been consistently experimentally measured over values calculated on theoretic bases, such as those suggested in Staples *et al.* and the Cousins and Mackay (2000, *Chemosphere*, 41 (9):1389-1399) publications.

COMMENT NO. 24: Gary Whitmyre, risksciences, LLC (see Comments, C-7, p.149), states that a recent review of the toxicology of DEHP was not discussed in the NSRL document [Doull *et al.* (1999). A cancer risk assessment of di(2-ethylhexyl)phthalate: Application of the new U.S. EPA risk assessment guidelines. *Regul Toxicol Pharmacol* 29(3):327-357].

Response: The Doull *et al.* publication is one of many reviews of the carcinogenic potential of DEHP. Although its content was considered for edification of data not included in the OEHHA assessment it was not relied on in the development of the NSRL. OEHHA disagrees with the findings of this paper, particularly with the margin-of-exposure approach in the assessment of potential cancer risks for this compound.

COMMENT NO. 25: Gary Whitmyre, risksciences, LLC (see Comments, C-7, p.149), agrees with OEHHA that the mechanism of DEHP carcinogenesis involves peroxisome proliferation.

Response: OEHHA has not stated that the mechanism of DEHP carcinogenesis involves peroxisome proliferation, only that the class of compounds called peroxisome proliferators, which includes DEHP, cause peroxisome proliferation as well as cancer. The relationship between peroxisome proliferation itself and cancer is presently unclear.

COMMENT NO. 26: Gary Whitmyre, risksciences, LLC (see Comments, C-7, pp.149-150), states that OEHHA has given less weight to human *in vitro* data and human *in vivo* data on peroxisome proliferators other than DEHP.

Response: OEHHA has given appropriate weight to all relevant human data, *in vitro* and *in vivo*. In the NSRL document, OEHHA states what the limitations to these data are and where additional data may inform a better assessment of cancer risk to humans from exposure to DEHP.

COMMENT NO. 27: Gary Whitmyre, risksciences, LLC (see Comments, C-7, p.151), states that there is a non-linear dose-response to DEHP which is suggestive of a threshold and that OEHHA has applied an inappropriate model for the dose-response. Further, the commenter states that the cancer response is threshold-based, involving peroxisome proliferation. A non-threshold model is only appropriate when the mechanism is unknown or when there is reason to suspect the chemical could be carcinogenic to humans (*e.g.*, from epidemiological data). The commenter asserts that neither of these conditions has been met in the case of DEHP. The commenter states that the use of the non-threshold model is in conflict with the interpretation of the “blue-ribbon panel” published by Doull *et al.* (1999).

Response: OEHHA disagrees with the commenter’s characterization of the dose-response data and the criteria for selection of a threshold model. The tumor response data show a very clear increase in tumor incidence with increasing dose of administered DEHP, which is consistent with a low-dose linear relationship. OEHHA has justified the use of the non-threshold model based upon data that the induction of cancer is a receptor-mediated process and that the receptor involved is likely to have endogenous ligands to which additional activation by xenobiotics such as DEHP is additive.

COMMENT NO. 28: Gary Whitmyre, risksciences, LLC (see Comments, C-7, p.150), states that humans do not have a functional amount of peroxisome proliferator activated receptor-alpha adequate to cause a peroxisome proliferation response in humans.

Response: There is mixed evidence of a peroxisome proliferation response from human *in vivo* exposures to fibrate hypolipidemic agents, which are peroxisome proliferators, from which OEHHA concluded that “Overall, no well-conducted, systematic evaluation of human responsiveness from *in vivo* exposure to DEHP has been conducted to date. Thus, this particular set of data does not provide strong evidence of either human responsiveness or a lack thereof.” That humans have a “functional amount” of peroxisome proliferator activated receptor-alpha is evidenced by the fact that humans respond to the subset of peroxisome proliferators that are hypolipidemic pharmaceuticals, such as gemfibrozil and clofibrate. These compounds’ pharmacological properties are a direct result of their interaction with functional amounts of this receptor. As has been stated, the relationship of peroxisome proliferation itself to carcinogenicity is presently unclear, which obscures the relevance of such findings to the assessment of carcinogenic risk and the development of the NSRL for DEHP.

COMMENT NO. 29: Gary Whitmyre, risksciences, LLC (see Comments, C-7, pp.150-151), states that there is a lack of applicability of the proposed NSRL for DEHP to exposures from medical devices based upon the relative infrequency of their use, the reversibility of the effects of DEHP (citing David *et al.*, 1997), and the “decades of safe use” of such medical devices.

Response: Since it is unclear which, if any, of the proposed mechanisms by which DEHP causes cancer are operative, it cannot be determined presently how the frequency of

exposure affects the cancer risk without studies directly examining this relationship. Such studies do not currently exist for DEHP. The studies of David *et al.* in which rats and mice were treated for 18 months with DEHP, allowed to recover for almost six months, then assessed for tumors, do not show convincing evidence of recovery for both rats and mice. Rats showed fewer tumors than expected (if recovery was not occurring) following the recovery period, but mice showed more liver tumors than expected. If, in fact, the carcinogenic effects of DEHP are reversible, then one would expect the phenomenon to occur in both species. The available data do not bear this out. The statement that DEHP has enjoyed “decades of safe use” requires back-up with strong epidemiological evidence. Such epidemiological evidence has not been published. For these reasons, the NSRL will be considered applicable to exposures from medical devices.

COMMENT NO. 30: Gary Whitmyre, risksciences, LLC (see Comments, C-7, pp.151-152), states that OEHHA used a procedure that is potentially controversial in applying a 10-fold reduction factor to the cancer potency for DEHP in mice. The commenter also asserts that it is unclear whether this approach is “completely science-based, or if it is in part a policy-decision.” The commenter also claims it is unclear what the basis for the magnitude of this reduction factor is, and whether it would be more appropriate to assign it a higher value.

Response: The explanation for the application of the factor is included in detail in the NSRL document and is “science-based.” This justification included statements that multiple studies of human tissues showed lower levels of expression of the peroxisome proliferator activated receptor-alpha (mRNA and protein) than rodents, generally on the order of ten-fold, or greater, and that *in vitro* evidence from human cells compared to rodent cells showed lower induction of enzyme markers of peroxisome proliferator responsiveness, also on the order of ten-fold.

COMMENT NO. 31: Gary Whitmyre, risksciences, LLC (see Comments, C-7, p.152), states that OEHHA should use a margin of exposure approach in the risk assessment, using the “appropriate yet conservative” No-Observed-Effect-Level of 20 mg/kg-day for peroxisome proliferation and increased liver weight in mice identified by Doull *et al.* (1999). This approach is conservative because there is strong scientific evidence that humans are nonresponsive to peroxisome proliferators. This approach would result in an NSRL that is orders of magnitude higher than that proposed by OEHHA.

Response: OEHHA has explained the use of a non-threshold model in the NSRL document and has taken an appropriate approach in applying a 10-fold adjustment to the cancer potency derived from the animal studies.

COMMENT NO. 32: Gary Whitmyre, risksciences, LLC (see Comments, C-7, pp.152-153), suggests that the NSRL document for DEHP should be reviewed by an independent committee, namely the Carcinogen Identification Committee, for several reasons. These are the complexity of the toxicology, controversy as to whether there is a threshold in the carcinogenic response, OEHHA’s “new policy” of 10-fold adjustment of the cancer

potency, and a need for further exploration of species differences. The commenter also suggests that “all interested parties” should have input into the selection of key scientists to be included in a review process.

Response: As required by 22 CCR Section 12705 (b) (2), the NSRL document was sent to the Carcinogen Identification Committee for review during the public comment period. This constitutes a review as suggested by the commenter. OEHHA routinely evaluates complex and controversial toxicological problems, so these factors alone are not a justification for review beyond the internal and public review the NSRL document has received as required under 22 CCR Section 12705(b)(2). The 10-fold adjustment to the cancer potency is not a “new policy,” rather, an adjustment which is scientifically justifiable based upon the available data. Species differences have been addressed explicitly in the NSRL document and in regulation [22 CCR Section 12703(a)]. These differences drawn from the extensive published data form the basis for the potency adjustment just mentioned. In the course of developing the NSRL document for DEHP, OEHHA did not identify a compelling need to depart from the review process currently in place for the set of chemicals for which NSRLs are being promulgated. Since there is a public review process, “all interested parties” and any “key scientists” they identify are already eligible to participate in the review process.

LEAD, LEAD ACETATE, LEAD PHOSPHATE, LEAD SUBACETATE

C-3 = Lead Industries Association, Inc. (King and Spalding)

C-5 = Health Risk Consultants, Inc.

C-6 = International Lead Zinc Research Organization, Inc. (ILZRO)

C-8 = Battery Council International

COMMENT NO. 33: International Lead Zinc Research Organization, Inc. (ILZRO) (see Comments, C-6, p.132) in comments also endorsed by Lead Industries Association, Inc. (King and Spalding) (see Comments, C-3, pp.54-55) and Battery Council International (see Comments, C-8, p.155-156), expressed concerns regarding the adequacy of the discussion of the epidemiological evidence for the carcinogenicity of lead and lead compounds in the NSRL document, OEHHA (2001c), and in the Initial Statement of Reasons. They stated that the document needs to be updated with more recent information and that the totality of the evidence suggests that the kidney, a target of lead-induced carcinogenicity in animals, is not a target in humans.

Response: As outlined in the NSRL document, while not all epidemiological studies have shown an increase in kidney cancer among subjects exposed to lead, one set of workers has shown an association between kidney cancer risk and lead exposure. An original cohort study of almost 2000 lead smelter workers published in 1985 [Selevan SG, Landrigan PJ, Stern FB, Jones JH. 1985. Mortality of lead smelter workers. *Am J Epidemiol* **122**(4):673-83] showed an excess of kidney cancers which persisted in a follow-up study published in 1992 [Steenland K, Selevan S, Landrigan P. 1992. The mortality of lead smelter workers: an update. *Am J Public Health* **82**(12):1641-4]. These workers were exposed to other metals that cause cancer, namely arsenic and chromium,

but neither of these metals is known to cause kidney cancer. The Selevan *et al.* and the Steenland *et al.* reports are limited by the availability of detailed data on the exposure levels of the smelter workers to lead. Overall, the current evidence regarding a specific association between kidney cancer and lead exposure in humans is not conclusive. However, as with many carcinogens, there is not an expectation that cancer will necessarily develop in humans at the same site as that observed in experimental animals, in this case kidney. As discussed in the NSRL document, sites reported with increased cancer risk in humans from lead exposure include the lung, kidney, gastrointestinal tract, and brain. A lack of understanding of the mechanism by which lead causes cancer precludes a determination that the kidney is the only organ at risk in humans. For this reason, OEHHA does not limit its carcinogenicity concern for human exposure to lead compounds to cancer of the kidney.

Several relatively recent studies were identified by the commenter, including Anttila *et al.* (1995), Gerhardsson *et al.* (1995), Lundstrom *et al.* (1997), Englyst *et al.* (2001) and Wong and Harris (2000). The commenter also cited an unpublished personal communication by Englyst *et al.* which further characterized the identification of arsenic as a confounder in the studies of smelter workers also exposed to lead.

The commenter's characterization of these additional studies is largely accurate, although it is a selective set of study descriptions and the overall conclusion that kidney is not a target of carcinogenic action in humans cannot be made based on the available data. To the contrary, a recent review not cited by the commenter of the epidemiological evidence stated that "kidney cancer remains a concern" in humans [Steenland K, Boffetta P (2000). Lead and cancer in humans: where are we now? *Am J Ind Med* 38(3):295-9]. The suggestion that the section of the document on human studies should be updated has been considered; however, the extensive characterization of information which has little value for the development of a safe harbor is not warranted. The citations for the additional studies identified by the commenter (as well as a few which were not identified) will be added to this section, although OEHHA's conclusions regarding the usefulness of these studies in the development of an NSRL remain unchanged.

OEHHA agrees that excess cancers observed in some studies of workers exposed to lead may be confounded by exposures to other carcinogenic chemicals. However, the presence of confounding does not necessarily rule out a carcinogenic effect of lead exposure, and it contributes to the difficulty in making quantitative estimates of cancer risk from lead exposure. OEHHA maintains that there is epidemiological evidence for an association between lead exposure and cancer, but this evidence is not presently useful for the development of a no significant risk level for lead or lead compounds under Proposition 65.

COMMENT NO. 34: ILZRO (see Comments,C-6, p.132) stated that the NSRL document should contain greater detail of the key animal studies of lead compounds, particularly those which may dictate more appropriate methods of establishing the dose-response relationship.

Response: OEHHA has considered the mechanistic information which is in the scientific literature, including data in the primary bioassays which formed the basis of the NSRLs. The mechanistic data have not provided a convincing demonstration of which of several proposed mechanisms of action is responsible for the development of kidney cancer in experimental animals. Without a clear understanding of which processes govern the development of tumors or influence carcinogenic risk (the mechanism(s) of action), a departure from default assumptions, *i.e.*, low-dose linearity and the application of the linearized multistage model, is not warranted.

COMMENT NO. 35: ILZRO (see Comments, C-6, pp.139, 141-142) questions the interpretation of the studies by Azar *et al.*, suggesting that diagnostic criteria have changed since the studies were conducted and that the tumors called “adenomas” in the original study may mean “focal hyperplasia” by current criteria. The commenter suggests that this has resulted in an over-estimate of the cancer potency for lead from this study, and that the sex-specificity of the response suggests the tumors may have been associated with the aging male rat kidney. The commenter further states that the response data from this study are non-linear and should be modeled with a log-probit model.

Response: OEHHA is not aware of any publications which have described the changes in diagnostic criteria such that the renal adenomas described in the 1973 Azar *et al.* studies could be reasonably expected to be diagnosed as focal hyperplasia by criteria in use today. OEHHA does not have a reason to believe that the tumors described in the Azar *et al.* studies were misdiagnosed. As to the possibility that the kidney tumors in the male rats may have been associated with the aging male rat kidney, OEHHA expects that if this were the case for the renal tumors induced by lead compounds, there would be a consistent sex difference in the induction of renal tumors in the rats. While there is notable sex difference in cancer potency in the Azar *et al.* study, the potencies derived from other studies do not bear this out (*e.g.*, the studies by Van Esch (1962)). Further, the studies by Van Esch and Kroes (1969) – summarized in the NSRL document – describe kidney tumors in male mice as well, further indicating that the carcinogenic effects are not specific to the male rat kidney. As to the commenter’s suggestion that the data should be modeled using a log-probit model, non-linearity in a dose-response relationship alone is not a clear rationale for selecting a probit model over the linearized multistage model which was used in the potency calculations in the NSRL document. The multistage model is non-linear (it incorporates a polynomial function in dose) and provided an adequate fit to the available data in the lead studies. OEHHA also has no evidence that the underlying assumptions in the log-probit model are met in the case of lead carcinogenicity; that is, that animals have a threshold response to lead and that there is a distribution of these thresholds among animals.

COMMENT NO. 36: ILZRO (see Comments, C-6, pp.139-140) was “surprised” by OEHHA’s reliance on the Van Esch (1962) studies for deriving a cancer potency for lead since they only included two doses and did not distinguish between kidney adenomas and carcinomas, the diagnosis of adenomas is questionable, and the modest increase in tumors between doses is not “commensurate” with the increase in dose.

Response: OEHHA did not rely on a single study for development of the NSRLs for lead compounds. The NSRLs were calculated from the mean value of cancer potencies derived from several studies. Also, OEHHA determined that, due to the non-linearity in the dose response relationship, studies conducted in the high dose range were less relevant than studies conducted in the low dose range, and were excluded. Because the potencies derived from individual studies varied significantly and the more sensitive sex or route could not be identified, OEHHA determined the most scientifically appropriate approach was to derive the NSRL from the geometric mean. As was the case with the tumors described in the Azar *et al.* studies, OEHHA does not have evidence that the tumors in the Van Esch (1962) studies were misdiagnosed. Since kidney adenomas have the potential to progress to carcinomas, both adenomas and carcinomas combined can reasonably be used for quantitative risk assessment, and lead has been shown to induce both types of tumors. It should be noted that in the Van Esch (1962) studies, the low- and high-dose experiments were conducted for different experimental lengths – the low-dose experiment for 126 weeks and the high-dose experiment for 104 weeks. While the difference between the tumor incidences between doses in these studies was small, the additional time of observation in the low-dose group provides at least a partial explanation for the lack of difference. The high-dose studies of Van Esch (1962) were not used in developing the potency estimates because of concerns that they were conducted at relatively high doses and may not be as readily predictive of the risks at low levels of exposure as studies conducted at lower doses.

COMMENT NO. 37: ILZRO (see Comments, C-6, pp.140-142) suggests that the studies of Fowler and Lipsky (1999) show a possible threshold in the 50 ppm dose group for lead-induced tumorigenicity. The commenter suggests that the aging male rat syndrome combined with the mitogenicity of lead compounds accounts for the kidney tumor response. The commenter states that the “induction of renal cancer in the rat is generally believed to proceed via a nongenotoxic process that exhibits a highly nonlinear if not thresholded, dose-response.” This is supported by the Fowler and Lipsky data regarding cell turnover and “putative preneoplastic changes” which occur only above 50 ppm. The commenter concludes that this mode of action suggests a threshold mechanism and is inconsistent with a linear low dose response relationship.

Response: OEHHA agrees that the data from the Fowler and Lipsky (1999) studies show a possible threshold in the 50 ppm dose group; however, these data are also consistent with a low-dose linear or non-threshold dose-response relationship. That is, these bioassay data do not show that the rats in this dose group are not at increased risk of kidney cancer from exposure to lead. The next highest dose group, 250 ppm, showed a total of five kidney tumors among the male rats. If a linear, rather than threshold, relationship between dose and cancer risk were operative, only one tumor would be expected among the rats in the 50 ppm group. The difference between the observed and expected tumor incidence is within a statistical confidence range for a group of animals this size if a linear/non-threshold relationship is assumed. Since the mechanism by which lead compounds cause kidney cancer is not known, the approach used is the default: non-threshold. As noted above, evidence for the development of kidney tumors in both male

and female rats as well as male mice precludes a conclusion that “aging male rat syndrome” is specifically responsible for the carcinogenicity of lead compounds. While OEHHA agrees that the dose-response relationship is somewhat sub-linear, particularly in the multi-dose Azar *et al.* studies, the multistage model, which was fit to the data in these studies, readily accommodates such data, as is indicated by the Goodness-of-Fit statistic ($p \leq 0.05$).

COMMENT NO. 38: ILZRO (see Comments, C-6, p.141) states that the complexity of the pharmacokinetics of lead is offered as a justification for linearity in the dose-response relationship.

Response: OEHHA has not offered the complexity of the pharmacokinetics as a justification for the use of a linear model in describing the dose-response relationship, but rather the failure of pharmacokinetic models to describe what happens to lead levels with increasing dose at sites within the animals’ bodies that are of concern (*e.g.*, the kidney) as a basis for adjusting dose.

COMMENT NO. 39: ILZRO (see Comments, C-6, p.140-141) suggests that the NSRL document should accommodate the differing bioavailability of various lead compounds. The commenter agrees that water solubility is not a good predictor of *in vivo* bioavailability, but that *in vitro* bioavailability tools are commonly applied in establishing clean-up criteria, such as at Superfund sites, and that “a robust database exists that should be used to adjust any derived cancer estimates for bioavailability.”

Response: The adjustments in use for clean-up criteria at Superfund sites are based upon differences in bioavailability from different soil types. This type of information is of limited usefulness for the estimation of the carcinogenic potency of different lead compounds. OEHHA conducted a thorough literature search but did not locate in the published literature specific data on bioavailability upon ingestion of different lead compounds that would provide a more confident assessment of the cancer risks from exposure to different lead compounds. In the NSRL document OEHHA acknowledges that, “[s]ince the estimation of risk in this assessment is based upon studies conducted with relatively highly absorbed lead compounds, the cancer potencies derived here are expected to be larger (on lead bases) than those for lead compounds which are less well absorbed.”

COMMENT NO. 40: ILZRO (see Comments, C-6, pp.142-143) introduces the hypothesis raised by Goyer in 1993 that the cystic changes and nephropathy caused by lead compounds may be responsible for the kidney tumors. A review by ATSDR in 1999 notes the possibility that the development of kidney tumors in experimental animals by lead compounds may not be relevant to humans.

Response: In the review article, Goyer discusses the context of the findings of kidney tumors in experimental animals, stating that “renal carcinogenicity occurs on a background of promimal tubular cell hyperplasia, cytomegaly and cellular dysplasia” (Goyer RA, Lead toxicity: Current concerns. *Environ Health Perspect*, 100: 177-187,

1993). However, regarding mechanism, Goyer states that among the possible mechanisms (including mutagenicity, nuclear protein effect, promoter activity, cellular proliferation, and cystic hyperplasia), supportive evidence is not complete in any of these cases and mechanisms may not be exclusive. OEHHA agrees that the mechanism of lead carcinogenicity is not understood.

Regarding the relevance of the kidney tumors, the ATSDR (1999) document states that: "...the relevance of chemically-induced male rat kidney tumors to potential carcinogenicity in humans has been questioned." While this statement is true, the kidney carcinogenicity caused by lead compounds has not been demonstrated to involve the mechanism suspected for several other compounds which cause kidney tumors in male rats only (*i.e.*, the mechanism involving alpha-2u-globulin).

COMMENT NO. 41: ILZRO (see Comments, C-6, p.143) questions the findings of the Waalkes *et al.* (1995) studies of lead exposure during development.

Response: The Waalkes *et al.* studies, which demonstrated a possible increased risk of cancer from *in utero* and perinatal exposures to lead, were not used as a basis for estimating the NSRLs for lead and lead compounds. Risks from such exposures were explicitly not considered in the NSRL assessment, but this study raised concerns that the cancer potencies presented in the NSRL document may underestimate risks from such exposures.

COMMENT NO. 42: ILZRO (see Comments, C-6, p.143) states that the discussion of bone metabolism of lead adds little to the document, that the O'Flaherty pharmacokinetic model is not intended for high doses such as those administered to animals in bioassays, and that the relevance of the discussion is not clear. The commenter also mentions that the release of bone lead is independent of systemic lead.

Response: OEHHA recognizes that the O'Flaherty pharmacokinetic model was constructed primarily to inform the relationship between bone and blood lead. It was described briefly in the NSRL document since such types of models may be useful in refining risk estimates. Since long-term exposure to lead compounds will result in the appearance of lead in the bone, and since long-term exposures to lead may also increase cancer risks, this model was considered (and discussed) for its potential in adjusting the cancer potency.

COMMENT NO. 43: Health Risk Consultants, Inc. (see Comments, C-5, pp.121, 124, 127) suggests that the NSRL for lead should be adjusted to provide an additional margin of safety in light of uncertainty associated with carcinogenicity to an unborn child. The NSRL analysis did not consider the effects on the fetus and neonate that were demonstrated in the studies of Waalkes *et al.* (1995). An uncertainty factor was proposed as an appropriate approach to addressing this uncertainty and a factor of ten was proposed for adjustment to the cancer potency.

Response: In the NSRL document, OEHHA described the Waalkes *et al.* study and considered and acknowledged the possibility of increased cancer risk from perinatal exposure to lead and lead compounds. The considerable uncertainty regarding the levels of exposure to the neonatal mice in the study, however, makes placing the carcinogenic risk in the context of the risk from adult exposures extremely difficult to establish with confidence. For this reason and at this time, an additional factor will not be applied to the potency estimate. On-going studies, some of which are identified by the commenter, may permit a more confident estimate of carcinogenic risk from such exposures, and may be considered in future refinements of this assessment.

COMMENT NO. 44: Health Risk Consultants, Inc. (see Comments, C-5, p.122), states that OEHHA suggests that it is “likely” that the cancer slope factor for lead may be underestimated by an order of magnitude.

Response: OEHHA has not stated that it is “likely” that the cancer slope factor is underestimated by an order of magnitude. OEHHA acknowledges that the slope factor “may” be an underestimate when perinatal and *in utero* exposures are considered, but the considerable uncertainties regarding lead exposures in the available study (Waalkes *et al.*, 1995) do not permit a confident assessment of the likelihood that the cancer slope factor developed in the NSRL document is an underestimate and if it is, what the magnitude of the difference is.

COMMENT NO. 45: Health Risk Consultants, Inc. (see Comments, C-5, p.125), suggested that the study of Koller *et al.* (1985) should not be excluded from the NSRL analysis for lead because it supports confidence in the Van Esch (1962) studies. A potency of $0.64 \text{ (mg/kg-day)}^{-1}$ was proposed based on the inclusion of the Koller *et al.* studies.

Response: OEHHA notes that the Koller *et al.* studies were conducted at doses which may have been at the low end of the range of doses that may not show a linear cancer response with increasing dose. While the findings lend qualitative support to the findings of the other studies (with respect to the renal endpoint and with respect to another administration vehicle – drinking water), there was enough uncertainty about the position of this single dose study on the dose-response curve that the potency calculated from the study was excluded from the overall potency used in the calculation of the NSRL.

COMMENT NO. 46: Health Risk Consultants, Inc. (see Comments, C-5, p.126), suggested that, although inhalation is a possible route of exposure to lead compounds, a statement should be included in the NSRL document that no studies by the inhalation route were located in the literature.

Response: The NSRL document states that the safe harbors for lead and lead compounds are intended for oral exposures. Oral studies are most appropriate for the derivation of an oral NSRL. Statements explaining that no inhalation studies were identified in experimental animals and why carcinogenic potency by the inhalation route was not estimated will be added to the NSRL document. The potential applicability of oral

studies for the estimation of inhalation potency and derivation of a corresponding NSRL was not examined, and pharmacokinetic methods for route to route extrapolation were not explored. For this reason OEHHA did not develop an inhalation NSRL.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED DURING THE COMMENT PERIOD OF THE FIRST 15-DAY NOTICE OF MODIFICATIONS TO TEXT OF PROPOSED REGULATIONS (FEBRUARY 11, 2002 – FEBRUARY 27, 2002)

CADMIUM

PH1-1 = National Food Processors Association
PH1-2 = Coalition For Safe Ceramicware
PH1-3 = Michelle Corash, Morrison & Foerster LLP.

COMMENT NO. 47: Three commenters, PH1-1, PH1-2 and PH1-3, commented on OEHHA's deferral of action on cadmium announced in the Notice of Proposed changes issued on February 11, 2002. PH-1 and PH-2 submitted comments in support of OEHHA's rationale for the Maximum Allowable Dose Level (MADL) proposed for cadmium in the Initial Statement of Reasons and objecting to OEHHA's deferral regarding cadmium. PH-3 also commented that the MADL proposed for cadmium should be finalized without further delay. (see Comments, PH1-1, PH1-2 and PH1-3, pp.183-187, 190-195, 197-198).

Response: OEHHA notes these comments. Because OEHHA is proceeding with the final rulemaking for cadmium, further response to the objections for the deferral of cadmium are not necessary.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED DURING THE COMMENT PERIOD OF THE SECOND 15-DAY NOTICE OF MODIFICATIONS TO TEXT OF PROPOSED REGULATIONS (MARCH 29, 2002 – APRIL 16, 2002).

BENZENE

PH2-1 = Alliance of Automobile Manufacturers, technical comments prepared by Dr. Jaroslav J. Vostal

Additional comments prepared by Dr. Jaroslav J. Vostal were submitted by the Alliance of Automobile Manufacturers on April 15, 2002. (Comments, PH2-1). Most of the relevant points in these additional comments had been brought up by a previous commenter (Western States Petroleum Association, commenter C-1 and C-1a) and had also been considered by OEHHA in developing the MADL. Relevant responses to the previous commenter are provided by reference to the comment number.

COMMENT NO. 48: The commenter suggests that changes in nucleated red blood cells (nRBCs) represent an "accelerated maturation" of erythrocytes. "The increased loss of

nucleated red cell precursors represents, therefore, not an adverse response but rather a beneficial acceleration of red blood cell maturation” (see Comments, PH2-1, pp.207, 214).

Response: The disappearance of nRBCs from blood is a maturational process associated with localization of erythropoiesis in the bone marrow. Data on immature granulocytes in the Keller and Snyder (1988, as cited above) paper indicates that this maturational process has not been generally accelerated. Only the immature erythrocytes are decreased in numbers. There is no sign of decreases in immature granulocytes, which would be the case if a general acceleration of maturation were occurring. (See also the response above to COMMENT NO. 2, paragraph 9).

COMMENT NO. 49: The commenter notes that reported changes... “have not been seen in previous or more recent studies from the same laboratory.” (See Comments, PH2-1, p.208).

Response: The commenter discussed studies of colony forming units (CFUs) from the Snyder laboratory. An *in vitro* assay was used to measure CFUs and methodology has developed over the years. A straightforward cell count was used to determine nRBC numbers used as the basis for the MADL. (See also the response above to COMMENT NO. 2, paragraphs 2-3). The Keller and Snyder (1988, as cited above) paper is the only report presenting data on nRBCs in peripheral blood in neonates. Thus there are no direct contradictions or inconsistencies in findings on the endpoint used for MADL development. (See also the response above to COMMENT NO. 4, paragraphs 6-8).

COMMENT NO. 50: It is stated that “The observations have never been replicated or verified by other laboratories.” (see Comments, PH2-1, p.208).

Response: No attempt at replication of this experiment has been undertaken by other laboratories. It is neither a requirement of risk assessment nor a common practice that two identical experiments would be performed in different laboratories to verify an experimental finding. None of the studies reviewed in the benzene Hazard Identification Document has been replicated in a different laboratory. Sensitivity and quality of the study are the main considerations in its use for risk assessment. If a study has been replicated and findings differed between the two replicates, this would be taken into account. Although a replication of the study with *in utero* exposure has not been conducted, benzene continues to be studied for its hematopoietic effects in connection with leukemia induction in adults. Further, benzene exposure has been implicated as a potential risk factor for childhood leukemia and benzene in some studies.

The commenter suggests that replication is required by the “arbitrary interpretation of benzene adversity.” Although a replication would provide verification of the data, it would not influence the interpretation of the effects as adverse.

COMMENT NO. 51: The commenter suggests that pharmacokinetic differences and species differences should be taken into account, and the MADL adjusted accordingly. (see Comments, PH2-1, pp.208-209, 219).

Response: The controlling regulation (22 CCR §12803(a)(6)) provides that “when available data are of such quality that anatomic, physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the assessment.” In the present case there are no pharmacokinetic data on species differences using a maternal-fetal (pregnancy) model. The commenter cites data for humans from a study in adult men. Although qualitative differences in benzene pharmacokinetics could be roughly inferred from work in nonpregnant mice and humans, a quantitative adjustment cannot be made without the appropriate modeling. Thus, the pharmacokinetic data are not of the quality required by the regulation.

COMMENT NO. 52: The commenter states that “erythroid progenitor cells ... are the least sensitive type of cell in hematotoxicity of high benzene exposures of adult humans” (see Comments, PH2-1, p.216)

Response: This argument is not based on empirical data, but rather on the relative half-lives of various blood cell types in peripheral circulation. Empirical data provided by Farris et al. (1997, as cited above) demonstrated that nRBCs were the first population affected when adult male mice were exposed to 100 ppm benzene. Further, it is important to clarify that erythroid *progenitor* cells were not the cell type studied by Keller and Snyder (1988, as cited above) but rather erythroid *precursor* cells. Thus, comments discussing the sensitivity of erythroid progenitor cells are not directly relevant to the MADL (see COMMENT NO. 2, paragraph 3).

COMMENT NO. 53: The commenter also states that “[t]he authors erroneously assumed that ‘actively expanding cells of the developing hematopoietic system’ should be the most sensitive model for demonstrating the ‘in utero’ effect of low benzene exposure.” (See Comments, PH2-1, p.218).

Response: The commenter implies that other models would have been more sensitive. This suggests that the NOEL for this effect may actually be lower, but does not challenge the validity of the NOEL that is available from Keller and Snyder (1988, as cited above). The commenter’s account of developmental production of blood cells (hematopoiesis) is not up-to-date since it does not include work on the early stages of definitive hematopoiesis occurring between yolk sac and hepatic stages in nonlocalized areas of the embryo containing hematopoietic stem cells beginning on or about gestation day 10 (Medvinsky et al., 1998) [Development of the definitive hematopoietic hierarchy in the mouse. *Dev Comp Immunol* **22**, 289-301].

CADMIUM

PH2-2 = Center for Ethics and Toxics

PH2-3 = Roger Carrick on behalf of the American Environmental Safety Institute (April 12, 2002 and April 16, 2002)

Comments identified for reference as PH2-3 were submitted by the same commenter who also submitted comments C-9 and C-9a.

COMMENT NO. 54: Comment PH2-3 consists of a set of primary comments and two attachments to it, all submitted on April 12, 2002, and one set of supplemental comments, submitted April 16. The primary comments comprise sixteen pages (see Comments, PH2-3, pp.240-255). The first attachment comprises copies of slides presented by OEHHA staff to the DART Committee at its meeting of December 4, 1996 (see Comments, PH2-3, pp.257-262). The second attachment is a copy of the *curriculum vitae* of Dr. Richard P. Weeden. (see Comments, PH2-3, pp. 266-289). The supplemental comments of April 16, consists primarily of e-mail correspondence and a re-statement of some information contained in prior submissions. (See Comments, PH2-3, pp.230-238)

Response: The two attachments to the April 12 comments are referred to only in footnotes indicating that they are provided as references. Thus, no further responses to these sections are required. The April 12 comments are summarized below in the order in which they appear, with responses immediately following; this is then followed by summary and responses to the April 16 supplemental comments.

COMMENT NO. 55: The commenter begins by reviewing the statutory and regulatory bases for addition of cadmium to the Proposition 65 list of chemicals known to cause reproductive toxicity, quoting passages from the Act and from the Initial Statement of Reasons for 22 CCR §12803(a) and 22 CCR §12803(a)(4). (Comments, PH2-3, pp.240-242).

Response: There are no factual errors in the commenter's initial review of the statute and regulations.

COMMENT NO. 56: The commenter then offers the following interpretation of a quoted passage from the Initial Statement of Reasons for 22 CCR §12803(a)(4):

“Clearly the focus of 22 CCR §12803(a)(4) is on ‘the most sensitive’ study. Sufficient quality is noted, but the emphasis is on ‘the most sensitive of the studies’ of sufficient quality, which is likely to be a study of the ‘most sensitive animal species’.” (see Comments, PH2-3, p.243).

Response: The relevant passage of the regulation states that “the NOEL shall be based on the most sensitive study *deemed to be of sufficient quality*” (emphasis added) (22 CCR §12803 (a)(4)). The passage in the Initial Statement of Reasons for 22 CCR §12803 (a)(4) quoted by the commenter states that “Paragraph (a)(4) provides that the analysis should be based upon the most sensitive of the studies *which ... are deemed to be of sufficient quality*.” (emphasis added). Thus, the regulation clearly requires that a study

must be “of sufficient quality” to serve as the basis for setting the MADL. Therefore, it is of little use to argue one is “more important” than the other.

COMMENT NO. 57: The commenter states that “as a general proposition, then, to be used in setting a MADL, a study must have been used pursuant to 22 CCR §12803(a)(1) to make the initial reproductive toxicant identification.” (See Comments, PH2-3, p.243).

Response: OEHHA cannot agree with the commenter’s interpretation of 22 CCR §12803(a)(1). That provision of the regulation provides in pertinent part as follows: “Only studies producing the reproductive effect which provides the basis for the determination that a chemical is known to the state to cause reproductive toxicity shall be utilized for the determination of the NOEL.” Thus, the regulation requires that the listing and the MADL be based on the same endpoint. Chemicals may be added to the Proposition 65 list on the basis of developmental toxicity, male reproductive toxicity, female reproductive toxicity or any combination of those three endpoints. 22 CCR §12803(a)(1) further provides that the NOEL [which forms the basis for the MADL] must be for the reproductive effect for which studies provide the lowest NOEL. The lowest NOEL from a study of sufficient quality is provided by the developmental toxicity study of Ali et al. (1986, as cited above); hence, the MADL is based on developmental toxicity rather than male reproductive toxicity. The regulation does not require that a particular study must have been used as the basis for the listing in order to be used as the basis for setting a MADL.

Further, since both the study used by OEHHA as the basis for the MADL (Ali et al., 1986, as cited above) and the study proposed by the commenter as the basis for a MADL (Baranski et al., 1983, as cited above) were considered by the DART Committee in its decision to add cadmium to the Proposition 65 list, this comment would be of no relevance here even if it were accurate. Finally, the commenter’s view is also directly contradicted by the language of the Act, the pertinent section of the implementing regulation and the Initial and Final Statements of Reasons for the regulation:

The warning requirement does not apply to “an exposure for which the person responsible can show that ... the exposure will have no observable effect assuming exposure at one thousand (1,000) times the level in question for substances known to the state to cause reproductive toxicity, based on evidence and standards of *comparable scientific validity* to the evidence and standards which form the scientific basis for the listing of such chemical ...” (Health and Safety (H&S) Code § 25249.10(c)) (emphasis added)

“The determination of whether a level of exposure to a chemical known to the state to cause reproductive toxicity has no observable effect ... shall be based on evidence and standards of *comparable scientific validity* to the evidence and standards which form the basis for the listing of a chemical as known to the state to cause reproductive toxicity.” (22 CCR §12801(a)) (emphasis added)

“Subsection (a) requires that all risk assessments be based [sic] evidence and standards of *comparable scientific validity* to the evidence and standards which form the basis for the listing of the chemical.” ... “The subsection goes on to provide certain default assumptions or principles which the Agency considers to be ‘generally accepted.’ However, the regulation provides that other assumptions, principles *or data sets* should be used where scientifically more appropriate.” (Initial Statement of Reasons for 22 CCR §12801(a), p. 33) (emphasis added)

“Subsection (a) requires that all risk assessments intended to establish a ‘safe harbor’ no observable effect level within the meaning of the Act be based upon evidence and standards of *comparable scientific validity* to the evidence and standards which form the basis for the listing of the chemical.” (Final Statement of Reasons for 22 CCR §12801(a), p. 70) (emphasis added)

Thus, although not relevant to the development of a MADL for cadmium, it is clear that a study or studies not used in the identification of a chemical as known to the state to cause reproductive toxicity may be used in the development of a MADL, provided that the study or studies meets the requirement of “comparable scientific validity” to the study or studies used for listing. Use in development of a MADL only of studies that had been used to make the initial reproductive toxicant identification would obviously remove the necessity for any comparison of scientific validity between the studies used in the initial identification and those used in MADL development, since they would be inescapably the same.

COMMENT NO. 58: The commenter described the origin and activities of the Agency for Toxic Substances and Disease Registry (ATSDR), and stated that “ATSDR thus determined that the study entitled [Baranski et al., 1983] found the lowest dose at which the most sensitive indicator of developmental toxicity occurs as a result of the ingestion of cadmium in animals.” The commenter went on to assert that OEHHA may not ignore its own prior findings regarding this same Baranski study, especially in light of precisely the same findings made by a federal agency applying the same criteria. The commenter also states that OEHHA previously relied upon the same Baranski study in OEHHA’s own recommendation to the DART Committee. These assertions are prefaced by a reference to application of H&S Code § 25249.10(c) and especially H&S Code § 25249.8(b), as interpreted by *Western Crop Protection Assn. V. Davis*. (See Comments, PH2-3, pp.243-244).

Response: As noted above in response to an earlier comment by the same commenter, OEHHA agrees that the Baranski et al. (1983, as cited above) study reports an association between maternal oral exposure to cadmium and neurobehavioral effects on offspring at doses which are lower than those reported by other investigators (see response to COMMENT NO. 15, paragraph 1). There are, however, several factual errors in the commenter’s other assertions. OEHHA summarized for the DART Committee’s review all of the known and available relevant data pertaining to the potential for cadmium to cause developmental and reproductive toxicity, in the document “Evidence on Developmental and Reproductive Toxicity of Cadmium” (OEHHA, 1996) [Evidence on

Developmental and Reproductive Toxicity of Cadmium]. This document is generally referred to as a Hazard Identification Document (HID). However, OEHHA made no recommendations to the DART Committee with regard to use of individual studies or any other aspect of the listing decision for cadmium either in that HID or in any other context. The data summarized included the study by Baranski et al. (1983, as cited above), the study by Ali et al. (1986, as cited above) that forms the basis for the MADL, and numerous other studies. The DART Committee members conducted a weight-of-evidence review of all the available information and concluded, by five affirmative votes to one negative vote, that cadmium had been clearly shown to cause developmental and male reproductive toxicity. No specific endpoints of developmental toxicity were identified as the basis for the Committee's conclusion, nor were any study or studies so identified. Thus, the commenter's statement that OEHHA relied upon the Baranski et al. study in its recommendation to the DART Committee appears to have no factual basis.

Similarly, the assertion that OEHHA made "prior findings" with regard to the Baranski et al. study, and that these findings should be viewed in light of "precisely the same findings made by a federal agency applying the same criteria" is also without factual basis. The determination by the DART Committee that cadmium had been clearly shown to cause developmental and male reproductive toxicity constitutes identification of a hazard. Hazard identification is the first step of risk assessment in the standard four-step model developed by the National Academy of Sciences (NAS, 1983) [Risk Assessment in the Federal Government: Managing the Process]. In this four-step model, dose-response assessment is the second step. Although the dose-response relationship between a chemical and the manifestations of its toxicity may be taken into account in hazard identification, quantitative dose-response assessment (i.e., determination of the doses at which no effect or the lowest observable effect are manifested) does not occur in the context of Proposition 65 until a chemical has been added to the list of chemicals known to the state to cause reproductive toxicity. As discussed above (see response to COMMENT NO. 56), 22 CCR §12803 (a)(4) clearly recognizes that some studies may not be of sufficient quality to serve as the basis for a MADL; any other interpretation renders meaningless the subsection which reads "the NOEL shall be based on the most sensitive study *deemed to be of sufficient quality*" (emphasis added). The simple consideration of a study in the weight-of-evidence hazard identification process in no way constitutes a "prior finding" that the study is of sufficient quality to serve as the sole basis for a quantitative dose-response assessment. This is in addition, of course, to the fact that there is no basis for concluding that the DART Committee based its decision solely or even in part on the Baranski et al. (1983, as cited above) study, as discussed in the preceding paragraph.

COMMENT NO. 59: The commenter also asserts that ATSDR made "precisely the same findings ... applying the same criteria"; this assertion is represented by the commenter to be supported by application of H&S Code § 25249.10(c) and especially § 25249.8(b), as interpreted by *Western Crop Protection Assn. v. Davis*. (see Comments, PH2-3, p.244). The pertinent section of *Western Crop Protection Assn. v. Davis* (p. 749) is identified by the commenter in a footnote (see Comments, PH2-3, p.242) where the commenter interprets the court opinion as "the court found that the federal and California standards

for utilization of animal studies in making the reproductive toxicant determination were the same.”

Response: The pertinent section of the court opinion is as follows:

“..the statutory standard for inclusion of a chemical on the TRI [Toxic Release Inventory] list is satisfied by sufficient evidence, based on generally accepted scientific principles or laboratory tests, or appropriately designed and conducted epidemiological or other population studies to establish the chemical is ‘known to cause or can reasonably be anticipated to cause’ reproductive toxicity in humans. (42 U.S.C. § 11023(d)(2)). Thus, the federal standard, ‘known to cause,’ is the same as the California standard.”

The section of the U.S.C. cited by the court authorizes addition of chemicals to the TRI list by the Administrator of the U.S. Environmental Protection Agency (U.S. EPA). No mention is made either directly or by reference in *Western Crop Protection Assn. v. Davis* to ATSDR. It is quite clear from the context of the Court’s opinion and the specific citation to the TRI authorizing statute that the reference to the “federal standard” is specific to the standard applied by U.S. EPA in adding chemicals to the TRI list. Again, that standard is “known to cause or can reasonably be anticipated to cause reproductive toxicity in humans.” There is nothing to indicate that the court intended its reference to “the federal standard” in the middle of a decision dealing with a particular federal agency -- U.S. EPA -- to be applicable to all federal agencies conducting any assessment for any purpose. Nor is there any other factual information identified to support the commenter’s assertion that ATSDR applied the same criteria as OEHHA with regard to identification of cadmium as causing reproductive toxicity. In addition, the court decision related to a formal identification of chemicals as causing reproductive toxicity by a specifically-designated Proposition 65 “authoritative body”, the U.S. EPA. ATSDR is not designated as an authoritative body for purposes of Proposition 65 and, consequently, cannot “formally identify” chemicals as that term is used in H&S Code § 25249.8(b). Thus, the inference drawn by the commenter does not appear to be supported by analysis of the document cited.

With regard to the finding made by ATSDR, both the OEHHA HID (OEHHA, 1996, as cited above) and the ATSDR Toxicological Profile included brief discussions of the Baranski et al. (1983, as cited above) study, primarily identifying the species tested, the route, duration and period of exposure, the effects reported and the levels of exposure at which they were reported to have occurred. (The OEHHA HID contained a typographical error, identifying locomotor effects in the Baranski et al. study to have been reported at a low dose of 0.4, rather than 0.04, mg/kg/day). As noted above, the OEHHA HID did not address quantitative dose-response assessment and made no comment on the suitability of the Baranski et al. (1983, as cited above) or any other study for such a purpose. Similarly, the ATSDR Toxicological Profile noted that the lowest oral exposure shown to cause impaired neurological development was in the study by Baranski et al. (1983, as cited above), but was silent as to the suitability of the study for quantitative dose-response assessment. The result of such a quantitative dose-response

assessment by ATSDR is also reported in its document, but is based on a study conducted by Nogawa et al. (1989) [A dose-response analysis of cadmium in the general environment with special reference to total cadmium intake limit. *Environmental Research* 48: 7-16] of a different endpoint of toxicity rather than on the Baranski et al. (1983, as cited above) study. Thus, neither the ATSDR nor OEHHA documents made any statements regarding the suitability of the Baranski et al. (1983, as cited above) study for use in quantitative dose-response assessment, contrary to the assertion by the commenter.

COMMENT NO. 60: Under the heading “The [American Environmental Safety] Institute’s Prior Participation in the Proposed MADL Listing”, the commenter describes various prior actions by the commenter and his client. (see Comments, PH2-3, pp.244-245).

Response: The previous submissions to and discussions with OEHHA are accurately described. OEHHA has no independent knowledge of other actions described by the commenter and so cannot provide any further response.

COMMENT NO. 61: Under the heading “The Proper Method for Calculating a MADL for Cadmium by Route of Ingestion”, the commenter makes several statements. First, the commenter indicates that he and OEHHA are in agreement as to the method by which the MADL is to be calculated. Second, the commenter reiterates the [American Environmental Safety] Institute’s belief that the Baranski et al. (1983, as cited above) study best meets the standard set forth in 22 CCR §12803(a)(4), referring to discussion of the development of that standard presented earlier in the comments. Third, the commenter discusses OEHHA’s use of the study by Ali et al. (1986, as cited above) as the basis for the MADL, noting that the same developmental toxicity endpoint was found in that study as in the Baranski et al. (1983, as cited above) study but that a different method of oral administration of cadmium and a lower dose level were used and that the Ali et al. (1986, as cited above) study is not the “most sensitive study.” Finally, the commenter submits that OEHHA is erring as a matter of fact and law in not relying on the Baranski et al. (1983, as cited above) study, citing in support of that submission the “applicable legal standard established by *Western Crop Protection Assn. v. Davis* by which to interpret H&S Code § 25249.10(c) and 25249.8(b), for which 22 CCR §12803 is the implementing regulation.” (see Comments, PH2-3, pp.245-246).

Response: With regard to the commenter’s first point, OEHHA agrees that the method for calculating a MADL is set forth specifically in 22 CCR §12803. The commenter’s second point has been responded to earlier (see responses to COMMENTS NO. 56 and 57). With regard to the third point, OEHHA notes that the applicable standard is the most sensitive study of sufficient quality, not the “most sensitive study” (see response to COMMENT NO. 56). The study by Ali et al (1986, as cited above) meets the applicable standard, the study by Baranski et al. (1983, as cited above) does not. The lack of any factual basis for the commenter’s final submission has also been discussed earlier (see response to COMMENT NO. 59).

COMMENT NO. 62: Under the heading “The Most Sensitive Study of Sufficient Quality is the Baranski Study”, the commenter notes that the critical issue is not whether the Baranski et al. (1983, as cited above) study is the “most sensitive”, since OEHHA concedes this to be the case, but rather why OEHHA now finds that this study is not of “sufficient quality” notwithstanding its use to justify the listing of cadmium as a developmental toxicant in 1996. The commenter goes on to list three reasons why he believes OEHHA errs in that decision.

First, the commenter asserts that OEHHA’s current position does not comport with its prior designation of the Baranski et al. (1983, as cited above) study as a key study in OEHHA’s 1996 HID used to advise the DART Committee and thus the Governor, leading to the listing of cadmium in 1996. Slides presented to the DART Committee at its meeting of December 4, 1996 are referenced by footnote in support of that contention.

Second, the commenter claims that OEHHA disregarded ATSDR’s designation of the Baranski et al. (1983, as cited above) study as the lowest dose study demonstrating the altered locomotor behavior which was the key endpoint of developmental toxicity of ATSDR’s findings on cadmium by route of ingestion. In support of this contention, the commenter states that this is done in disregard of the plain language of H&S Code § 25249.8(b).

Third, the commenter reiterates earlier comments interpreting 22 CCR §12803(a)(4) and 22 CCR §12803(a)(1) as compelling OEHHA to use the Baranski et al. (1983, as cited above) study, since it was used in support of OEHHA’s original determination to list cadmium as a developmental toxicant. (see Comments, PH2-3, p.246).

Response: OEHHA does not agree that the Baranski et al. (1983, as cited above) study is the most sensitive. Rather, OEHHA notes that effects were reported at the lowest exposure level, but has concluded the study is not of sufficient quality (see responses to COMMENTS NO. 15 and 73) and that the results are unreliable. As such, the Baranski et al. (1983, as cited above) study is not the most “sensitive” study as that term is used in 22 CCR § 12803(a)(4)

With regard to the first point, as discussed previously, OEHHA did not designate the Baranski et al. (1983, as cited above) study as a “key study” in its 1996 HID (see response to COMMENT NO. 58). The slides referenced by the commenter make no mention of the Baranski et al. (1983, as cited above) study, nor any other individual study. Rather, they provide a brief overview of pertinent information including several specific manifestations of developmental toxicity, one of which was altered locomotor behavior. As noted earlier, both the Ali et al. (1986, as cited above) paper (used as the basis for the MADL) and the Baranski et al. (1983, as cited above) paper reported effects on locomotor activity, as did a number of other studies that are also referenced in OEHHA’s Hazard Identification Document.

With regard to the second point, H&S Code § 25249.8(b) reads as follows:

A chemical is known to the state to cause cancer or reproductive toxicity within the meaning of this chapter [6.6] if in the opinion of the state's qualified experts it has been clearly shown by scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity, or if a body considered to be authoritative by such experts has formally identified it as causing cancer or reproductive toxicity, or if an agency of the state or federal government has formally required it to be labeled or identified as causing cancer or reproductive toxicity.

ATSDR is not the "state's qualified experts." Nor is ATSDR considered to be "authoritative" by the state's qualified experts. 22 CCR § 12306(*l*) designates the four bodies recognized as authoritative for the identification of chemicals as causing reproductive toxicity: the International Agency for Research on Cancer (solely as to transplacental carcinogenicity); the National Institute for Occupational Safety and Health; the U.S. Food and Drug Administration; the U.S. Environmental Protection Agency. ATSDR, as an agency of the federal government, has not formally required cadmium to be labeled or identified as causing reproductive toxicity. Thus, the commenter's statement that OEHHA has disregarded the plain language of H&S Code § 25249.8(b) appears unsupported by an examination of the actual provisions of the statute.

As noted previously, OEHHA agrees that the ATSDR document noted that the lowest oral exposure associated with impaired neurological development was in the study by Baranski et al. (1983, as cited above), but notes that the ATSDR document was silent as to the suitability of the study for quantitative dose-response assessment (see response to COMMENT NO. 59, paragraph 4). Even if ATSDR had identified the Baranski et al. (1983, as cited above) study as a suitable basis for quantitative risk assessment (such as setting a MADL), neither H&S Code § 25249.8(b) nor any other section of the controlling statute and regulations provides legal authority for incorporating such a designation into the development of a MADL.

With regard to the third point, responses to the commenter's interpretation of 22 CCR §12803(a)(4) and 22 CCR §12803(a)(1) have been provided earlier (see responses to COMMENTS NO. 56 and 57). It should be noted, however, that OEHHA made no determination or even recommendation to list cadmium as a developmental toxicant. The listing occurred as a result of the opinion of the DART Committee, the state's qualified experts for the identification of chemicals as causing reproductive toxicity, that cadmium had been clearly shown by scientifically valid testing according to generally accepted principles to cause reproductive toxicity.

COMMENT NO. 63: Concluding the comments under the heading "The Most Sensitive Study of Sufficient Quality is the Baranski Study," the commenter states that both the federal government and OEHHA have previously determined that the Baranski et al. (1983, as cited above) study was of "sufficient quality" to guide both of their respective determinations that cadmium is a developmental toxicant. The commenter goes on to assert that OEHHA may not depart from its own prior designation of the Baranski et al. (1983, as cited above) study as "of sufficient quality" to be relied upon in the prior listing

of cadmium in now reaching the decision of what should be the proper MADL for cadmium by route of ingestion. In support of that assertion, the commenter cites the “express command” of H&S Code § 25249.10(c) and 25249.8(b), as implemented by 22 CCR §12803(a)(1), (3) and (4). The commenter also asserts that OEHHA may not ignore an “authoritative federal agency’s” comparable use of the Baranski et al. (1983, as cited above) study as “the most sensitive indicator of developmental toxicity” at the “lowest exposures shown to cause these effects” in setting the MADL for cadmium. The commenter cites in support of that assertion the interpretation of H&S Code § 25249.8(b) set forth in *Western Crop Protection Assn. v. Davis*. (See Comments, PH2-3, p.247).

Response: These comments largely reiterate others made earlier in this submission. The issue of previous determinations of study quality is addressed in the responses to COMMENTS NO. 58 and 59. The text of H&S Code § 25249.10(c) is cited in the response to COMMENT NO. 57. The commenter provides no explanation here for the assertion that this section of the Act constitutes an “express command” to OEHHA not to depart from its own prior designation of the study by Baranski et al. (1983, as cited above) as “of sufficient quality.” (Again, as explained in response to COMMENT NO. 62, OEHHA made no prior designation of the Baranski et al. (1983, as cited above) study as being of “sufficient quality”). It is therefore assumed that the underlying rationale is that expressed in COMMENTS NO. 57 and 58 (see response to COMMENTS NO. 57 and 58). The commenter’s interpretation of H&S Code § 25249.8(b), stated here to especially provide such an “express command”, is addressed in the response to COMMENT NO. 62 and the interpretation of 22 CCR §12803(a)(1) is addressed in the response to COMMENT NO. 57. 22 CCR §12803(a)(3) specifies that animal bioassay studies used in identification of a NOEL for use in development of a MADL shall meet generally accepted scientific principles, while 22 CCR §12803(a)(4) specifies that the NOEL shall be based on the most sensitive study deemed to be of sufficient quality. The reasons why the study by Baranski et al. (1983, as cited above) does not meet either of these related requirements are discussed extensively in the responses to COMMENTS NO. 15 and 73.

With regard to an “authoritative federal agency’s comparable use” of the Baranski et al. (1983, as cited above) study and the commenter’s interpretation of *Western Crop Protection Assn. v. Davis*, these have also been discussed extensively in prior responses (see responses to COMMENTS NO. 58, 59 and 61).

COMMENT NO. 64: Under the heading “OEHHA Has Previously Recognized the Importance of the Baranski Study”, the commenter states that OEHHA has recognized the Baranski et al. (1983, as cited above) study’s importance in its prior reviews on the reproductive toxicity of cadmium, and goes on to discuss the OEHHA 1996 HID (as cited above) and the OEHHA 1999 Public Health Goal for Cadmium in Drinking Water. The commenter states that the OEHHA 1996 HID specifically identifies the Baranski et al. (1983, as cited above) study as providing important evidence of developmental toxicity, indicating that Dr. Baranski is the most oft-cited author in the document. The commenter also notes that the lowest dosing level found to have statistical significance on the Baranski et al. (1983, as cited above) study was mis-cited by OEHHA. Similarly, the

commenter states that OEHHA again identified the Baranski et al. (1983, as cited above) study as important in the OEHHA 1999 Public Health Goal for Cadmium in Drinking Water, indicating that Dr. Baranski is the second most oft-cited author in the document. The commenter also notes a mis-citation by OEHHA in this document of the lowest dose Dr. Baranski found statistically significant. (See Comments, PH2-3, pp.247-248)

Response: The commenter is correct that typographical errors regarding dose levels were made in both documents. However, since original published papers, rather than the summarized information contained in either of the documents noted, were consulted in MADL development these typographical errors had no influence on the MADL development process (see response to COMMENT NO. 14). The commenter's statement that the OEHHA 1996 Cadmium HID specifically identifies the Baranski et al. (1983, as cited above) study as providing "important evidence" of developmental toxicity is supported only by the commenter's count of how many papers authored by Dr. Baranski were cited in the document. Nowhere in the document is a statement made that the Baranski et al. (1983, as cited above) study provides particularly important evidence of developmental toxicity, nor does the document contain any wording that can fairly be interpreted as having such a meaning. The single paper by Dr. Baranski at issue, Baranski et al. (1983, as cited above), is one of 294 references cited in the OEHHA 1996 Cadmium HID. As noted earlier (see response to COMMENT NO. 58), the OEHHA HID summarized for the DART Committee's review all of the known and available relevant data pertaining to the potential for cadmium to cause developmental and reproductive toxicity. The data summarized included the study by Baranski et al. (1983, as cited above), the study by Ali et al. (1986, as cited above) that forms the basis for the MADL, and numerous other studies. OEHHA recognizes that the contribution of individual studies to the entire body of evidence considered by the DART Committee in its weight-of-evidence hazard evaluation is for the members of the Committee to decide, and OEHHA makes no attempt to influence that decision.

The commenter provides a similar rationale for the statement that OEHHA again identified the Baranski et al. (1983, as cited above) study as important in the OEHHA 1999 Public Health Goal (PHG) for Cadmium in Drinking Water. Both the Baranski et al. (1983, as cited above) and the Ali et al. (1986, as cited above) studies were cited and minimally discussed in the PHG document, but neither was used in the quantitative dose-response assessment. The PHG document was developed to provide estimates of the levels of contaminants in drinking water that pose no significant health risk to individuals consuming the water on a daily basis over a lifetime (OEHHA, 1999, as cited above). The most sensitive endpoint from chronic exposure in the PHG document was determined to be toxicity to the kidney. The PHG was based on human data for this endpoint (Buchet et al., 1990) [Renal effects of cadmium body burden of the general population. *Lancet* 336: 699-702]. This document was not developed for purposes relating to Proposition 65, and does not develop a MADL for reproductive or developmental toxicity for oral exposure to cadmium.

COMMENT NO. 65: Under the heading "The Baranski Paper Has Been Identified by the Federal Government As the Most Sensitive Study of Sufficient Quality on the Key

Endpoint of Developmental Toxicity of Cadmium By the Oral Route of Exposure”, the commenter primarily discusses the interpretation of the Baranski et al. (1983, as cited above) study by ATSDR, and the relevance of that interpretation to the development of a MADL. The commenter prefaces that discussion by stating that there is no reasonable doubt as to the “quality” of Dr. Baranski’s research being “sufficient” for regulatory use by OEHHA. The commenter supports that statement by reference to the arguments addressed above in COMMENT NO. 64. The commenter goes on to state that “the only question, then, is whether Baranski’s paper is the ‘most sensitive study deemed to be of sufficient quality’ as required by 22 CCR §12803(a)(4), which must be read to interpret H&S Code § 25249.8(b), which in turn requires the Governor (and thus OEHHA) expressly to utilize a federal agency’s science and findings if the ‘federal agency has formally required [the chemical] to be labeled or identified as causing cancer or reproductive toxicity’.” (see Comments, PH2-3, pp.248-249)

Response: These comments largely reiterate others made earlier in the submission. The interpretation of the Baranski et al. (1983, as cited above) study by ATSDR, and the relevance of that interpretation to the development of a MADL have been addressed in the responses to COMMENTS NO. 58, 59 and 62. The commenter’s statement that “OEHHA [is] expressly [required] to utilize a federal agency’s science and findings if the ‘federal agency has formally required [the chemical] to be labeled or identified as causing cancer or reproductive toxicity’” does provide a clarification of a comment made earlier (see COMMENT NO. 62). OEHHA disagrees with the commenter’s assertion that 22 CCR §12803(a)(4) must be read to interpret H&S Code § 25249.8(b). Section 25249.8(b) concerns the various mechanisms by which chemicals may be added to the Proposition 65 list. 22 CCR §12803 was not adopted to implement this provision of the Act. The lead agency did not cite H&S § 25249.8 as either authority or reference for the adoption of 22 CCR §12803.

In addition, the provision of H&S Code § 25249.8(b) that “a chemical is known to the state to cause cancer or reproductive toxicity within the meaning of this chapter if ... an agency of the state or federal government has formally required it to be labeled or identified as causing cancer or reproductive toxicity” must be viewed in light of its implementing regulation, 22 CCR §12902. That regulation provides controlling definitions for several terms used in the relevant portion of H&S Code § 25249.8(b). The critical definition is as follows:

“‘has formally required’ means that a mandatory instruction, order, condition, or similar command, has been issued in accordance with established policies and procedures of an agency of the state or federal government, to a person or legal entity outside of the agency. The action of such agency may be directed at one or more persons or legal entities and may include formal requirement of general application.” (22 CCR §12902(b)(3)).

The commenter has offered no evidence that ATSDR has issued such a mandatory instruction, order, condition, or similar command, or indeed that ATSDR has any authority to do so. OEHHA is aware of no such action or authority on the part of

ATSDR. Thus, although the commenter's statement is factually correct in the broad sense, it is clearly inapplicable to the present situation. Further, even if ATSDR had issued such a mandatory instruction, order, condition, or similar command, this would provide a basis for addition of cadmium to the Proposition 65 list, had it not already been listed, but would have no bearing on development of a MADL.

The meaning and relevance of the commenter's statement that there is no reasonable doubt as to the "quality" of Dr. Baranski's research being "sufficient" for regulatory use by OEHHA is unclear. In the context of development of a MADL for cadmium by the oral route, OEHHA has deemed the study by Baranski et al. (1983, as cited above) not to be of sufficient quality, as that term is used in 22 CCR §12803(a)(4) (see responses to COMMENTS NOS. 15 and 73); OEHHA has neither offered nor formulated an opinion of Dr. Baranski's research beyond consideration of this particular study for this specific purpose. If the comment is intended to refer to regulatory uses in other contexts such as hazard identification, the use of the Baranski et al. (1983, as cited above) study for such a purpose has been addressed earlier (see responses to COMMENTS NO. 57 and 58), and the use of any others studies by Dr. Baranski for such a purpose should be viewed in the same light. The earlier arguments referred to by the commenter are addressed in the response to COMMENT NO. 64.

COMMENT NO. 66: Under the heading "The Baranski Paper Is Of a Higher Quality Than the Ali Study", the commenter suggests that the gavage method of oral administration used by Baranski et al. (1983, as cited above) is superior to the drinking water administration used by Ali et al. (1986, as cited above), citing oral comments from Dr. Richard Weeden made to OEHHA in a teleconference of January 29, 2002. The commenter goes on to note that in the Ali et al. (1986, as cited above) study animals were dosed with cadmium only during the gestation period, while in the study by Baranski et al. (1983, as cited above) rats were dosed for five weeks prior to pregnancy as well as throughout gestation. The commenter states that this is an important difference because cadmium is a cumulative poison, citing the ATSDR 1999 Toxicological Profile for Cadmium. (see Comments, PH2-3, pp.249-250)

Response: Consistent with the Initial Statement of Reasons for 22 CCR §12803(a)(4) which provides that "the analysis should be based upon the most sensitive of the studies which ... are deemed to be of sufficient quality", OEHHA did not directly compare the quality of the Baranski et al. (1983, as cited above) study with that of the Ali et al. (1986, as cited above) study. Rather, the method of cadmium administration was taken into account as part of the independent assessment of study quality conducted for each of these studies. Both gavage and drinking water methods of oral administration are considered acceptable (U.S EPA, 1996a) [U.S. Environmental Protection Agency. Health Effects Test Guidelines OPPTS 870.3700 Prenatal Developmental Toxicity Study. 1996], (U.S. EPA, 1996b) [U.S. Environmental Protection Agency. Health Effects Test Guidelines OPPTS 870.3E00 Reproduction and Fertility Effects. 1996]. Administration of a test substance throughout the gestational period, as was done in the study by Ali et al. (1986, as cited above), is entirely consistent with generally accepted scientific principles (e.g., U.S. EPA 1996a,b, as cited above). The statement in the

ATSDR document concerning cumulative toxicity is explicitly made in the context of concern over long-term exposure to elevated levels in the diet, and not with respect to gestational exposures of the developing conceptus.

COMMENT NO. 67: The commenter, under the same heading as in COMMENT NO. 66, goes on to compare the use of both male and female pups by Baranski et al. (1983, as cited above) with the use of only male pups by Ali et al. (1986, as cited above); the behavioral assessment techniques used in both studies; and the methods of selection of pups for testing. The commenter also provides a footnote citing Dr. Baranski's submission of additional information in response to questions posed by OEHHA with regard to relevant information not contained in the paper by Baranski et al. (1983, as cited above), and his re-interpretation of Dr. Baranski's response. (Comments, PH2-3, p.250)

Response: As noted in the response to COMMENT NO. 66, OEHHA did not directly compare the quality of the Baranski et al. (1983, as cited above) and the Ali et al. (1986, as cited above) studies. With regard to use of male and female pups or male pups only, empirical demonstration of toxicity in either or both sexes may serve as the basis for a MADL. Similarly, OEHHA considers both behavioral assessment methodologies acceptable. With regard to the methods of selection of pups for testing, in this parameter the Ali et al (1986, as cited above) paper provided sufficient information to determine that an appropriate procedure was used, while the paper by Baranski et al. (1983, as cited above) did not, as discussed in the response to COMMENT NO. 15. The commenter mis-quotes the Ali et al. (1986) study as stating that "Batches of 10 male pups drawn by littermate control were used". In fact, the paper states that "Different batches of 8-10 male pups, drawn at random by littermate control, were used for the developmental and behavioral evaluation by observers unaware of the treatment schedules. Care was exercised for minimal handling of the pups." The accurate quotation reflects the acceptable quality of the Ali et al. (1986, as cited above) study in terms of study design, conduct and reporting.

The commenter's footnote is superseded by the additional submission by the commenter noted above (see COMMENT NO. 54). This submission is discussed below (see response to COMMENT NO. 73).

COMMENT NO. 68: The commenter completes this section of his comments by stating Dr. Weeden's opinion that the limitations of the Ali et al. (1986, as cited above) study he described previously do not warrant discarding that study, but that the Baranski et al. (1983, as cited above) study is the more sensitive of the two studies. He further states Dr. Weeden's opinions on the appropriateness of using the lowest dose at which adverse effects were found to protect the human population. The commenter also inserts an extensive footnote discussing Dr. Weeden's opinion that the acceptable limit on cadmium determined by either the Baranski et al. (1983, as cited above) or the Ali et al. (1986, as cited above) study is too high to protect the kidneys from damage due to environmental cadmium. The commenter states that the ATSDR "minimum risk level" [MRL] for ingested cadmium is 0.000075-0.00013 mg/kg/day, which translates in the middle of the

range for a 10kg infant into 1.025 µg/day. Dividing this by 1,000, the commenter arrives at a figure of a 0.001025 µg/day MADL to protect the kidneys of an infant consuming cadmium through ingestion. The commenter also states that although OEHHA must act under Proposition 65, it should be sensitive to the ultimate health effects of its decision under any statute. (See Comments, PH2-3, p.251)

Response: OEHHA agrees that the study by Ali et al. (1986, as cited above) should not be discarded. As noted above, OEHHA has concluded that the study by Baranski et al. (1983, as cited above) is not of sufficient quality to serve as the basis for a MADL (see responses to COMMENTS NO. 15 and 73). In establishing the MADL, OEHHA is guided by the controlling regulation, 22 CCR §12803(a)(4), which specifies that the NOEL shall be based on the most sensitive study deemed to be of sufficient quality. The issue of toxicity of cadmium to the kidney and the perceived lack of protectiveness of the MADL value was raised in a previous comment (see response to COMMENT NO. 13). The lack of relevance of that endpoint to Proposition 65 was also addressed in the response to COMMENT NO. 13. OEHHA's implementation of the Proposition 65 statutes must comport with the statutory and regulatory provisions of the Act. Thus, OEHHA has no authority to make Proposition 65 regulatory decisions based on considerations outside the scope of the law it is implementing.

There are a number of factual errors in the commenter's argument that lead to an erroneous conclusion with regard to the protectiveness of the MADL for kidney toxicity. The ATSDR MRL is 0.0002 mg/kg/day, as correctly noted in COMMENT NO. 13. The range of 0.000075-0.00013 mg/kg/day cited here by the commenter as the MRL is reported by ATSDR as having been arrived at through an alternative procedure investigated for ATSDR by a private consulting group. ATSDR has not adopted those values. The values of 0.000075-0.00013 mg/kg/day were explicitly based on 70 years of daily exposure. Application of this value to a hypothetical 10 kg infant is both scientifically and legally inappropriate; not only is the modeled exposure period entirely inconsistent with the possible age range of a 10 kg infant, but also the relevant developmental exposure period under Proposition 65 is limited to the period prior to birth. The appropriate body weight to apply to the value at the middle of the range, using the logic proposed by the commenter, would be 58 kg (for an adult woman), resulting in a value of 5.9 µg/day. This may be compared to the MADL of 4.1 µg/day. The commenter's division of his incorrectly-derived value by 1,000 to arrive at a MADL to protect the kidneys of an infant consuming cadmium through ingestion also represents a misunderstanding of the applicability of that 1,000-fold factor. The 1,000-fold factor represents the difference between a level of exposure at which a warning is required, and a level of exposure at which there would be no observable effect (H&S Code § 25249.10(c)). Thus, had the MRL value for kidney toxicity of cadmium in infants been appropriately calculated, it would be protective of that effect (i.e. there would be no observable effect at that level of exposure) and should not be divided by 1,000. The range of values cited by ATSDR already incorporates an uncertainty factor of 10 to account for variability in the human population.

COMMENT NO. 69: Under the heading “The Baranski Study Should be Used to Calculate the MADL for Cadmium by The Route of Ingestion”, the commenter reiterates his opinion that OEHHA cannot depart from its prior application of Proposition 65 regulatory science in the listing decision in determining which study should guide the MADL, referring again to his interpretation of H&S Code § 25249.10(c) and *Western Crop Protection Assn. v. Davis*. The commenter then describes his interactions with Dr. Baranski and his colleagues. (see Comments, PH2-3, pp.251-252)

Response: The commenter’s interpretation of H&S Code § 25249.10(c) and *Western Crop Protection Assn. v. Davis* has been discussed in response to previous comments (see responses to COMMENTS NO. 57, 58 and 59). OEHHA has no independent knowledge of the interaction between the commenter and Dr. Baranski and his colleagues, so can provide no response to this comment.

COMMENT NO. 70: Under the heading “The Science of Listing Must Guide the Science of Risk Assessment”, the commenter again states his opinion that OEHHA’s development of the MADL pursuant to H&S Code § 25249.10(c) must conform to the standards used, pursuant to H&S Code § 25249.8(b), in the 1997 listing decision. (See Comments, PH2-3, p. 252)

Response: This has been discussed in the responses to previous comments (see responses to COMMENTS NO. 57 and 58).

COMMENT NO. 71: Under the same heading, the commenter goes on to discuss a concern raised at the December 4, 1996 meeting of the DART Committee by Dr. Carl Keen, a member of the Committee. Dr. Keen expressed his opinion that there is compelling evidence that the mechanism of teratogenicity is to a large extent due to induction of a secondary zinc deficiency, and noted that it is possible that the potential risk of cadmium in human populations could be underestimated. Dr. Keen also noted the desirability of additional testing in this regard. (Comments, PH2-3, pp.252-254)

Response: No such additional testing has been conducted. The MADL must be based on the relevant empirical data available from studies of sufficient quality. The most sensitive study of sufficient quality is that by Ali et al. (1986, as cited above). Should additional relevant data from studies of sufficient quality become available in the future that identify a more appropriate NOEL or LOEL, the MADL may be adjusted accordingly at that time.

COMMENT NO. 72: The commenter concludes by noting that the Baranski et al. (1983, as cited above) study must be used to calculate the proper MADL, and that any other decision would be arbitrary and capricious and would require judicial review and reversal. The commenter also states that “OEHHA has resisted three significant, written attempts by the [American Environmental Safety] Institute to help OEHHA correct this matter, suggesting that the actual decision-making on this issue is already closed. (See Comments, PH2-3, p.254)

Response: The commenter or any other party may avail themselves of judicial review if they feel such action is warranted. OEHHA notes that the three written submissions by the [American Environmental Safety] Institute have been discussed in the response to comments above and below (see responses to COMMENTS NOS.12-15, 54-73). While some of the factual information in these submissions appears to resolve some of the specific concerns previously expressed by OEHHA, the additional information also raises additional concerns. The numerous documented factual errors, inconsistencies and contradictions in these submissions reduce confidence in the quality of the study and the reported results of Baranski et al. (1983, as cited above).

COMMENT NO. 73: The supplemental comment described above (see COMMENT NO. 54) refers to a problem that OEHHA had with the methodology additionally described in submission C-9a, which was identified and discussed with the commenter by OEHHA staff in a telephone conversation of April 12, 2002. The comment states that “the [American Environmental Safety] Institute’s representatives on the (sic) April 12, 2002 informed OEHHA that such an interpretation of Dr. Baranski’s comment by OEHHA was factually incorrect.” The written comment includes additional e-mail correspondence with Dr. Baranski. In the e-mails, the commenter reiterated Dr. Baranski’s statement from submission C-9a:

“One female and one male pup was selected in randomized way from each litter. Only one technician was doing all the testing so it appeared that she was only able to test 8 animals from each group, in addition since all testing was quite lengthy the time available for testing was also limited, thus we have randomly chosen 8 litters represented by 1 female and 1 male to be tested.”

The commenter then followed this with a “statement... designed to refute the state’s argument”:

“The import of this comment is that Dr. Baranski and his team corrected for any selection bias by the testing technician by randomly choosing 8 litters from among all of the locomotor test results available for the 25 litters, using the results of the one female and one male pup from these randomly chosen litters to create their experimental database as reported in Figures 1 and 2 on page 299 of the Baranski Study.”

Dr. Baranski responded to this with the statement “I do agree with your interpretation, which is correct.” (see Comments, PH2-3, pp.230-238).

Response: With regard to the telephone discussion of April 12, 2002, OEHHA disagreed with the commenter’s assertion that OEHHA’s interpretation of Dr. Baranski’s statement was incorrect, and noted that the disagreement was over interpretation of language, rather than fact. With regard to the “statement... designed to refute the state’s argument” endorsed by Dr. Baranski, it in fact reinforces OEHHA’s concerns over the quality of the study for several reasons.

A summary of relevant information provided in the original publication by Baranski et al. (1983, as cited above) and submissions C-9a and PH2-3 by the commenter is provided in Table 1. With regard to the neurobehavioral test data reported in the Baranski et al. (1983, as cited above) paper that forms the basis for the commenter's contention that this study should be used as a basis for the MADL, OEHHA's original concern was over the lack of information on the process for selection of pups for testing. The paper presented separate graphs of the results of neurobehavioral testing of male and female pups, with the statement that "the values represent means \pm SE [standard error] with eight animals in each group." It is therefore unclear whether eight animals of each sex from each of the four groups discussed in the paper were tested, or whether a total of eight animals of both sexes from each group were tested. However, the presentation of means and SE, stated to be for eight animals and presented separately for each sex, suggests that data on eight male and eight female pups per treatment group were presented. The paper contains no information on the number of litters from which these pups were drawn. This concern was addressed by the statement in Comment C-9a that "one female and one male pup was (sic) selected in randomized (sic) way from each litter." Thus, if data on eight males and eight females per treatment group were presented in the paper by Baranski et al., (1983, as cited above), eight litters per treatment group must have been tested for a total of 32 litters for the four treatment groups, and a total of 64 pups (32 males and 32 females) tested from these litters.

Comment C-9a also provided data on the number of litters treated and examined, which were omitted from the Baranski et al. (1983, as cited above) paper. In the 0 (control), 0.04, 0.4 and 4.0 mgCd/kg/day groups there were 14, 16, 17 and 12 litters, respectively. Since substantially more litters were available for examination than were used in the neurobehavioral tests, this additional information therefore raised an additional concern over the procedure followed by the technician in selecting among the available litters when it "appeared that she was only able to test 8 animals from each group" (see the response to COMMENT 15, paragraph 2). As noted above with regard to the same statement in the original paper, the literal meaning of this statement is that a total of 32 pups were tested (i.e., eight animals per group for four groups). However, consistent with the presentation of data in the original paper, OEHHA recognizes that Dr. Baranski may have intended to say that eight animals of each sex from each group were tested, for a total of 64 pups tested. As noted in a response to a previous comment (see response to COMMENT NO. 15), the statement by Dr. Baranski indicates the absence of an *a priori* rationale or protocol for selecting only a subset of available litters for testing and the consequent possibility of a confounding bias in litter selection.

The commenter's statement in submission PH2-3 that "Dr. Baranski and his team corrected for any selection bias by the testing technician by randomly choosing 8 litters from among all of the locomotor test results available for the 25 litters, using the results of the one female and one male pup from these randomly chosen litters to create their experimental database" cannot be reconciled with either the original paper by Baranski et al. (1983, as cited above) or the information provided in submission C-9a. If the data in the Baranski et al. (1983, as cited above) paper were based on only eight litters and equal numbers of males and females were tested, either an average of four pups per sex per

litter must have been tested in order for results for a total of 32 male pups and 32 female pups to be reported (i.e. eight animals per sex per group, from four treatment groups), or an average of two pups per sex per litter must have been tested in order for results for a total of 16 male pups and 16 female pups to be reported (i.e. eight animals per group, from four treatment groups). This directly contradicts the statement by Dr. Baranski in submission C-9a that “one female and one male pup was (sic) selected in randomized (sic) way from each litter.” Use of “the results of the one female and one male pup from these [eight] randomly chosen litters” as stated by the commenter in submission PH2-3, would provide data for only eight pups of each sex (i.e., for a total of 16 pups). This directly contradicts the presentation of data for either 32 or 64 pups in the original publication by Baranski et al. (1983, as cited above).

If the commenter’s statement is intended to convey that eight litters per treatment group were randomly selected *post hoc* from a larger number of litters that had undergone testing, this represents a direct contradiction to the information provided in submission C-9a. In that submission, Dr. Baranski stated that the “technician ... was only able to test 8 animals from each group, ... thus we have randomly chosen 8 litters represented by 1 female and 1 male to be tested.” As discussed above, at best this meant that all of the available data for all of the litters tested were presented in the original paper. The statement that “locomotor test results [were] available for the 25 litters” is not explained, nor is the number 25 reconcilable with the total number of litters available for any individual group or any combination of groups. (As noted above, the numbers of litters per group were 14, 16, 17 and 12). As also noted above, testing only eight litters per treatment group requires that a total of 32 litters be tested, rather than 25. *Post hoc* selection of eight litters per group from a larger number tested would, of course, require that a total of more than 32 litters be tested. Thus, the statement provided by the commenter and endorsed by Dr. Baranski factually contradicts both the Baranski et al. (1983, as cited above) paper and the earlier additional information provided by Dr. Baranski in several critical particulars.

The commenter’s statement, if accepted, would also indicate a major deviation from generally accepted scientific principles. *Post hoc* random selection of a subset of test results for analysis would serve no useful purpose, and would reduce the power of the statistical analysis. No rationale for this extraordinary procedure is provided.

TABLE 1.

	Baranski et al., 1983 (original paper)	Submission C-9a	Submission PH2-3
Number of pups tested for neurobehavioral effects	Ambiguous Probably 64 total: 8 males and 8 females per group, for 3 treated groups and a control group $(8 \times 4) + (8 \times 4) = 64$ Possibly 32 total: 8 animals per group, for 3 treated groups and a control group $(8 \times 4) = 32$	“8 animals from each group” (for four groups, this would represent 32 pups) “8 litters represented by 1 female and 1 male” (this would represent 16 pups) [if this statement was intended to indicate that 8 litters per group were tested, then it would indicate that 64 pups were tested from 32 litters]	“one female and one male pup from ... [8] randomly selected litters” (this would represent 16 pups)
Number of pups per litter tested	Not reported	1 male and 1 female per litter	1 male and 1 female per litter
Number of litters from which tested pups were drawn	Not reported	8 litters [may have been intended to indicate 8 litters per group, which would result in a total of 32 litters used across four groups]	8 litters [may have been intended to indicate 8 litters per group, which would result in a total of 32 litters used across four groups]
Number of litters available for testing	Not reported	0 mgCd/kg (control) = 14 litters 0.04 mgCd/kg = 16 litters 0.4 mgCd/kg = 17 litters 4.0 mgCd/kg = 12 litters	Not reported
Total number of litters used in neurobehavioral testing	Not reported	8 litters [may have been intended to indicate 8 litters per group, which would result in a total of 32 litters used across four groups]	“locomoter test results [were] available for ... 25 litters ”

COMMENT NO. 74: Commenter PH2-2 suggests that use of a behavioral teratogenicity endpoint is appropriate and justified and that, if this endpoint is used, the proper MADL is 0.232 micrograms per day based on the study by Baranski et al. (1983, as cited above). The commenter describes the Baranski et al. (1983, as cited above) study as “the most reliable and most sensitive study available”, based on the level of exposure at which effects were seen and the greater reliability of the gavage exposure paradigm in terms of assuring a constant dosage to the dams during gestation. (see Comments, PH2-2, pp.225, 227)

Response: The MADL is based on an endpoint of neurobehavioral developmental toxicity, which is equivalent to the term “behavioral teratogenicity” used by the commenter. Baranski et al. (1983, as cited above) report an association between maternal oral exposure to cadmium and neurobehavioral effects on offspring at a dose level lower than that reported in any other study (see response to COMMENT 15, paragraph 1). As discussed extensively above, however, OEHHA has concluded that the study by Baranski et al. (1983, as cited above) is not of sufficient quality for dose response analysis, and issues discussed above, including pup selection, call into question the reliability of the reported results (see responses to COMMENTS NO. 15 and 73). Additionally, administration of cadmium by gavage has also been discussed previously (see response to COMMENT NO. 66).

COMMENT NO. 75: Commenter PH2-2 indicates that he had difficulty deriving the 0.706 mg/kg/day value from the water concentration used in the Ali et al. (1986, as cited above) study. The commenter suggests that recalculation of the Ali et al. data yields a value of 0.40 mg/kg/day, resulting in a MADL of 2.34 micrograms per day, slightly more than half of the proposed MADL [4.1 micrograms per day]. (see Comments, PH2-2, p.226)

Response: Although the commenter refers to recalculation of the Ali et al. data, in fact the commenter’s calculation is based on substitution of assumed values for the empirical data reported in the Ali et al. (1986, as cited above) paper. The commenter assumes a body weight at the beginning of gestation of 250 g, while the Ali et al. (1986, as cited above) paper reports a range of 200-225 g. The commenter assumes water intake of 9.5 ml per 100g body weight, the median value of a range of intakes between 8-11 ml per 100g body weight (which is based on a personal communication rather than published data) and an assumed average body weight over gestation of 275 g, while the data in the Ali et al. paper corresponds to an average daily intake of 16.8 ml per 100 g body weight and a body weight of 250 g. Comparable water intake values for adult rats published by U.S. EPA (1988) [U.S. Environmental Protection Agency. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. (EPA/600/6-87/008)] range from 8-13 ml per 100 g body weight; this publication also notes that the effects of reproductive status on water intake can be substantial, and gives the example of a four-fold increase in water intake during gestation in cows. This suggests that the empirical value reported by Ali et al. is well within the range of biological plausibility. A statement by the commenter that Ali et al. “did not measure or control water intake during pregnancy” is contradicted by the statement in the paper by Ali et al. (1986, as cited

above) that “diet and water consumption rates were monitored on alternate days.” Thus, no adjustment to the MADL has been made on the basis of this comment.

After consideration of all the comments received and discussed above, OEHHA has concluded that the most sensitive study deemed to be of sufficient quality is the study by Ali et al. (1986, as cited above). Accordingly, no revision has been made to the MADL, which continues to be based on the Ali et al. (1986, as cited above) study.

DI(2-ETHYLHEXYL)PHTHALATE (DEHP)

COMMENT NO. 76: Courtney Price, CHEMSTAR / American Chemistry Council (see Comments, p. PH2-4, pp.298-299) re-iterated the comments summarized in COMMENT NO. 17.

Response: See OEHHA response to COMMENT NO. 17 above.

ALTERNATIVES DETERMINATION

In accordance with Government Code Section 11346.5(a)(7), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed, or would be as effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective than, or as effective and less burdensome to affected persons than, the proposed regulation.

For chemicals listed under the Act as known to the State to cause cancer, the Act exempts discharges to drinking water and exposures to people without provision of a warning if the discharge or exposure poses “no significant risk” of cancer (Health and Safety Code Section 25249.10(c)). For chemicals listed under the Act as known to cause reproductive toxicity, the Act exempts discharges to drinking water and exposures to people without provision of a warning if the discharge or exposure produces no observable effect on reproduction assuming exposure at 1,000 times the level in question (Id.) The Act does not specify numerical levels of exposure which represent the one one-thousandth of the no observable effect level, or no significant risk of cancer.

The purpose of this regulation is to provide “safe harbor” levels for certain chemical exposures. In other words, this regulation establishes the numerical no significant risk levels for 19 carcinogens. Below these levels, the Act does not require a warning regarding cancer or prohibit discharges to drinking water based on carcinogenicity concerns. Similarly, this regulation establishes maximum allowable dose levels for three chemicals that cause reproductive toxicity. The discharge prohibition is not affected by exposures below these levels and warnings regarding reproductive toxicity concerns are not required. Thus, these levels will allow persons subject to the Act to determine whether a given discharge to drinking water or exposure to people involving these chemicals is subject to the warning requirement and discharge prohibition provisions of

the Act related to the occurrence of cancer or reproductive toxicity (Health and Safety Code Sections 25249.6 and 25249.5 respectively). Although Sections 12703 and 12803 describe principles and assumptions for conducting risk assessments to derive safe harbor levels, many businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees needs the ability to determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Given the wide use of several of the chemicals covered by this regulation, the absence of this regulation would leave numerous businesses without an efficient way of determining if they are in compliance with the Act without the expenditure of significant resources on their part.

LOCAL MANDATE DETERMINATION

OEHHA has determined the regulatory action will not pose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. The Office of Environmental Health Hazard Assessment has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from the proposed regulatory action. Thus, the proposed regulations do not impose any mandate on local agencies or school districts.