Responses to Major Comments on the Technical Support Document

Public Health Goal

For

Atrazine

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 atrazine as discussed at the PHG workshop held on October 6, 1998, or as revised following the workshop. Some commenters provided comments on both the first and second drafts. 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.org. OEHHA may also be contacted at:

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This suggests that about 80% of the dose is absorbed.' Is this conclusion of OEHHA? Compare this with another view that '100% oral absorption is assumed' on page 9, last line. These discrepancies should be corrected."

Response 3: Yes. The 80% absorption is based on pharmacokinetic data from animal studies. The reference to 100% absorption on page 9 is deleted.

Comment 4: "Page 11, Subchronic toxicity, line 2. What was the dose used?"

Response 4: This study is deleted from the toxicity review because of insufficient information on the study.

Comment 5: "The conclusion that atrazine undergoes metabolic activation independently from the liver, possibly in the stomach (p. 13), resulting in a mutagenic product is difficult to understand as it relates to another statement, it is mutagenic with yeast in a host-mediated assay (p. 13). Is this a correct interpretation and discussion?"

Response 5: Yes, we have reviewed the discussion and believe it to be correct.

Comment 6: "Induction of p53 (assuming it is the tumor suppressor gene) should not mean that atrazine is mutagenic. (p15). This reviewer does not see a connection between induction of the p53 protein and mutagenicity?"

Response 6: The paper talks about the expression of mutant protein, which can occur only after

mutation.

Comment 7: *Ten additional references were provided.*

Response 7: All references were obtained and read. Most of the papers were not relevant to the discussion. However, one reference (Loosli, 1995) was reviewed and added to the text.

Comment 8: "However, the section on genetic toxicity could be improved since some statements do not make sense. For example p 13, para 2 in the genetic toxicology section says, 'Atrazine was mutagenic in the host mediated assay with yeast and E. coli'. It is not clear from this text what was mutagenized, how and what doses were used. Some discussion, such as that on p53 does not appear to be of importance. The significance of the micronucleus assay is not clear since the doses used are relatively high. Data on clastogenicity, however, raises an issue and this should be discussed in greater detail if it is do be used authoritatively."

Response 8: Some details are added to the text to make it more explicit.

Comment 9: "The carcinogenicity data includes information from Ciba-Geigy, which shows an increase in mammary cancer in Sprague-Dawley rats. Other data sets from other animal species are given and suggests that increased cancer incidence is only in rats. Other cancers are not detected. The discussion on hormonal effects is interesting, and could potentially be of significance. Data from non-mammalian vertebrates is not given but should be considered since similar effects are observed in these animals."

Response 9: Derivation of PHGs is based predominantly on toxicological data from mammalian systems, if human data are not available. These studies are more closely relevant to human toxicity (which is the intent of health risk assessment) than non-mammalian vertebrates. On the other hand, for a comprehensive review of endocrine effects, we acknowledge that inclusion of data from non-mammalian systems would be important. Such a review, however, was beyond the scope of this document.

Comment 10: "There is sufficient data to suggest that atrazine affects endocrine function. These effects are observed both in vitro and in vivo in vertebrate animals, and they appear to be beyond those affecting a central modulatory site. In some instances, the binding of natural hormones to their receptors is modulated. However, atrazine by itself does not bind directly to any of the hormonal receptors that have been investigated. Since we presently do understand the biological consequences of these endocrine effects we have to be cautious on human exposure levels.

Response 10: No response required.

Comment 11: "The toxicity of the degradates is as high as that of the parent compound. If the PHG is based on only atrazine than real exposures are going to be higher than that of the parent compound alone."

Response 11: The risk characterization has been expanded to include this point in discussion.

Comment 12: "The NOEL determined for non-carcinogenic effects at 3.5mg/kg is appropriate based on the effects seen both in weight loss and to some extent to cardiac effects. The data presented in this case does support the conclusions that are derived. The values for carcinogenic effects are dependent on the model used for estimation."

Response 12: No response required.

Comment 13: "No-threshold linear model for carcinogenic effects appears appropriate given the data presented in this review. However, this reviewer is uncertain whether appropriate factors are used for in the calculation in the PHG determination."

Response 13: We agree with the comments regarding the use of a linear model for carcinogenicity. The various factors used in calculation of the atrazine PHG are either standard defaults used to calculate all PHGs, or are specific to atrazine as derived from the scientific literature.

Comment 14: There are minor spelling errors, and another spellcheck is required.

Response 14: Done.

U.S. EPA Office of Water

Note: U.S. EPA Office of Water had no critical comments on the atrazine PHG, but indicated that the atrazine database is under review by the agency. The following statements were made:

1. "California is proposing 0.00015 mg/L as a PHG for atrazine in drinking water. This value is associated with a cancer risk of 1 x 10-6. Review of the extensive toxicity database for atrazine has been presented in the California draft document in support of this proposed PHG value. To discuss the carcinogenicity of atrazine, the draft California document used the incidence of the mammary gland tumors in the Sprague-Dawley rat and both the 1986 EPA cancer guidelines and the 1996 EPA proposed cancer guidelines to quantify the cancer risk. The cancer potency (q1*) using the multistage model, as well as the LED10 (95% lower confidence

limit on a dose associated with 10% extra risk) and the cancer slope factor (CSF) approaches were used in these discussions. However, the draft document indicated that "since the mechanism of action of atrazine is unknown, OEHHA has adopted the default option of linearity for this chemical and has used the cancer slope factor.

"OW comments on the carcinogenicity issue are limited to the fact that the implementation of the proposed EPA 1996 guidelines to the atrazine data base is still under evaluation by the Agency and the re-evaluation of atrazine carcinogenicity using the new guidelines needs to be peer reviewed by the Science Advisory Panel before a final decision can be made. It is not clear yet if a linear approach will be used, whether the LED10, or the ED10, or the CSF will be used. Also, it is not clear yet what risk level would be selected for drinking water exposure (i.e., 10^{-4} to 10^{-6}). Finally, the draft California document adequately described on page 36 the status of the EPA's MCL and the data used in its derivation."

Response: No response is required

2. "The California draft document indicates that the most significant and sensitive endpoint for noncarcinogenic effects is cardiopathy (myocardial atrial degeneration) that was observed in a one year dog study, with a NOEL of 0.48 mg/kg."

Response: No response is required.

University of California, Berkeley

General comments:

Comments 1: *The reviewer summarized the document and concluded that the* "draft document has a major focus on the health effects portion of the risk and is weak on the exposure assessment of the risk."

Response 1: Major and relevant data available on exposure were reviewed in the document. A standard default value of 2 L water/day was used in determining the PHG value and was considered appropriate. Also, in absence of real exposure values available from food sources, a default 20% relative source contribution was used.

Specific comments.

Comment 2: Atrazine's metabolites were not accounted for in the risk assessment.

Response 2: Appropriate language is added in the risk characterization portion of the document to make this point more explicit. There is very little or no monitoring data on metabolites in drinking water and therefore actual data that can be used is lacking.

Comment 3: The reviewer suggested a modern sensitivity analysis.

Response 3: OEHHA disagrees with the reviewer that a sensitivity analysis would add more confidence to the atrazine PHG value.

Comment 4: A missing reference is pointed out.

Response 4: Reference added.

Comment 5: Reviewer indicates that dermal exposure is not included in the derivation of PHG.

Response 5: Dermal dose from shower and bathing would be negligible for atrazine because of relatively short dermal exposure and an expected low absorption rate. Therefore, this pathway was not included in determining the PHG value.

U.S. EPA Office of Prevention, Pesticides and Toxic Substances

*Comment 1: **Hormonal and Cyclicity Data**: The reviewer suggested a role of atrazine in hormonal perturbation in mammary tumor development in the Sprague Dawley rats based on registrant data and indicated confirmation of these results from Ralph Cooper's laboratory in North Carolina. The reviewer* "potential for atrazine to affect neuroendocrine pathways of the hypothalamus to accelerate the onset of reproductive senescence in female Sprague-Dawley rats."

Response 1. OEHHA has reviewed all available information on hormonal effects of atrazine including data on the affects of atrazine on the neuroendocrine pathways at the hypothalamus/pituitary level. This information is extensively reviewed in the document and summarized starting on page 25.

*Comment 2. **Pinter Study in Fischer 344 Rats:** The reviewer said that U.S. EPA is evaluating the significance of increased incidences of mammary tumors in male and of leukemia/lymphoma in female Fischer 344 rats mainly for the following issues.*

1. *length of the study,*
2. *the late occurrence of mammary tumors in the F344 male in contrast to early occurrence in females in other studies.*
3. *lack of increase in male mammary tumors in studies performed by the registrant, and*
4. *the lack of uterine adenocarcinoma and leukemia/lymphoma response in any of the registrant studies.*

The reviewer further recommends an in-depth evaluation of the Pinter et al. study including the analysis of individual animal data with all possible considerations. The reviewer states that "Overall, tumor response in the Pinter et al. study should be viewed in the totality of all the evidence bearing on the carcinogenicity of atrazine."

Response 2: OEHHA has reviewed the study as reported in the literature, but has not obtained individual animal data. While OEHHA agrees that the study must be reviewed "in the totality of all the evidence bearing on the carcinogenicity of atrazine," OEHHA does not share the concern with the four issues pointed out by the reviewer. These factors may be related to the length of this study (up to 140 weeks) as compared to the standard (104 weeks) duration used in the carcinogenicity study. Males usually do not develop mammary tumors and therefore may require a long exposure. This may also be the reason for lack of mammary tumors observed in the registrant studies.

Comment 3. ***Mutagenicity Data****: The reviewer pointed out that OEHHA's document as written* "indicates that atrazine is a mutagenic carcinogen and thus implies that a mutagenic mode of action may be an important potential influence on the carcinogenic process." *The reviewer recommends that the OEHHA document should not totally dismiss the mutagenic mode of action, but should indicate that* "mammary tumors in female Sprague-Dawley rats associated with reproductive senescence is not easily explained by a mutagenic mode of action."

Response 3. OEHHA has made changes to indicate that atrazine is genotoxic at high doses and at low doses, and the significance of the genotoxic process in the development of mammary tumors is not easily explained.

Comment 4. ***Structure–Activity Relationships (SAR)****: The reviewer recommended that OEHHA include a discussion on SAR. A draft position document on SAR of s-triazine pesticides and related compounds was enclosed with the reviewer's comments.*

Response 4. Time does not permit an independent review of the structure-activity relationship data of s-triazines for this PHG development. A summary has been added based on OPPTS' draft position document on SAR of s-triazine pesticides and related compounds.