Responses to Major Comments on Technical Support Document

Public Health Goal
For
2,4-DICHLOROPHENOXYACETIC ACID
In Drinking Water

Prepared by

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INTRODUCTION

The following are the combined 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 2, 4-dichlorophenoxyacetic acid, based on the two drafts posted for comment. Changes have been made in response to these comments in the final version posted on the OEHHA Web site. For the sake of brevity, we have selected the more important or representative comments for specific 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 Arthur L. Lawyer, Technology Sciences Group, Inc., Sacramento, representing Industry Task Force II (August 6, 2007)

Comment 1: "[The tolerances] are much more complex than represented above…The addition of tolerance values complicates the understanding of what these enforcement levels mean within the context of actual use and actual residues that are expected on these sources."

Response 1: We have acknowledged in the document that the list of tolerances is incomplete. The "Food" section constitutes an important part of the "Environmental Occurrence" of 2,4-D and provides basic information related to the maximum allowable residue levels of 2,4-D (tolerances), as well as briefly discussing the residues that occur in practice, in order to provide some perspective on potential exposures. We feel this is an important part of the background for a pesticide risk assessment, and agree that it is not a formal exposure analysis.

Comment 2: "…The USEPA's RED may be a useful source for summarizing this relatively complex (extensive) set of acute studies."

Response 2: Yes, the REDs are important information sources for our pesticide reviews, and we have used the RED in this case.

Comment 3: "The 2,4-D database on genetic toxicity is complex…We provide an alternate summary below to that being proposed in the draft PHG document. We also are providing a recent summary from the published literature (Gollapudi et al 1999)…."

Response 3: Our brief section on "Genetic Toxicity" confirms the varied results of studies on 2,4-D genetic toxicity. We have now included the following additional information on the negative results of Gollapudi *et al.* (1999) on 2,4-D and its derivatives: "The lack of genotoxicity for 2,4-D 2-butoxylethylester, 2,4-D isopropylamine and 2,4-D triisopropanolamine was confirmed in tests using cultured mammalian cells and evaluating induction of chromosomal aberrations in primary cultures of rat lymphocytes and forward mutations at the HGPRT locus of Chinese hamster ovary cells."

Comment 4: "Many of the [genetic toxicity] studies described in the remainder of this paragraph have inadequacies that make their reference here questionable without adding that context."

Response 4: We agree that many of the studies have significant inadequacies, and therefore reported only a summary of the available studies, without details.

Comment 5: "We are enclosing a summary of the developmental toxicity studies (Charles et al 2001) that may be a useful complement to the summaries prepared by the USEPA.…"

Response 5: The summary provided some useful perspective, and we have updated the discussion to provide a more concise overview.

Comment 6: "We are not clear why OEHHA chose the following studies for the discussion of neurotoxic effects of 2,4-D. The DPR and USEPA recognize two studies as being of sufficient quality for use in their evaluations of 2,4-D. These studies are a single dose (acute) neurotoxicity study (DPR Doc. No. 142-156, DPR Record No. 132078, USEPA MRID 43115201) and a chronic exposure neurotoxicity study (DPR Doc. No. 142-157, DPR Record No. 132079, USEPA MRID 43293901). These two studies have been published in a single article, Mattsson *et al.,* 1997. OEHHA may find the HED and RED summaries to be more appropriate for use here rather than the summary of the studies that are currently proposed for inclusion."

Response 6: Our choice of studies was made to show the variety of neurotoxic effects reported to be caused by 2,4-D. We acknowledge the inadequacy of some of these studies for use in a quantitative risk assessment, and as we stated at the end of the "Neurotoxicity" section, "No developmental neurotoxicity studies are available that would allow quantitative assessment of neurotoxicity caused by 2,4-D."

Comment 7: "The weight of evidence from these epidemiology studies is not consistent or conclusive, and must be considered weak due to the substantial whole-animal chronic toxicity/carcinogenicity database."

Response 7: OEHHA agrees that the evidence of an association between 2,4-D and increased cancer rates is weak. We have provided some additional details and references in this section, and a conclusion that the evidence of an association is not compelling.

Comment 8: *Regarding the discussion of human reproductive/developmental toxicity*, "The Task Force finds these rural/urban reports, and their attempts to link their "findings" to 2,4-D to be unscientific. We are concerned about putting any more than trivial weight to these endeavors. They have been used repeatedly and erroneously by the public media."

Response 8: We agree that these reports do not show causative associations, and have indicated so in the updated document.

Comment 9: *Regarding the "Other Human Toxicity data" section,* "It is unclear to us why these studies are placed within the human data section. It appears that these data would be more appropriately placed within the genetic toxicity section. These studies should be compared and contrasted within the discussion of the genetic toxicity studies. In this way their relevance, which we believe is insignificant, could more easily be put

into perspective. We would suggest deleting this section or summarizing these data elsewhere."

Response 9: We agree that the limited human data from *in vivo* exposures should have been mentioned in the "Genetic Toxicity" section, and have now mentioned them there. However, the studies described in "Other Human Toxicity Data" are relevant to the overall discussion of human effects in this section and have been retained.

Comment 10: "At the June 2007 Workshop on this Draft PHG OEHHA stated that the 95th %tile was selected because it was the most conservative (health protective) percentile that encompassed statistically reliable data. Since this is apparently the first time that OEHHA has used the USEPA's 2004 survey data in establishing a PHG, we believe it is important for OEHHA to more fully describe both the rationale for the approach used and provide data/documentation on how the conclusion on the statistical justification and other determinations were made. This expanded discussion would help both the regulated community and the Department of Public Health assess the relationship of the PHG to the exposed public and to help the industry predict how PHGs and other assessments products produced by OEHHA will be developed in the future."

Response 10: U.S. EPA's 2004 survey data provided important information about current consumption of drinking water in the U.S. It showed that the previously used 2 L/day for adults, representing about the 75th percentile of adult tap water consumption (normalized to body weight), may not be adequately health protective. According to the survey, the 95th percentile of drinking water intake for the general population (all ages) is 30 percent higher (2.6 L/day) than the previous default value of 2.0 L/day. The difference is even greater for infants, children, and pregnant women. Since AB 2342 (2004) amended the California Safe Drinking Water Act (HSC section 116365.2) to mandate consideration of the greater exposure of susceptible populations including infants and children, OEHHA has developed and has begun to use these new, more health-protective consumption values in our updated drinking water risk assessments, such as in the revised glyphosate PHG, published in June 2007. OEHHA believes that using the 95th percentile drinking water consumption value is the best approach for protecting the health of the entire population. A similar approach for estimating exposures to toxic air contaminants, utilizing upper 95th percentile breathing rates, has been incorporated into OEHHA's Toxic Hot Spots program, and has been approved by the Scientific Review Panel (OEHHA, 2003).

Comment 11: *Referring to the Other Regulatory Standards section, the Task Force says:* "We do not believe that this was a correct summary of the IARC findings. IARC classification is for the chlorophenoxy group of herbicides. Note the 1987 monograph, Table 14 on page 60, 2,4-D was classified separately with no classification for human carcinogenicity and "I" (inadequate evidence) for animal carcinogenicity. Moreover, the footnote to Table 1 specifically states: "This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group."

Response 11: We agree that the 2B cancer classification is listed as applying to "Chlorophenoxy Herbicides" as a group, and have amended our statement to make that clear. Our summary now includes the specific statement from the IARC report that the evidence for carcinogenicity to animals is inadequate for 2,4-D.

Comment 12: "We suggest that OEHHA use caution in the use of IRIS as a citation since its summary of 2,4-D toxicology has not been updated for more than 15 years and does not reflect current studies or EPA's evaluation and findings on the database."

Response 12: We agree and note that in our reference to IRIS, although it appears to us that the majority of the findings presented in IRIS are still applicable. It should also be noted that evaluations of chemicals by OPPTS, the authors of the 2,4-D RED, are not always consistent with those of the Office of Research and Development's NCEA, the managers of the IRIS system.

Comment 13: *The Task Force recommended adding an explanation in several places in the PHG document that effects were occurring because of saturation of renal clearance.*

Response 13: We did not accept most of these editorial interpretations in the individual studies. However, the document does mention the role of renal clearance in 2,4-D toxicity several times in appropriate sections. The following paragraph has been added to the Summary section: "Limitations in renal clearance play an important role in the degree and variety of toxic effects caused by 2,4-D exposures. Available animal and human data indicate that saturation of renal clearance, which prolongs the systemic half-life, leads to 2,4-D accumulation and the most severe effects in animal studies." The Subchronic Toxicity and Developmental and Reproductive Toxicity sections have similar enhancements.

Comment 14: *The Task Force suggested many editorial changes in the text, usually substituting weaker terms, such as "allege" instead of "show," "may be claimed" instead of "is likely," "lack of conclusive findings" instead of "difficulty in interpreting," "has been alleged" versus "was observed," "abnormalities" versus "malformations."*

Response 14: The strength of evidence and interpretations was carefully considered regarding each of these choices. Some of the suggestions were accepted and the original wording was retained in other cases.

Comments from Arthur L. Lawyer, Technology Sciences Group, Inc., Sacramento, representing Industry Task Force II (August 4, 2008)

Comment 1: "The Task Force believes that the summaries provided in the Draft PHG (excerpted above) do not adequately address the deficiencies of these studies and, as a result, give these studies inappropriate weight within the Genetic Toxicity section of the Draft PHG. Many of the studies described in the above excerpt have inadequacies that

make their reference within the Draft PHG questionable and, we believe, should not be included unless their context is appropriately described. The genetic toxicity database includes many studies that upon detailed assessment, have insufficient or inappropriate experimental design and/or controls."

Response 1: OEHHA agrees that the studies cited in the genetic toxicity section have significant limitations, and have modified the wording here and there to provide more acknowledgement of this factor.

Comment 2: *In the study of Pillinskaya (1974), the positive results reported by the authors* "fell within the range of the negative controls. Therefore to state that 2,4-D "increased the frequency of abnormal chromosomes in their bone marrow cells" is a misleading conclusion."

Response 2: This reference offered no critical information and has been removed.

Comment 3: "As summarized in the recent review by Garabrant and Philbert (2002), "Investigations of 2,4-D and seven of its salt and ester forms in gene mutation in bacteria (Ames test), forward mutations at the HGP locus of Chinese hamster ovary cells, the induction of DNA damage and repair in rat hepatocytes, the induction of chromosomal aberrations in primary cultures of rat lymphocytes, and induction of cytogenetic abnormalities in mammalian cells in vivo in the mouse bone marrow micronucleus test have recently been published in the literature (Charles et.al., 1999a,b; Gollapudi et.al., 1999). All of these studies were negative and add to the weight of evidence that 2,4-D does not have any genotoxic/mutagenic potential in vitro and in vivo.""

Response 3: We have added this reference and acknowledged the opinion of these authors.

Comment 4: "The Draft PHG section on neurotoxicity does not discuss the two existing GLP studies conducted according to international regulatory testing guidelines that are central to the evaluation of 2,4-D by the EPA and DPR. … As reported in Mattson et al, 1997, there are two FIFRA guideline studies that assess and identify neurotoxicity endpoints. These studies are a single dose (acute) neurotoxicity study (DPR Doc. No. 142-156, DPR Record No. 132078, USEPA MRID 43115201) and a chronic exposure neurotoxicity study (DPR Doc. No. 142-157, DPR Record No. 132079, USEPA MRID 43293901)."

Response 4: These two studies (Mattsson *et al.*, 1994a,b), which were described by Mattsson *et al*. (1997), have been summarized in the revised document.

Comment 5: "The Draft PHG also states that "No developmental neurotoxicity studies that would allow quantitative assessment of neurotoxicity caused by 2,4-D are available at this time." Developmental neurotoxicity assessments of 2,4-D were performed by the USEPA as part of their development of their RED on 2,4-D (USEPA 2005). The USEPA

did conclude that in order to complete these assessment, further scientific data would need to be developed, particularly a developmental neurotoxicity (DNT) study. In the USEPA RED (USEPA, 2005), no specific value for developmental toxicity LOEL or NOEL were established by the Agency, consistent with the Draft PHG conclusion regarding the qualitative nature of the development neurotoxicity effects."

Response 5: We appear to be in agreement on this point.

Comment 6: "There have been several studies published over the years that attempt to connect 2,4-D specifically with [reproductive] effects that are observed generally in agricultural regions. These studies show, at best, weak associations with urban versus rural effects and, due to the many confounders inherent in these broadly constructive epidemiological surveys, associations to 2,4-D can, at best, only be considered suggestive."

Response 6: We agree, and have made minor wording changes to make the tone more consistent with this interpretation.

Comment 7: *In the study of Garry et al. (2006),* "exposure misclassification, limited biological plausibility and unexplained nonspecificity of birth defects that are observed call into question the authors conclusions. … The Task Force finds these rural/urban reports, and their attempts to link their "findings" to 2,4-D to be unscientific. We are concerned about putting any more than trivial weight to these endeavors. A recent assessment (Jurek et al., 2008) of studies that potentially use disease misclassification and non-differential exposure values, that includes the findings of Garry et al, may be useful to OEHHA further evaluations of these reports."

Response 7: We believe our amended conclusion on this study, "This is consistent with earlier studies which show various abnormal health outcomes to be increased in rural areas compared to urban areas, and vice-versa, but does not clearly point to specific causes of the differences," is appropriately noncommittal regarding an association with 2,4-D. We appreciate the identification of the useful paper of Jurek *et al.* on misclassification bias.

Comment 8: "The review article by Sever et al., (1997) cited by OEHHA provides no support for the conclusion that 2,4-D is associated with reduced sperm counts or sperm abnormalities. In fact, the article does not discuss any research concerning 2,4-D and sperm measurements and this review paper should be removed from the OEHHA document."

Response 8: We agree. The Sever *et al.* review has been removed.

Comment 9: *Several limitations of the study of Arbuckle et al. (2001) were pointed out.*

Response 9: We agree with the gist of the comments, and limit the brief discussion of this study to simple facts; 2,4-D was detected in the urine and semen of the farmers, and

the reported preconceptional exposure was "associated with a moderate increased risk of early abortions (odds ratio 1.5, 95 percent confidence interval 1.1-2.1).

Comment 10: "The above paragraph is essentially a summary of in-vitro genetic toxicity studies that used human cells as their testing material. We believe that these studies are inappropriate for use in the summary of human toxicity data. The sentence concluding that 2,4-D is "likely to be...mutagenic" in humans is inconsistent with nature and findings of studies reported in the genetic toxicity section. "The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to 2,4-D or its amine salts and esters." (page 41 EPA HIARC 2004) Typically, these studies, if significant contributors to the understanding of potential toxicity, would be summarized along with other in vitro experimentation (e.g., genetic toxicity studies). In fact, two of the studies, Figgs et al., 2002 and Holland et al., 2002, were already summarized in the Draft PHG Genetic Toxicity section. We request that this section be deleted."

Response 10: We agree that there is some overlap, but customarily we do mention human *in vitro* data in the section on human toxicity, and we prefer to keep it that way. We have changed the summary statement to say "Available human data indicate that 2,4-D may be cytotoxic and mutagenic," which is completely consistent with the results of the studies presented in this section.

Comment 11: "The additional 10-fold factor that contributes to the overall 1,000 UF is based on the need for two additional toxicity studies. These two studies are being generated at this time by the Task Force. Since the submission and evaluation of these studies by the EPA is expected to result in the elimination of the additional 10-fold UF, the Task Force believes that it is important to clearly state the potential transient nature of the additional factor since by the time the California Department of Public Health is using OEHHA's draft PHG to develop the California MCL for 2,4-D, the UF for 2,4-D and, accordingly, the basis of the PHG will require reconsideration. We suggest that the Draft PHG be modified so that the document clearly acknowledges the anticipated transient nature of the current 1,000-fold UF for 2,4-D."

Response 11: We feel it is inappropriate to cite potential effects on the risk assessment of studies not yet completed. PHGs are updated on a regular basis to incorporate new information.

Comment 12: "The Task Force still believes that the Draft PHG would benefit from the addition of a discussion of why the 95th percentile was chosen from the drinking water consumption survey. Though the Task Force does not disagree with this decision, we believe a brief justification would be helpful since this is a relatively new practice for drinking water assessments developed by OEHHA."

Response 12: Agreed. An expanded discussion on the point has been added to the final PHG document.

Comment 13: "The last paragraph [on page 10] states: "No subchronic inhalation toxicity study is currently available". A new subchronic 28-day inhalation toxicity study has been completed and submitted to EPA April 14, 2008, MRID no. 47398701. A copy of this study is being submitted to DPR and OEHHA."

Response 13: We received a copy of the study and have now discussed it in the PHG document.

Comment 14: *Various other minor inconsistencies or omissions are pointed out.*

Response 10: We have incorporated most of the suggested minor word changes.

REFERENCES

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