Responses to Major Comments on Technical Support Document

Public Health Goal
For
Silvex
In Drinking Water

Prepared by

Pesticide and Environmental Toxicology Section
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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 silvex as discussed at the PHG workshop held on 7/22/02, or as revised following the workshop. 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 the Office of Water, U.S. Environmental Protection Agency

Comment: "California EPA proposed a public health goal for silvex of 25 ppb based on the NOAEL of 0.9 mg/kg-day for liver changes from the chronic dog study (Mulison, 1966). An rsc of 80% (0.8), and an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for variability within the human population, and 10 for database deficiency) was used."

"The MCL and MCLG for Silvex are both 50 ppb (USEPA, 1991). USEPA has also derived a lifetime health advisory (HA) of 0.052 mg/L for silvex, using the same chronic study (Mulison, 1966). However, USEPA used 0.75 mg/kg-day as the NOAEL (diet adjusted from 0.9 mg/kg, using standard assumption of food consumption per ppm of diet), an rsc of 20%, and uncertainty factor of 100."

Response: OEHHA believes our calculation method to be reasonable, following generally accepted risk assessment principles. The two-fold difference between the PHG and the U.S. EPA MCL is within the limits of accuracy of such risk assessments.

Comments from University of California, Riverside (Department of Cell Biology and Neuroscience)

Comment 1: "The absence of neurotoxic and immunotoxic data is surprising. Given that there is much that has been done with the immunotoxic effects of TCDD, an impurity in Silvex, it would be prudent to refer to company literature, if this was available. Since I am not privy to such data, and teratogenic effects were observed, albeit at low levels, this data on immunotoxic effects would have been useful in assessing if the proposed risk model is appropriate."

Response 1: As stated in the draft PHG, no data were located on the neurotoxicity or immunotoxicity of silvex. Since silvex is no longer manufactured in the United States (see below), no company literature is available.

Comment 2: "On page 3, the level of Silvex production in the 1980s is given. This was still substantial. What is the present production in the U.S.? If there is substantial production now does it mean that there are additional risks?"

Response 2: The manufacture of silvex in the United States ended by 1984. This information has been added to the draft PHG.

Comment 3: "Some information on the environmental stability of Silvex should have been included. A major reason for low levels of 2,4,5-trichlorophenol being observed in vertebrates is the presence of a tertiary carbon in Silvex. In contrast with a secondary

carbon higher rates of phenol formation should be expected with 2,4,5-T. However, it is not clear that microbiological conversion would be the same as that predicted for vertebrates. Therefore is 2,4,5-trichlorophenol formed in the soil? Are they any studies on these? These are critical if the major risks being discussed are those from Silvex already in the environment.

Response 3: Only a limited number of studies were located on the environmental stability of silvex. All such data were included in the draft PHG, in the section "Environmental Occurrence and Human Exposure." This included the finding that 2,4,5-trichlorophenol results from the biodegradation of silvex in the soil.

Comment 4: "Since the risks posed are because of contamination in water, a discussion on the photostability of Silvex and 2,4,5-trichlorophenol would also been useful."

Response 4: The photostability of silvex in air and water is discussed in the section "Environmental Occurrence and Human Exposure."

Comment 5: "The data set that is included in this case is relatively small as it relates to Silvex. Although there is a larger data set for 2,4,5-T much of this in not included in the draft PHG. This reviewer understands the rationale for keeping these two compounds separate provided there is an existing limit for 2,4,5-T and 2,4,5-trichlorophenol in drinking water. If not then these limits should be set."

Response 5: No response needed.

Comment 6: "Because of limitation of the data available in PubMed there is adequate discussion of the data set needed for a review of the PHG. There is a good discussion of the toxicity to different animals used in studies related to Silvex. The only issue not adequately described is the mechanism by which the National Academy of Science came to a value that is different from that proposed here. It appears that the only apparent discrepancy is the different RSC values used. Is this true?"

Response 6: The NAS used an RSC of 0.2, compared to 0.8 in the draft PHG. This is the primary reason why their final value is lower than that calculated in the draft PHG. This issue is discussed in more detail in the response to comment 7 below.

Comment 7: "A key determinant in estimating the PHG of 25 ppb is based on estimating that water will provide 80% of the risks. There is apparent discrepancy between this estimate and that done by the National Academy of Science, which estimates that water will provide only 20% of the risks. If one is to use the NAS estimate the PHG would be ca 6ppb. There is no clear justification provided as to how the value of 80% was derived. How and why did the NAS come up with a different RSC value? Given that there is no clear rational given in the present draft PHG, I would recommend that the NAS recommended RSC of 0.2 be used in determining the PHG. This assumption would also

be valid since Silvex can get into the human food chain by other means even if water is the primary carrier."

Response 7: The use of 0.8 as the RSC value is discussed in the section "Calculation of PHG." It states there that "An RSC value of 80 percent (0.80) was chosen because any significant human exposure to silvex is expected to occur through drinking water, as a result of material leaching from waste dump sites and entering the groundwater (Gintautas *et al*., 1992). Other routes of exposure such as food or air are unlikely, because silvex use was banned in this country approximately 15 years ago." At the time the NAS calculated their value (1977), other routes of exposure to silvex were considered possible, since it was still being used in agriculture. It also states in this section of the draft PHG that "absorption by secondary inhalation during household water use is unlikely, due to the low volatility of silvex. Therefore, significant exposure to silvex is considered to occur only through ingestion of drinking water…."

Comment 8: "A key feature of uncertainty in the PHG calculation involves two factors – the safety factor and the other involves the RSC value. Given that there is justification from NAS, the value recommended by that body should be considered. The factor of 1000 is in general justified given the small body of literature available for Silvex. If the toxicity data for 2,4,5-T is used in place, then there is sufficient justification for this factor."

"An additional factor not considered here is the issue of TCDD risk. However, this should be more directly dealt with by having its own PHG value."

Response 8: An uncertainty factor of 1000 has been retained in the final PHG, as well as the RSC of 0.8. The selection of an RSC is discussed in response #7.

Comments from second University of California, Riverside (Environmental Toxicology Graduate Program)

Comment 1: "With a few exceptions (indicated below), the information appears to be accurate. There is little information in the document on potential modes of action."

Response 1: No response required.

Comment 2: "To identify the recommended PHG, the agency has reviewed the available literature, identified a NOAEL based upon chronic effects seen in the most sensitive species and sex, and used uncertainty factors to estimate a safe exposure level. This is a well established approach for non cancer-inducing agents and seems to be appropriate based upon the effects observed with silvex."

Response 2: No response required.

Comment 3: "A number of studies have been conducted to assess the toxicity of silvex, and those accessible in the scientific literature have been identified in the draft PHG document. These were almost all conducted by Dow Chemical Company in the 1960s using protocols from that period, and are reported in only summary form. In most cases, the specific details of the experiments and the detailed results are not presented. The two-year feeding study of the potassium salt of silvex (Kurosal) to beagle dogs reported by Mullison (1966) was selected to be the data set for deriving the PHG. In this study, pathological changes were seen in the liver of male dogs that consumed the 190 ppm diet of silvex. According to Gehring and Betso (1978), the damage consisted of mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation, and the evaluation was apparently based on the three animals of each sex that were alive at the end of the two-year study. The NOAEL was identified as 56 ppm for the male dogs, which was reported by Mullison as being equivalent to 0.9 mg/kg/day of the silvex acid. This was the lowest NOAEL seen in any of the studies and is appropriate for deriving the PHG. A similar NOAEL of 2.6 mg/kg/day was obtained in a 2-year study with 25 male and 25 female rats."

"One item that was not clear to this reviewer was how the 56 ppm "no ill-effect" level was converted by Mullison to the 0.9 mg/kg/day value. He indicates that the acid equivalent of the Kurosal SL formulation was 53.4%. If so, the formulation contained ingredients other than the potassium salt of Silvex. If the composition is available, it would be useful to mention these other ingredients in the report. The conversion from 30 ppm (56 ppm x 0.534) to 0.9 mg/kg/day appears to have been based upon the actual food consumption of the dogs, although this is not spelled out in the text. In spite of this weakness, I would agree that the use of the doses reported by the author should be preferred over that derived using default food consumption values."

Response 3: The composition of the Kurosal SL formulation used in the dog study was not included in any of the publications. It is correct that this proposed PHG assumes that the final NOAEL includes a correction for food consumption. This is now stated where the study is discussed, in the "Chronic Toxicity/Carcinogenicity" section.

Comment 4: "As indicated above, the agency has identified a NOAEL and used uncertainty factors to estimate a safe exposure level. This is a well established approach and seems to be appropriate in this situation. This would also seem to be the only feasible method given the limited information available on silvex and presented in the Mullison report. The agency has used three uncertainty factors – one 10X factor to account for interspecies differences, a 10X factor to account for variability within humans, and a 10X factor to account for numerous study deficiencies and data gaps. The first two uncertainty factors are standard. The use of a third uncertainty factor would seem justified given the small sample size of the dog study, as well as the inadequacies in the cancer studies."

Response 4: No response required.

Comment 5: "The hepatic effects induced by silvex were considered relatively mild. In addition, dogs are likely to exhibit enhanced sensitivity to this herbicide, due to their reduced ability to excrete organic acids compared to other species (Gehring and Betso, 1978). This might be used as the basis for a modifying factor to reduce the magnitude of the third uncertainty factor mentioned above."

Response 5: The studies considered deficient by the proposed PHG document include developmental toxicity, reproductive toxicity and carcinogenicity. These are normally conducted in rodents, and in the case of developmental toxicity, also in rabbits. Since it is problematic to predict carcinogenicity or developmental/reproductive toxicity in rodents/rabbits based on chronic toxicity in dogs, we think it reasonable to retain a factor of ten for these serious study deficiencies and data gaps.

Comment 6: "There is minimal explicit description of the uncertainties in the evaluation. However, several of these are readily apparent and mentioned in explaining the uncertainty factors used."

Response 6: No response required.

Comment 7: "photochemically produced hydroxyl ions" should read "photochemically produced hydroxyl radicals."

Response 7: This correction has been made in the document.

Comment 8: "Kuron is the propylene glycol isobutyl ether ester of silvex rather than the butyl ether ester as listed."

Response 8: The PHG document has been corrected accordingly.

Comment 9: "In addition to the mutagenicity testing in Salmonella, silvex has also been tested in the SOS microplate assay. These results should also be mentioned. References to the three published studies are presented below."

Response 9: Two of these references are now discussed in the "Genetic Toxicity" section of the PHG document.

Comment 10: "The use of (p=0.01) doesn't make sense in this context. This should be eliminated or clarified." (Page 10.)

Response 10: The PHG document has been corrected to read p>0.01.

Comment 11: "The discussion of the adverse effects of TCDD/herbicides seems somewhat limited. I would recommend using the conclusions from the Institute of Medicine's reports on Agent Orange: TCDD and herbicides to summarize the carcinogenic and non carcinogenic effects associated with TCDD and herbicide exposure.

Response 11: A discussion of the Institute of Medicine's report has been added to the section "Toxicological Effects in Humans."

Comment 12: The Gintautas et al. (1992) article also indicates that phenoxy herbicides showed an unexpected resistance to microbial degradation. This would seem to be an important point, that if applicable to silvex, should be included in the Water section.

Response 12: The greater apparent resistance of the chlorphenoxyproprionic acids to microbial degradation is now discussed at the end of the "Water" section.