Responses to Major Comments on Technical Support Document

Public Health Goal

For

Toluene

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 toluene 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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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments by U. S. EPA

Comment 1: **Chemical Profile**

The structure did not print out correctly on the copy I received. The aromatic ring is not properly placed.

Response 1: This has been a recurrent problem, it is fixed now.

Comment 2: **Toxicology**

The last four studies summarized on page 10 are less than subchronic (90-day). Three of them are 28-day studies.

Response 2: From Casarett & Doull, 1991, subchronic is defined as an exposure of one to three months. Four weeks are approximately equivalent to one month. We agree that this study represents a relatively short subchronic study, but it is still best to characterize it as subchronic study rather than an acute study.

Comment 3: **Dose Response Assessment**

Suggestion that the EPA lifetime Health Advisory number should be included in addition to or in place of the DWEL since the DWEL is not a recommended value for long term exposure. (Paraphrased)

Response 3: U.S. EPA defines DWEL as "A *lifetime* exposure concentration protective of adverse, non-cancer health effects…". It is, however, a good idea to compare the PHG to additional values such as a Health Advisory (HA). We prefer to compare a PHG with an MCL (which for toluene is the same value as the HA), and a description of this comparison was added to the technical support document.

Comment 4: **Dose Response Assessment**

It is not at all clear why the NOAEL for the Hsieh et al., (1989) study was used for the PHG. It is agreed that the effects on both liver and thymus weights can be seen as indications of effect on the immune system but the reviewer understands that some of the immunotoxic events from 14- to 28-day studies may resolve by the end of a 90-day study. In addition, the ATSDR toxicological profile discussion of this study indicates that there were also effects on mitogen stimulated lymphocyte proliferation and interleukin-2 immunity at the 22 mg/kg-day dose. I would accordingly call this dose marginal LOAEL and the 5 mg/kg-day dose a NOAEL.

Response 4:

Hsieh *et al.* (1989) studied the effects of toluene on various parameters of immunological responsiveness in CD-1 mice exposed to 0, 17, 80 or 405 mg/L toluene in drinking water for 28 days. At the highest dose of 405 ppm, there was a significant decrease in thymus weights and a corresponding decrease in antibody plaque forming cells (PFC)/10^{-6} spleen cells and per spleen to sheep red blood cells, IL-2 production as measured by ^{3}H-thymidine incorporation in IL-2 dependent HT-2 cell line and proliferative response to concanavalin-A, lipopolysaccharide and pokeweed mitogens. Mitogen responsiveness and

IL-2 activity measured in units based on probit transformation was also significantly reduced in the 80 ppm dose group in this study. In other immune function studies with toluene reported by Hsieh et al., (1989) either no effect was observed on mitogen responsiveness at 80 or 325 ppm dose level (1990) or reduced only at the highest dose of 405 ppm (1991) dose level suggesting that toluene suppressed the immune function parameters only at the high doses. Also, proliferative response to mitogen alone is not a good predictor of immunotoxicity (Luster et al, 1992). Therefore, the NOAEL for this study is set at 80 ppm (22 mg/kg-day). The document was revised to clarify the issue.

Comment 5: **Dose Response Assessment**

Also, the Hsieh et al (1990) neurotoxicity study with a similar design and the same doses is not discussed as a candidate for the PHG even though there is a considerable body of data that suggests that the nervous system is sensitive to toluene. [The sensitivity of the nervous system was recognized in the extra uncertainty factor used to obtain the OEHHA value]. The toxicology profile discussion for the Hsieh et al. (1990) study indicates that some biochemical effects were seen at the 5 mg/kg/day dose. There should be some discussion as to why the neurotoxicity data were not used.

Response 5: The study by Hsieh et al. (1990) involves a four-week administration of toluene in drinking water to five mice per treatment group at doses of 0, 5, 22, or 105 mg/kg-day, followed by brain dissection and HPLC assay of NE, 5-HT, DA, and their metabolites in six brain areas. No behavioral observations are reported, but these daily oral doses would not be expected to cause any behavioral changes. Low-dose oral administration of toluene in drinking water is followed by relatively efficient first-pass metabolism of toluene in the liver. Blood levels of toluene would be expected to be very low, compared to those of behaviorally effective acute doses. Behaviorally effective oral doses are reported elsewhere as being about 1 g/kg or more, although it is not possible to deliver daily doses of this magnitude in water because of the limit of solubility of toluene in water. Behaviorally effective doses are much lower by inhalation, where "bolus" effects with acute high brain levels of toluene are easier to achieve.

Various increases in brain amines are reported in this study, mostly without dose-response trends. Statistically significant increases in NE in the hypothalamus are reported, for example, at all doses, with greatest effects at 22 mg/kg, almost as much at 5 mg/kg, and lower at 105 mg/kg. This is related, in the conclusion, to the well known bell-shaped curved for behavioral effects of toluene and other solvents (i.e., behavioral activation at low doses, followed by sedation at higher doses). These "classical" effects occur at doses corresponding to much higher brain toluene levels. Also, such effects result from disinhibition of cortical inhibitory control, followed by inhibition of bioamine activation mediated through lower brain regions, rather than through a hypothalamic U-shaped dose response. No effects were reported on NE levels in the cerebral cortex in this study. Increased transmitter levels seemingly randomly scattered through the doses coupled with the small number (five animals per dose) and lack of internal confirmation make these data very weak. The fact that they are also inconsistent with earlier dose-response data for behavioral effects means that the putative mechanism does not apply. Therefore we conclude that the biogenic amine data are unlikely to represent effects of toluene.

Comment 6: **Calculation of PHG**

There should be some technical support for the RSC. Although toluene may not be found to any great extent in food or soil, what is the ambient air exposure given its presence in gasoline and the amount of gasoline used in this country?

Response 6: The RSC was determined to be 40% in accordance with OEHHA methods as explained in the technical support document. For an organic chemical that is too volatile to be found in food or surface soil, we generally use an RSC of 40% (along with a drinking water consumption value adjustment to 4 L/day). As described on page 4 of the report, ambient air concentrations for toluene are decreasing steadily with a mean concentration in 1996 of about 2.2 ppb.

Comment 7: **Calculation of PHG**

Uncertainty factor. … The critical study was a drinking water study and was not a subchronic study. Normally 28-day studies are not used as the basis for regulatory values.

Response 7:

- Drinking water dosing is preferred to gavage as it simulates the human drinking water route.
- Subchronic = is defined as an exposure of one to three months duration.
- 28-day studies are, indeed, not normally used for basis of regulation; however, the Hsieh et al. (1989) study showed clear dose-response relationship, established a lower LOAEL (than the previous NOAEL) and a lower NOAEL.
- The Hsieh et al. (1989) study also had good quality control in both dose quantity and chemical purity.
- Three lifetime studies of toluene in animals were performed; however, none was adequate from which to derive a NOAEL.

Comment 8: **Calculation of PHG**

Technical support should be provided for the 4 L/day exposure. If one accounts for ambient air exposures in the RSC there may not be a need to increase the volume to 4 L/day.

Response 8: The value of 4 L/day is used in accordance with OEHHA methods. The default is 2L/day, however the higher value accounts for additional equivalent exposure to volatile chemicals from various uses of drinking water such as bathing. U.S. EPA's Risk Assessment Forum (1991) recommended a default inhalation exposure from showering in water contaminated with volatile organic compounds equal to ingestion of that water. For a two liters ingestion the default for showering only would be an additional 2 Leq/day. This default was based on the average of a number of volatile organic compounds studied by U.S. EPA.