

**Responses to Major Comments on
Technical Support Document**

Public Health Goal

For

**Di-(2-ethylhexyl) adipate
In Drinking Water**

Prepared by

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INTRODUCTION

The following are responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for di-(2-ethylhexyl) adipate as discussed at the PHG workshop held on July 22, 2002, or on the revised version prepared following the workshop, posted online in December, 2002. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from reviewer 1, University of California, Davis

Comment 1: “The draft document is thorough, well written, and complete. The information used to support the need for calculating a PHG for DEHA is clearly presented, and the methodology used is clearly described. The rationale for the selection of the variables (e.g. BW, RSC, UF, etc.) is clearly stated and reasonable, and the uncertainties are clearly described. With a few minor editing changes the document will be complete.”

Response 1: Editing changes suggested by the reviewer were made in the final document.

Comments from reviewer 2, University of California, Davis

Comment 1: “Because the mechanism of action of skeletal malformation is apparently unknown, the UF of 3 for lack of multigenerational studies is too low. The cumulative uncertainty factor of 1000 applied to the PHG is appropriate.”

Response 1: The skeletal malformations observed in rat fetuses did not appear to be severe. The authors of the report said “minor skeletal defects were increased in a dose-related manner at 1800 and 1200 ppm DEHA (corresponds to 170 and 1080 mg/kg-day, respectively), while skeletal variants (as a percentage of fetuses affected) were increased at the top dose only.” At these two doses, ossification of certain vertebrae, skull, and transverse processes of the exposed fetuses appeared to be different from the controls. Incidence of kinked ureter was also found to be increased at these two doses. None of these adverse health effects were noticed in the fetuses exposed at the low dose (28 mg/kg-day). Considering the nature of the observed adverse health effects and the fact that the NOAEL (28 mg/kg-day) is approximately 6-fold lower than the LOAEL (170 mg/kg-day), OEHHA believes the combined uncertainty factor of 10 is adequate to account for the lack of multigenerational studies and the potential carcinogenicity of the compound.

Comment 2: “Only limited discussion of the ecological effects of DEHA is given, including the expected and observed bioconcentration factors (BCF) in fish. The explanation of the large differences between observed (27) and expected (2700) BCF seem plausible.”

Response 2: The purpose of the document is to describe and discuss human health risks associated with the use of drinking water contaminated with DEHA. Ecological risk assessment is outside the scope of the document. The BCF of DEHA in fish was discussed in the context of fish consumption as a plausible exposure pathway.

Comment 3: “The effectiveness of publicly operated treatment works (POTW) to remove DEHA from the waste water stream is not discussed, and should be included, as the urinary excretion of DEHA and its active metabolites appear to indicate that waste water would be the likely source of drinking water exposure downstream. The discussion of partitioning of DEHA onto particulates is useful, as is the discussion of solubility, but a direct assessment of removal of DEHA from waste water would be helpful for a complete assessment of exposure pathways.”

Response 3: A discussion of removal of DEHA from wastewater is outside the scope of this human health risk assessment. We agree that wastewater could be a significant source of DEHA, but doubt that human excretion would be a major contributor in this source.

Comment 4: “Uncertainty exists in the literature, especially with regard to mechanism of action of the critical effects, but this is not discussed in the draft PHG. If the mechanism of the abnormal ossification in rats were explained, it could possibly reduce the uncertainty, although only to a limited extent.”

Response 4: Based on the information available in the literature, the mode of action that caused abnormal ossification in rat fetuses is not known.

Comment 5: “Some concern has been expressed in other countries that invertebrate organisms cannot metabolize DEHA, and this may result in bioaccumulation in some organisms that could result both in toxicity to those organisms, and possibly increased food exposure (for example shrimp or oysters). While this is a human health risk document on water, additional mention could be made of environmental fate and potential exposures.”

Response 5: No data were located concerning the fate of DEHA in invertebrates. While ingestion of shrimp and oysters is a plausible exposure pathway, there are little or no monitoring data. The major contribution of food sources to total DEHA exposure was noted in the document and in the PHG calculation.

Comment 6: “An UF of 100 was used for inter- and intra-species variation, which seems excessive, in light of the selection of the lowest NOAEL for 3 species studies. This already amounts to the application of a safety factor based on species differences. The combined UF of 10 for lack of multigenerational study and possible cancer risk seems low, in light of the observed developmental effects that have no mechanism of action explanation. I believe the overall uncertainty factor of 1000 is acceptable, although my estimation differs in weighting of individual Ufs”.

Response 6: The uncertainty factor of 10 for inter-species variation used in the assessment is a default. Although the NOAEL of the most sensitive species was chosen among the animals tested, this does not preclude the possibility that humans are more

sensitive still. Unless there is specific information, such as study data showing humans are less sensitive than the test animals or pharmacokinetic modeling results indicating the parent chemical or its metabolites have different fates in humans and animals, the default assumption is usually used in human health risk assessment. As already discussed in the response to comment #1, OEHHA believes an uncertainty factor of 10 is adequate to account for the lack of multigenerational studies and the potential carcinogenicity of the compound, given the observed health effects are not severe and the fact that the NOAEL (28 mg/kg-day) is approximately 6-fold lower than the LOAEL (170 mg/kg-day). However, disagreements with this reviewer among the individual uncertainty factors seem less critical than the agreement that the overall uncertainty factor is appropriate.

Comments from University of California, Berkeley

Comment 1: "California's current drinking water standard is 0.4 mg/L for DEHA, identical to the EPA standard. Hence it appears that the proposed PHG represents an increase of 50% in the allowable contamination of DEHA in drinking water. However, the draft report states, "By Federal Law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists. If I interpret the draft report correctly, it is setting an illegal standard."

Response 1: Based on comments from U.S. EPA, the NOAEL was lowered from 170 mg/kg-day to 28 mg/kg-day. The resulting change in the calculation led us to rethink the relative source contribution, increasing it from 0.1 to 0.2. Accordingly, the proposed PHG for DEHA of 0.6 mg/L has been changed to 0.2 mg/L (ppm) in the final version, which makes the above comment moot.

However, PHG values developed by OEHHA are advisory in nature, not regulatory standards. The California Department of Health Services (DHS) has the sole authority in setting drinking water standards or MCLs for the state. In developing the drinking water standards, DHS must take into consideration not only toxicity of the chemical, but also engineering feasibility and economic consequence of the regulation. The reviewer is correct in stating that California MCLs cannot be higher than the federal MCLs, but PHGs are not constrained in this way. Some are higher than the corresponding MCLs, others are equal or lower.

Comment 2: "I question the approach used in developing the draft PHG. While the key studies that exist have been identified, and the data evaluation and interpretation appear accurate, I do not believe they support the conclusions. The conclusion is based on an "overall uncertainty factor of 1,000." First, this is 3 times less conservative than the EPA, with little justification. Second, it is arbitrary and does not appear to be based on any scientific basis. And, third seems to ignore any uncertainty related to carcinogenicity."

Response 2: The risk assessment discussed at length why carcinogenic hazard posed by the chemical is not believed to be a great concern in humans. Also provided in the assessment are the supporting evidence, mode of action information, and structure

activity evaluation. As indicated by the other two peer reviewers, the use of an overall uncertainty factor of 1,000 is deemed appropriate and adequate to protect public health. The decreased value of the final PHG may also address some of the reviewer's concern.

Comment 3: "The draft PHG is not risk based. It is based on a No-Observed-Adverse-Effect-Level (NOAEL) of 170 mg/kg-day, for reproductive and development effects observed in rats. Cancer risk is ruled out (although there is no human data) based on two animal studies. The draft report states that EPA "developed an oral slope factor of 1.2×10^{-3} (mg/kg-day)⁻¹ for the compound." Even though DEHA is classified as a class C carcinogen, no risk estimate is made. If the oral ingestion rate were 170 mg/kg-day, the risk would be very high (10%) unless the same factor of 3,000 were used for uncertainty. OEHHA needs to explore this further."

Response 3: The NOAEL has been lowered from 170 mg/kg-day to 28 mg/kg-day. The risk assessment discussed at length why carcinogenicity is not believed to be a great concern in humans. Because of this, OEHHA does not believe the linear high to low dose extrapolation method is appropriate for estimating the cancer risk of DEHA exposure.

Comment 4: "The final draft goal for DEHA is based on arbitrary factor of 1,000 for uncertainty. There are sophisticated Monte-Carlo methods for quantifying uncertainty. OEHHA should at least comment on this."

Response 4: The uncertainty factors used to account for inter- and intra-species variability in the risk assessment are defaults. There are no data available indicating humans are less or more sensitive to the critical effects than the test animals; Monte Carlo simulation alone cannot bridge the data gap.

Comments from Office of Science and Technology/Office of Water, U.S. EPA

Comment 1: "The ICI studies - with a NOAEL of 170 mg/kg/day used in this document, based on U.S. EPA's previous assessment - are being re-evaluated by the U.S. EPA. The World Health Organization (WHO, 1996) and the Scientific Committee on Toxicity, Ecotoxicity, and the European Commission (EC, 1999) considered the NOAEL to be the next lower dose of 28 mg/kg/day. Similarly, IARC (IARC, 2000) seemed to lean towards a NOAEL of 28 mg/kg/day. Therefore, it is suggested that the ICI studies be similarly re-evaluated for the California Public Health Goal."

Response 1: We agree. In the revised risk assessment, 28 mg/kg-day is identified as the NOAEL of the ICI reproductive and developmental toxicity studies.

Comment 2: "There are discussions on the health effects of two metabolites of DEHA - 2-ethylhexanol and 2-ethylhexanoic acid. The health effects in animals from these two

metabolites are accounted for in studies in which animals were fed DEHA. So, unless this information is included to show the potential toxic metabolites or the health effects of these mammalian metabolites of DEHA from human exposure to these metabolites - as environmental degradates in water - this information should be removed in the interest of keeping the hazard analysis for DEHA straightforward to the point with minimum distractions.”

Response 2: The discussion of health effects of 2-ethylhexanol and 2-ethylhexanoic acid is important in understanding the mode of action of the developmental toxicity as well as the carcinogenic potential of DEHA. As the data in Tables 10 and 11 of the document show, the 2-ethylhexyl moiety has been linked to increased incidence of hepatocellular tumors in rats and mice. In the evaluation of many carcinogens (e.g., benzo(a)pyrene, styrene, benzene), it has often been considered appropriate to identify the metabolic products (proximal carcinogens) and determine their mutagenic and carcinogenic activities in order to properly evaluate the carcinogenicity of the parent compound. We think similar reasoning is relevant in this case.

Comment 3: “The discussion on peroxisome proliferators is so exhaustive, DEHA-related information is almost lost in the mix. The discussion should be abbreviated and related to DEHA and its analogs.”

Response 3: The activation of peroxisome proliferators is believed to be the mode of action of the liver tumors observed in the DEHA treated mice. There is a wealth of information regarding activation of hepatocellular peroxisome proliferators and other toxicological effects such as: (a) increased frequency of replicative DNA synthesis in liver, (b) increased liver weight, and (c) increased incidence of liver tumor. Even though some of the data were generated by the use of chemicals other than DEHA, understanding the key steps and consequences in peroxisome proliferator activation enables us to reduce the two main uncertainties (high-to-low dose extrapolation and extrapolation of rodent data to humans) in evaluating liver cancer risks associated with DEHA exposure. Therefore we have chosen to retain this extensive discussion.

Comment 4: “A more relevant discussion on the species distribution and polymorphism of the PPAR isoforms should be developed to demonstrate the relevance of the mice PPAR α liver toxicity to humans since an argument exists that PPAR α is more predominant in humans than PPAR β , which predominates in rats and is responsible for the mechanism of DEHA carcinogenicity in rodents. The subsection titled, 'Species difference' on p. 37 attempts to do this. A re-write of this section to drive the message home will greatly benefit the document.”

Response 4: Species distribution and polymorphism of the PPAR isoforms is an interesting topic, however, its discussion is not likely to impact the development of the PHG value. A short discussion on the possible role of Kupffer cells in the carcinogenesis of liver tumors in rodents has been added to the Risk Characterization section, but very little more.

Comments from the Phthalate Esters Panel of the American Chemistry Council

Comment 1: “The panel believes that the appropriate NOAEL for DEHA is 170 mg/kg-day. OEHHA used this NOAEL in its original risk assessment. However, in the revised risk assessment, OEHHA identified a NOAEL of 28 mg/kg-day, based on slight but dose-related fetotoxicity and minor skeletal defects seen in rats exposed to 170 mg/kg-day. The panel believes that the effects seen at 170 mg/kg-day were not statistically or biologically significant. Therefore, the original selection of a NOAEL of 170 mg/kg-day is appropriate and protective of public health.”

Response 1: The change of the NOAEL from 170 mg/kg-day to 28 mg/kg-day followed a suggestion made by U.S. EPA. OEHHA scientists with expertise in reproductive and developmental toxicology agreed. It should also be noted that a similar conclusion was reached by health scientists at the World Health Organization (WHO). In the drinking water quality program, WHO (1993) used the ICI study (1988) and identified a NOAEL of 28 mg/kg-day; WHO proposed a guideline value of 80 µg/L for DEHA in drinking water. Our final PHG value, which included a larger relative source contribution than in the draft of December 2002, is 200 µg/L. While this is significantly larger than the WHO value, we believe it is adequate for public health protection, including protection of possible sensitive subgroups.

Comment 2: “The panel believes the application of a safety factor for potential carcinogenic effects of DEHA is unnecessary, because a large body of evidence indicates that DEHA will not cause cancer in humans at levels of exposure that can reasonably be expected to occur in California drinking water. This large body of scientific evidence has demonstrated that the mechanism by which DEHA causes liver tumors in rodents is not relevant to humans. Therefore, OEHHA should select a proposed PHG for DEHA that does not include an uncertainty factor for potential carcinogenic effects.”

Response 2: An overall uncertainty factor of 1,000 was used in the calculation of the PHG. A factor of 100 was used to account for the uncertainties in the inter-species and intra-species extrapolation. An additional factor of 10 was used to account for the lack of a multi-generation reproductive study and the potential cancer risk posed by the chemical. Toxicological data related to the genotoxic and carcinogenic potentials of DEHA were described and discussed in detail in the risk assessment. After evaluating these data, OEHHA decided not to use cancer as the critical end-point in deriving a PHG for DEHA. At the same time, OEHHA acknowledged the argument that DEHA may pose a cancer risk. As discussed in the Risk Characterization section of the risk assessment, there are indications that peroxisome proliferation may not be the sole mechanism by which DEHA or similar chemicals might cause rodent liver cancers. For this reason, OEHHA retained the uncertainty factor of 10 to account for the lack of a multi-generation reproductive study and the potential cancer risk posed by DEHA in the final version of the PHG.