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**RESPONSE TO KEY ISSUES RAISED BY PUBLIC REVIEW COMMENTS ON
HEALTH ASSESSMENT DOCUMENT FOR POLYCHLORINATED DIBENZO-*p*-DIOXINS**

EPA-600/8-84-014A, May 1984

External Review Draft

Prepared by

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November 1984

1. Comment: This is a concise, well-written review and evaluation of published information on 2,3,7,8-tetra-CDD, on 1,2,3,7,8-penta-CDD and two hexa-CDD isomers (1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD). It will be a most valuable reference work. However, from this reviewer's perspective it appears regrettable that the focus of the document was kept so narrow, given the wide range of potentially dioxin-contaminated industrial chemicals, herbicides and other pesticides, antimicrobials, and drugs identified in the 1980 U.S. EPA "Dioxins" document (EPA 600/2-80-197), and the published and unpublished studies available on 2,7-diCDD, 1,3,7-tri-CDD, 1,3,6,8-tetra CDD, 1,3,7,9-tetra CDD and octa-CDD. Some mention should also have been made of chlorinated azoxybenzenes etc. It might have been very useful to have at least an addendum with a comprehensive listing of additional relevant published references on these compounds.

Response: This document has been prepared at the request of the Office of Air Quality Planning and Standards (OAQPS). The OAQPS selected the congeners and isomers for discussion in this document.

2. Comment: 2.1. Summary. Regulatory limits for permissible levels of 2,3,7,8-TCDD in 2,4,5-T, fenoprop, and in fish and other food sources, as well as similar limits for dioxins in 2,4-D and chlorophenols, set by the U.S. and other countries might have been mentioned. For recent examples, see e.g. U.S. EPA Position document 4 on wood preservatives; Agriculture Canada Memorandum to Registrants No. R-1-216 and Trade Memorandum T-1-233 on 2,4-D which set byproduct "production limits" for 2,7-di-, 1,3,7-tri- and 1,3,6,8/1,3,7,9-tetra CDD (see Ref 1,2 attached), an Agriculture Canada Memorandum on chlorophenols also proposes production limits on HxCDD.

Response: Regulatory limits pertaining to the chemicals discussed in this document have been dealt with in Chapter 13.

3. Comment: Page 2-3, last paragraph. Should spell out the actual LD50 values of 1157-5051 µg/kg for the hamster.

Response: The final draft of this document will reflect this.

4. Comment: Page 2-6, last continued paragraph. Should be corrected to read 1 ng/kg/day.

Response: The final draft of this document will reflect this.

5. Comment: 2-2, line 8. "highest levels" suggest including numerical value so the reader can understand what is considered a high level.

Response: Since there is great variation in the range of the levels it is felt not to give the levels in the summary. However, detailed figures have been given in Table 6-3 and 6-4.

6. Comment: 2-3, lines 18-19. Change to "... some of the most acutely toxic compounds ... for male guinea pigs being 0.6-2.1 $\mu\text{g}/\text{kg}$ "

Response: Since 2,3,7,8-TCDD is acutely as well as chronically one of the most toxic compounds known, it is felt not to change the statement as it currently appears in HAD. However, it will be indicated that this is the lowest LD_{50} value.

7. Comment: 2-3, line 22. Although 2,3,7,8-TCDD is highly toxic in all species tested -- The chemical may be toxic in all species but is not highly toxic in all species. The species differences observed for TCDD should be given more importance in discussions rather than the toxicity.

Response: 2,3,7,8-TCDD is toxic at 0.6 $\mu\text{g}/\text{kg}$ dose for the guinea pig (the most sensitive species) and for the hamster (the least sensitive species) toxicity can be expressed at 5.5 mg/kg , a dose that is low in comparison with most other chemicals. Accordingly, the statement as it appears in HAD correctly reflects the current understanding of 2,3,7,8-TCDD toxicity.

8. Comment: 2-3, line 24. Characteristic symptoms -- more correct to state signs.

Response: The final draft of HAD will reflect this correction.

9. Comment: 2-4, line 1-6. A statement indicating that none of the responses observed are in and of themselves the cause of death.

Response: This is just the summary. The text explains this.

10. Comment: 2-4, line 7. Herbicide should be singular if the reference is to 2,4,5-T which is the only herbicide to contain 2,3,7,8-TCDD as a contaminant.

Response: 2,4,5-T: (2,4,5-Trichlorophenoxy) acetic acid and Silvex: 2-(2,4,5-Trichlorophenoxy) propionic acid are herbicides that contain 2,3,7,8-TCDD as contaminant. No change is warranted.

11. Comment: 2-4, lines 9-10. Change to "... with exposure leading in some cases to ..." remove "porphyria cutanea tarda".

Response: Since in animals 2,3,7,8-TCDD can induce porphyria and people exposed occupationally to 2,3,7,8-TCDD and other chemicals have developed porphyria cutanea tarda (PCT), it would not be considered prudent to remove PCT as one of the symptoms of 2,3,7,8-TCDD exposure.

12. Comment: 2-4, line 7-15. The paragraph should be reconstructed to indicate that signs of toxicity observed in man exposed to chemicals containing TCDD often reflect the signs of toxicity of the chemical as observed in animals, but the only signs associated with TCDD are skin lesions.

Response: Epidemiologic studies and case reports suggest that signs and symptoms in addition to chloracne are associated with 2,3,7,8-TCDD exposure; it is felt that the paragraph should remain as it appears now.

13. Comment: 2-4, lines 23-24. Certainly does not reflect the presentation in Chapter 10. Surprising that Section 2.3. "Needs for Future Research" does not have mutagenicity testing listed.

Response: The purpose of mutagenicity testing is to determine whether the chemical should be elected for animal bioassay. Since 2,3,7,8-TCDD is a proven animal carcinogen it will not be for the best interest for a regulatory Agency that further short term tests should be done and will not add further guidance for regulating 2,3,7,8-TCDD.

However, to determine the mechanism of carcinogenesis by 2,3,7,8-TCDD and other mutagenicity studies, DNA adduct, defective DNA repair, sister-chromatid exchange studies can be suggested.

14. Comment: 2-5, lines 19-20. These chemicals are highly toxic to certain animal species. Differences in species response should be made in these discussions.

Response: Same as for Comment 7.

15. Comment: 2-5, line 27. Fetus of certain species are sensitive to TCDD but a generalized statement should not be made.

Response: The words "in the species studied" will be added to this sentence.

16. Comment: 3.3. Analytical Methodology. Cochrane et al. (1981) might have been cited in connection with the identification of tetra-CDD in chlorophenoxy herbicides. (This reference is however cited in 4.3.1.2., p. 4-12.) For adipose tissue, Stanley et al. (1983), Ryan and Williams (1983), Schecter et al. (1983) or their later full publications might be cited (Refs. 3,4,5 attached).

Response: Such revisions will be made in the final draft of the document.

17. Comment: The Table 4-2 in the chapter on Environmental Sources lists major producers. The table is outdated.

Response: The title of the table will be changed to: "Locations of Companies that have been major producers and formulators of chlorophenols and their derivatives".

18. Comment: The HAD is incorrect to characterize the trace chemistries of fire report as limiting precursors to "many chlorinated hydrocarbons". ... Dow has recently published a paper by Nestruck and Lamparski in showing that burning of untreated wood, the unlocated nature of the wood carefully documented, produces dioxins.

Another unpublished study by Lamparski et al. found levels of dioxin in milorganite (municipal sludge sold as fertilizer), collected in 1933 in Milwaukee and sealed until 1982, to be roughly equivalent to dioxin levels found in 1982 milorganite sample. The year 1933 predates production of chlorinated phenols and many other of the narrow list of supposed precursors.

Response: No detailed reference of the paper by Nestruck and Lamparski have been supplied with the comment. EPA will contact these authors to get these papers.

J.M. Czuczwa and R.A. Hites (1984), in a presentation entitled "Trends in sediment case" at the 4th International Symposium on Chlorinated Dioxins and Related Compounds, discussed about their studies on the presence of PCDD and PCDF preserved in the sediments from the Great Lakes including the sediment core from Siskiwit Lake, Isle Royale. The sediment that came from Siskiwit Lake was used because it received only atmospheric inputs. In all cases the authors detected the flux of PCDD and PCDF, which began at about 1940. When this "1940 horizon" was compared with combustion trends in the last century, the authors found evidence that the combustion of synthetic chlorinated organic chemicals is the primary source of PCDD and PCDF. Furthermore, the authors responded that the flux of PCDD and PCDF to three Swiss Lakes, where combustion has been extensive during the last century, increased only after the development of the chlorinated organic chemical industry.

The trace chemistries of fire as proposed by the scientist from Dow Company as the source of PCDD into the environment remains still a controversial issue. Accordingly, no change in HAD is warranted.

19. Comment: 4.3.1.1., p. 4-5. Legend to Figure at bottom of page should read: 1,2,4,5-tetrachlorbenzene, not trichlorbenzene.

Response: The final draft will have this correction.

20. Comment: p. 4-6. Reference could be made to Canadian chlorophenol production figures (Jones, 1981, 1984; Refs. 6,7 attached) and Interdepartmental Committee on Toxic Chemicals 1983 (Ref. 8 attached).

Response: These references will be included in the final draft.

21. Comment: 4.3.1.4. The diphenylether pesticide TOK contains 2,7-dicdd; the same is true for dicamba.
- Response: Since these chemicals are beyond the scope of this document, this information will not be added in the document.
22. Comment: 4.5.2. The presence of 1,3,6,8- and 1,3,7,9-TCDD in epigeal parts of plants might also have been due to contamination by herbicides and other pesticides containing TCDDS (Yamagishi et al., 1981).
- Response: The above statement will be included in this section.
23. Comment: 4.4. For additional relevant information see also Jones (1981, 1984) (Refs. 6,7).
- Response: These references will be included in this section.
24. Comment: 7-18, last line. Remove "heavily" vague and the degree of contamination is not a question.
- Response: The final draft will reflect this suggestion and the word "heavily" will be removed.
25. Comment: 8-1, paragraph 1. "... may depend on the species or strain examined." Major differences exist with some strains tested.
- Response: The final draft will reflect this change.
26. Comment: 8-5, lines 1-4. Poorly worded -- Change to "In general, ... and guinea pigs (remove words) required a specific ..."
- Response: The final draft will reflect this change.
27. Comment: 8-60, paragraph 2, line 1. "Chronic exposure to 2,3,7,8-TCDD has probably occurred in ..." Current wording infers presently occurring and that it is positively known that the workers were exposed to 2,3,7,8-TCDD.
- Response: The final draft will reflect this change.
28. Comment: 8-60, paragraph 2, Line 3. "Chloracne is generally the first. Remove "normally" -- a poor word in this usage.
- Response: The final draft will reflect this change.
29. Comment: 8-60, paragraph 2, lines 6-7. a) Remove "porphyria cutanea tarda" -- there is not an adequate reference for this effect given. Also, see attached paper being submitted for publication that discusses this in detail.
- b) Also, change "associated with" to "reported in individuals that may have had" ...

Response: a) Same as Comment 11.

b) The final draft will read as ... "reported in individuals that have had" ...

30. Comment: The reinterpretation of the NTP-chronic toxicity study of 2,3,7,8-TCDD is unwarranted (Page 8-3).

The HAD concludes a NOEL was not established in the NTP study, because of "toxic hepatitis" in the lower and middle doses. This conclusion is unwarranted. First, the use of the category "toxic hepatitis" is non-specific and inappropriate. Second, the authors of the NTP study found that NOEL was established for "toxic hepatitis" at the low and middle dose levels. Third, the data do not support the HAD conclusion. For male mice, the incidence rates for "toxic hepatitis" was 0-4% for the various control groups, 2% for low, 0% for the middle dose and 72% for the high dose. In female mice, the incidence rates for toxic hepatitis were 0, 2, 4 and 72% for the control, low, middle and high dose groups. These data do not come close to suggesting an effect at the low and middle doses. A closer look at the diagnostic categories for liver toxicity included in the NTP report gives little indication of any dose response for liver degenerative, necrotic or inflammatory change at the middle or low dose levels.

Response: Toxic hepatitis describes general toxic effect in the liver.

Table D2 in page 172 of NTP gavage study document describes non-neoplastic lesions in vehicle control and dosed groups of male mice. This table indicates that the incidence of toxic hepatitis in vehicle control was 1(4%), low dose 5(10%), mid dose 3(60%) and high dose 44(88%).

The number of mice with lesions of the liver study used and the incidence of toxic hepatitis are enumerated in Table 11 (page 53) of the NTP gavage study. Toxic hepatitis incidence data of this study discussed in HAD concur with NTP's data.

The only error detected in HAD is the incidence for control group. The correct figure is 1/73 instead of 0/73. This correction will appear in the final draft.

31. Comment: The HAD also concluded that a NOEL was not established in the mouse study by Toth et al. Much more information is required on the alleged incidence of amyloidosis in the lowest dose, especially on the spontaneous incidence rate of amyloidosis in the strain of mice used, and the thoroughness of histopathologic examination in a very sketchily reported study.

Response: The concomitant control group had an incidence of adverse effect of 0. Although the incidence in the low dosed group was only 5/44, there appears to be a dose response relationship which supports the conclusion that the effects observed in this group were treatment related.

32. Comment: 8-62, line 10. Add after "... to 2,3,7,8-TCDD and other compounds ()." ;

Response: The final draft will be changed accordingly.

33. Comment: 8-63, lines 2-3. If the results were not significant, do not imply that aberrations were more frequent. Change to "Lymphocyte aberrations of exposed individuals when compared to values of "healthy" individuals showed no significant differences."

Response: The sentence reflects the raw data in the study and clearly indicates that the elevation of lymphocyte aberrations was not significant. No change is required.

34. Comment: 8-63, next to last sentence. "... was believed to be minimal." This should be removed; the exposure level was unknown as were the levels of exposure for other people in the area. To state that these people were "minimal" without a base for comparison is unfounded.

Response: This sentence reflects the observation by the authors on the work habits of the clean-up crew. No change is required.

35. Comment: 8-64, paragraph 2. The most notable results from the Missouri episode was that these children were exposed to levels that killed horses, small pets and birds and none of the children died and in fact all recovered. This information should be brought out here.

Response: There is no data on the exposure of different species and comparison between species here. Since such data are not available, no change in HAD is warranted.

36. Comment: 8-64 to 8-65, Poland study. The description should note that Poland examined for PCT but did not find any.

Response: We will add in the results of the study by Bleiberg et al. (1964), which originally described PCT in the group of workers. Further it will be stated that on re-examination after 6 years, Poland et al. (1971) could not detect PCT in any of the workers of the plant.

37. Comment: 8-65, lines 8-9. Remove sentence and insert "All eight workers had decreased levels of high-density lipoprotein cholesterol levels and elevated total cholesterol levels."

Response: The final draft will reflect change.

38. Comment: 8-67, 5th line from bottom. Change to "... (forest industries) who may have been exposed ..." Currently reads present tense, this should be past tense.

Response: The final draft will reflect this change.

39. Comment: 8-68, lines 2-5. Concerning sensitivity, the statement can be made that "To date the data for humans indicates that they are not a sensitive species to the effects from TCDD."

Response: Data is inadequate to conclude that humans are less sensitive.

40. Comment: 8-71, 8.3.1.2., line 10. Add "... biologic responses in animals which ..."

Response: Since many of these signs and symptoms have been observed in humans as well as in animals, no change is warranted.

41. Comment: 8-71, 8.3.1.2., lines 14-15. Item "4) PCT"; this should be removed as noted from previous comments.

Response: Same as Comment 11.

42. Comment: 8-72, paragraph 2, lines 5-9. "... an excellent correlation between ... 3 different items? Need to explain.

Response: Since the correlation is between toxicity and AHH induction, the statement should be kept as it reads now.

43. Comment: 8-73, lines 1-4. ... and again a correlation between 3 different items?

A correlation is between 2 items; also need to explain the "degree" is this numerical or judgmental?

Response: The word "between" on line 1 of the 8-73 will be changed to "among".

44. Comment: 8-83, 8.4.2., lines 2-3. Change to "... lead to chloracne. Other symptoms reported are altered ... abnormalities. (remove porphyria cutanea tarda).

Response: It is considered that separating chloracne from other symptoms does not further the clarification of clinical observations and hence this change is not warranted.

45. Comment: 8-83, 8.4.2., last line. Change to "... 2,3,7,8-TCDD subside or in the case of chloracne may persist..."

Response: There is evidence that signs other than chloracne may persist for many years. No change is warranted.

46. Comment: 8.1.1.2., 8.1.1.5.2., 8.3.3. The findings of Thunberg et al. (1984) on 2,3,7,8-TCDD and vitamin A storage are of interest here (Ref. 9).

Response: This reference will be included in sections 8.1.1.2., 8.1.1.5.2. and 8.3.3.

48. Comment: 8.2. Five cases of heavy chloracne in workers exposed to 2,4,5-T herbicide mixtures were described by Londono (1966), Med. cutanea 3: 225-232. A number of cases which have been observed in South American workers producing pentachlorophenol or its salts (E. Astolfi, personal communication).

In addition, chloracne may be caused by tetrachloroazoxybenzenes, a possibility which could lead to presumption of exposure to 2,3,7,8-TCDD.

Response: The Londono (1966) paper will be included in Section 8.2. EPA will contact E. Astolfi to get the data on South American workers for inclusion in this section.

49. Comment: 9-18, line 3. Remove "single".

Response: The final draft will reflect this change.

50. Comment: 9-18, line 15. It appears that the HAD is inferring that an increase in extra ribs is a teratogenic effect. This is not so.

Response: Since there is difference of opinion among the teratologist on this issue, it is felt that the statement should be kept as it reads now.

51. Comment: 9-18, lines 18-20. Confusing, rewrite "... was an increase ($p < 0.05$) in total soft-tissue anomalies from the control (0/87) to 3/78, 2/33 and 2/28 in the 0.1, 0.25 and 0.5 $\mu\text{g/kg}$ treatment group, respectively.

Response: Will be changed as follows: "There was an increase in total soft-tissue anomalies from 0/87 to 3/78, 2/33 ($p < 0.05$) and 2/28 ($p < 0.05$) in the control, 0.1, 0.25 and 0.5 $\mu\text{g/kg}$ groups, respectively. But there was no significant increase for the incidence where specific soft-tissue anomalies were concerned."

52. Comment: The NOEL in the Murray et al. reproduction study is .001 mg/kg/day.

This was the conclusion of the authors of the study. In addition, the EPA Science Advisory Panel specifically addressed this issue, and agreed with Murray et al., that .001 $\mu\text{g/kg/day}$ was the NOEL. The statistical reevaluation of Nisbet and Paxton contained a number of errors, as demonstrated during the cross-examination of Paxton during the 2,4,5-T cancellation hearings. The Nisbet and Paxton reevaluation focussed on statistical aspects of the data, and failed to adequately consider biological factors which aid trained toxicologists in making judgments on the existence of NOELs.

Response: HAD adequately reflects the conclusions derived by Murray et al. (1979), SAB (U.S. EPA, 1979b) and Nisbet and Paxton (1982). It is clearly indicated in the HAD that the review by SAB indicates that 0.001 $\mu\text{g/kg/day}$ is a NOEL in this study.

53. Comment: TCDD has shown to be teratogenic only in mice, not in rats or other species. Pages 2-4, 9-1 and 9-34 should be changed to reflect this.

Response: During the peer review process this issue was discussed extensively and it was felt by the panel that 2,3,7,8-TCDD is teratogenic in mice, rats, rabbits and ferrets.

54. Comment: Page 9-19. The section pertaining to the study by Muscarella et al. (1982) in ferrets is based on only sketchy details in a short abstract and has not been peer reviewed. If this study is to be considered the complete experimental data base should be evaluated.

Response: HAD clearly indicates that this study was reported in an abstract form. A detailed paper on this observation is not yet available.

55. Comment: The HAD acknowledges that the Alsea study has been criticized. Although mentioning three "unpublished" critical reviews (the Alsea study has also not been published) EPA failed to mention there were at least 15 other reviews critical of the Alsea study, and no favorable reviews.

In discussing the epidemiological evidence stemming from the accidental contamination of Seveso, Italy, the HAD notes several factors -- mainly involving the then existing Italian system for reporting birth defects -- complicating the task of conducting accurate studies. Nevertheless, it is certainly reassuring that no increase in reproductive problems have been seen in a population receiving the exposure to 2,3,7,8-TCDD many orders of magnitude higher than could be expected from exposures in the environment. This should be noted in the HAD.

Response: The HAD reports the available data and it is considered that the reader will be able to derive appropriate conclusion from this presentation. Consequently, no changes are warranted.

56. Comment: 9-23, lines 1-3. The Oregon study is too flawed to use as a reference here, the New Zealand study and Australian studies are both questionable. Thus, the first sentence should start "An association ..."

Response: The strength and weaknesses of individual studies are discussed in the text of this section. No change is warranted.

57. Comment: 9-28, next to last line. "In any event..." This should be removed, it implies that the statement is questionable.

Response: This change will be made in the final draft.

58. Comment: 9-30, lines 4-5. This sentence needs to be rewritten. It implies that there should be an effect.

Response: These lines will be changed as follows: "There are several inadequacies in these studies which might make them insensitive in detecting reproductive effects."

59. Comment: 9-31, lines 12-13. This sentence should be rewritten, it also implies that a positive result is expected and that a mistake was made in the attempt.

Response: This sentence reflects the conclusion derived by the author. No change is warranted.

60. Comment: 9-32, lines 10-15. With seven counties in Michigan showing the increase in cleft palate it is inappropriate to try and implicate that 2,3,7,8-TCDD may have played a part in this increase. [This whole section on Michigan is poorly written and extremely slanted to try and make TCDD appear as a bad actor.]

Response: This portion reflects the conclusion derived by the Michigan Department of Public Health (1983a).

61. Comment: 9-34, line 4. Change sentence to "For mice a MED of ..."

Response: This change will be made in the final draft.

62. Comment: 9-34, paragraph 2, lines 1-2. This is not a true statement, TCDD has not consistently produced teratogenic effects in all strains of rats.

Response: The word "consistently" will be deleted.

63. Comment: 9. At least one tetrachlorozaoxybenzene is also teratogenic, and might act as a confounding factor in studies on health effects of pesticides (Hassoun et al., 1984, Ref. 10).

The possible contribution of dioxins in 2,4,-D and 2,4,5-T to teratogenic and other adverse reproductive effects was evaluated in NRCC (1984, Ref. 11).

A full report on the Health Protection Branch teratogenicity experiments with 2,4-D and 2,4,5-T is found in Khera and McKinley (1972), Toxicol. Appl. Pharmacol. 22: 14-28; the reference to Khera et al. (1971) cited on p. 15-43 in the Review Draft is to a preliminary report only.

Response: The final draft will have the above discussions.

64. Comment: In connection with "Agent Orange" the already released U.S. Vietnam veteran studies (Ref. 13) and the Australian Vietnam Veterans birth defects study (Ref. 14) could be mentioned.

Response: These studies will be included in the final draft.

65. Comment: 9-34, paragraph 3, line 3. Again the assumption is being implied that TCDD does cause "a teratogenic response" in these species. [These types of statements implying effects that have not been noted or are questionable at best must be rewritten (removed) from the HAD. Science must be kept accurate, but the "act" of presenting the information must be strictly controlled.]

Response: The word "demonstrate" will be changed to "evaluate".

66. Comment: 9-34, paragraph 4, line 3. Change to "although two studies have shown a questionable association between ... other studies have not." The use of the word "failed" again implies that the negative studies were flawed and that a positive response should have been noted. [This is not good reporting of the facts and is very biased.]

Response: The word "failed" will be changed to "not".

67. Comment: 9-35, last sentence. Again, a one-sided sentence that implies humans will show teratogenic effects.

Response: The sentence is self-explanatory. No change is warranted.

68. Comment: It is stated in the External Review Draft of the Health Assessment Document for Polychlorinated Dibenzo-p-Dioxins that "Schwetz et al. (1973) demonstrated that HxCDD (isomers not specified) was both fetotoxic and teratogenic when administered to pregnant rats at 100 mg/kg on days 6-15 of gestation." This information should not stand alone. Statements should be added to the report detailing the differences between fetotoxicity and teratogenicity and making a clear distinction between the fetotoxic and teratogenic effects of HxCDD at the administered doses. It should be stated in the

report that HxCDD is fetotoxic and teratogenic to rats only at high doses, and man is unlikely to be exposed to these high doses.

Schwetz et al. (1973) administered 0.1, 1.0, 10 or 100 mg HxCDD/kg/day (purity >99%, two unspecified isomers in ratio of 89:11) in corn oil:acetone (9:1) solutions by gavage to groups of pregnant Sprague-Dawley rats on days 6 through 15 of gestation.¹ On day 21 of gestation, the pregnant rats were killed and necropsies performed, and the fetuses were examined. A dose-related decrease in maternal weight gain was observed during gestation; at gross necropsy, evidence of maternal toxicity was seen only in rats receiving 100 mg HxCDD/kg/day. The incidence of early resorptions did not increase with dosage of HxCDD but there was a significant increase in late resorptions. The 10 and 100 mg HxCDD/kg/day doses were highly fetotoxic during late gestation and surviving fetuses were of significantly decreased weight and length. The incidences of fetal soft tissue and skeletal anomalies were significantly increased with the 100 mg HxCDD/kg/day dose; the incidences of cleft palate, subcutaneous edema, split vertebral centra, and split sternbrae were significantly greater in the treated group than in the controls. Subcutaneous edema occurred with a significantly greater incidence in the 1.0 and 10 mg HxCDD/kg/day dosage groups than in the controls. Fetal anomalies were not significantly increased in the fetuses exposed to 0.1 mg HxCDD/kg/day. Schwetz et al. concluded that a 100 mg HxCDD/kg/day dose administered by gavage on days 6 through 15 of gestation was both teratogenic and embryotoxic to rats.

EPA has previously reviewed the Schwetz et al. (1973) study in Position Document 1 ("PD-1") which initiated in 1978 a rebuttable presumption against registration ("RPAR") review of pentachlorophenol under the Federal Insecticide, Fungicide and Rodenticide Act. In PD-1, EPA stated that HxCDD was both fetotoxic and teratogenic. AWPI solicited Dr. Schwetz' views regarding EPA's reliance upon his 1973 work as evidence that HxCDD includes fetotoxic and teratogenic effects. Dr. Schwetz' comments were as follows:

Regarding (HxCDD), a statistically significant incidence of a malformation, cleft palate, was observed in rats given 100 µg (HxCDD)/kg/day on days 6 through 15 of gestation (Schwetz et al., 1973). In Section II-A-2-b of the Position Document 1, the Working Group states that "They found statistically significant increases over the controls in all of the teratogenic parameters observed at 100 µg/kg." The only finding in this study indicative of a teratogenic event was the induction of cleft palate. The other findings, including dilated renal pelvis, subcutaneous edema, and abnormal vertebral development are evidence of

embryotoxicity but not teratogenicity. The Agency has correctly concluded that a (HxCDD) content of pentachlorophenol does not represent a teratologic hazard to humans.

Response: The document reflects the conclusions derived by the authors.

69. Comment: HxCDD (isomers not specified) is fetotoxic and teratogenic to rats only at extremely high doses; man is unlikely to be exposed to these high doses.

Response: Not enough exposure assessment on HxCDD has been done to derive a conclusion as stated in this comment. No change is warranted in the document.

70. Comment: 10-1, line 21. According to the paper, the concentrations were less than 2-3 ug/ml.

Response: This is correct. The document will be changed according to this comment.

71. Comment: 10-1, line 23. Some interpretation should be given to accepting a positive response at 1% survival. To list this on Table 10-1 without an indication of some doubt does not reflect good scientific judgment.

Response: The following statement will be inserted on page 10-1, two lines up from the bottom after "colonies/surviving cells,": "This positive response is questionable because of the extremely high toxicity observed." Also, the "+" will be changed in Table 10-1 under TA1532 for the Hussain et al. (1972) study to "QR".

72. Comment: 10-3, lines 19-22. The values for the duplicate sample run at 2 $\mu\text{g/ml}$ should be given as well as a criteria raised to judge the results. The results at 4 $\mu\text{g/ml}$ should also be discussed in relationship to the final conclusion. One might judge these results questionable rather than positive.

Response: The following sentences will be inserted after the sentence ending with "cell survival." on line 23, page 10-3: A duplicate sample resulted in an 82% decrease in survival and a mutation frequency of 34×10^{-6} . These results indicate that the reproducibility of the assay may not have been perfect, but both results are well above the control value of 2.2×10^{-6} . A dose-response relationship was not observed, indicating that the results at 2 $\mu\text{g/ml}$ are only suggestive of a positive response. In addition, the positive results were obtained at a concentration of 2,3,7,8-TCDD (2 $\mu\text{g/ml}$) that was well above solubility in water (0.2 $\mu\text{g/l}$), which also casts doubt on the significance of the positive result.

73. Comment: 10-5. The references to Bronzetti et al. should be checked. I believe the reference for 10-6 should be to the 1980 work not 1983.

Response: The correct reference is Bronzetti et al. (1982) and this reference will be corrected.

74. Comment: 10-6, lines 17-20. The discussion of Rogers et al. (1982) should include the result that: No significant mutation was noted in ouabain or cytosine arabinoside selective systems.

Response: "The discussion of Rogers et al. (1982) will include "No significant mutation was noted in ouabain or cytosine arabinoside selective systems."

75. Comment: 10-6, lines 26-28. The studies referred to are NTP government sponsored results and they cannot be evaluated because procedures used to obtain the data cannot be found. In view of the importance of this data it would seem a better interpretation than this could be made.

Response: Procedures used in this experiment are not available to EPA.

76. Comment: The National Cancer Institute (NCI) data for hexachlorodibenzo-p-dioxin (HxCDD) was seriously flawed and cannot be considered "sufficient" evidence of carcinogenicity. Even under the NCI's analysis, the data failed to show a significant increase in malignant tumors.

Response: Proliferative hepatic lesions in the liver of female Osborne-Mendel (OM) rats gavaged with HxCDD for 2 years have been examined or reviewed independently by the National Toxicology Program (NTP) pathologists and Drs. Squire, Schueler, Haberman, and Hildebrandt. The latter pathologists (Squire, Schueler, Haberman, Hildebrandt) all indicate in their review findings that the total incidence of neoplastic hepatic lesions were markedly reduced from that reported by the original NTP pathologists. Further, all pathologists agree that HxCDD induces significant hepatotoxicity. It is not uniformly agreed, however, what the exact nature of some of these proliferative hepatic lesions represent, i.e., non-neoplastic vs. neoplastic.

The association of hepatocellular carcinoma in man with long-term toxic liver injury (e.g., ethyl alcohol, aflatoxin) is well established. Animals, including the rat, respond to prolonged hepatotoxicity in a similar manner, even though some species differences exist. Therefore, in a 2-year rodent study (virtually a lifetime) with a compound that produces marked hepatotoxicity, it would be reasonable to expect an increased incidence of neoplasia in the liver of dosed animals. While Dr. Squire states that many hepatic nodules in this study were difficult to characterize as being neoplastic, it must also be emphasized that many nodules were

equally difficult to characterize as non-neoplastic. Dr. Squire also states that microscopic features of cirrhotic or regenerative nodules often appear more bizarre than neoplastic lesions. Since bizarre histomorphology was not reported by the latter pathologists (Squire, Schueler, Haberman, Hildebrandt) to be associated with the HxCDD-induced proliferative lesions, this might further point to their neoplastic as opposed to regenerative nature.

It is apparent that the histomorphologic separation of non-neoplastic proliferative hepatocellular lesions from benign neoplastic hepatocellular lesions in the rat is often unclear, especially in the case of toxic hepatic injury. There appear to be more similarities than differences between the lesions which does not always allow for a distinct or categorical diagnosis.

In view of this, no more definite evidence is available to conclude that these lesions are non-neoplastic than there is to conclude that they are neoplastic. Whether the lesions are neoplastic or not, most would agree that they are induced by HxCDD, they are proliferative, and many are likely to be neoplastic or would become neoplastic if allowed to progress.

The review of all data accumulated to this point suggests that the incidence of hepatic neoplasms, although probably lower than that originally reported by NTP, is still increased above historical controls in female rats and constitutes a tumorigenic response induced by HxCDD in rats.

Dr. Squire states in his January 9, 1984, letter that "the HxCDD bioassay conducted by the NCI provides only a weak hepatocarcinogenic response in female rats and mice "and that" one could change my wording to limited evidence, according to the International Agency for Research on Cancer (IARC) criteria."

Even if one were to use the pathology data for male and female rats from Dr. Squire's June 29, 1983, report, which had the lowest incidence figures of any reviewing pathologist, the combined incidences of hepatocellular carcinoma and adenomas in high-dose females is still statistically significant by Fisher's exact test when compared to vehicle controls and yields a borderline response in male rats (i.e., females--7/50 in high dose vs. 1/75 in vehicle controls for a P value of 0.006; males--3/49 in high dose vs. 0/75 in vehicle controls for a value of 0.059). In either case, the data were also positive for dose-trend.

In mice, the only neoplastic changes reported by NTP were increased incidences of hepatocellular adenomas and carcinomas in males and females. Using the original NTP data, the combined incidences of hepatocellular adenomas and carcinomas were statistically significant by Fisher's exact test

in both male and female mice (i.e., males--24/48 in high dose vs. 15/73 in vehicle controls for a P value of 7.33×10^{-4} ; females--10/47 in high dose vs. 3/73 in vehicle controls for a P value of 0.004). Even if one were to use the pathology data for female mice from Dr. Squire's June 29, 1983 report, the combined incidences of hepatocellular carcinomas and adenomas is still statistically significant in female mice (i.e., 8/48 in high dose vs. 3/74 in vehicle controls for a P value of 0.02). In either case, the data were also positive for dose-trend.

It can thus be concluded that the 1:2 mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD was carcinogenic in animals as indicated by a statistically significant dose-related increased incidence in liver tumors in both rats and mice as was stated before (memo dated January 3, 1984, from B. Haberman and S. Bayard/CAG to J. Bellin/OSW), even if one were to use Dr. Squire's incidence figures from his June 29, 1983, report.

Historically, the Carcinogen Assessment Group (CAG) has been using a modified IARC criteria scheme for weighing the evidence for carcinogenicity of various compounds. This scheme considered the combined incidences of certain benign and malignant tumors for purposes of carcinogen evaluation where there was evidence of a tumor progression, such as is seen in the liver. IARC (vol. 33, page 13, 1984) states with regard to the term carcinogenicity that "the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign tumours." Further, IARC (Monograph Supplement 2, page 69, 1980) states that "Chemical agents that markedly increase the incidence of benign tumours are now viewed with almost as much suspicion as potential human hazards as they would have been if the induced tumours had been malignant."

Using the U.S. Environmental Protection Agency (EPA) Proposed Guidelines for Carcinogen Risk Assessment (draft 1984), the experimental animal evidence for HxCDD carcinogenicity would be classified as "sufficient" (i.e., indicated by an increased incidence of combined malignant and benign tumors in multiple species). The overall evidence would then place HxCDD in Group B2--a probable human carcinogen, since there is inadequate evidence from human studies and sufficient evidence from animal studies.

77. Comment: The NCI data on HxCDD were severely flawed by the presence of tetrachlorodibenzo-p-dioxin as an impurity in the test material, which may have seriously affected the results. The use of corn oil gavage may have introduced other confounding factors.

Response: The HxCDD material containing the mixture of 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin had an impurity of 0.09%; this is partially attrib-

uted to 2,3,7,8-tetrachlorodibenzo-p-dioxin, which is one of the four TCDD isomers. The following table shows both observed and calculated liver tumor response for HxCDD and a 0.09% TCDD contaminant respectively. Since the calculated response for the 0.09% TCDD are so very low, it is reasonable to conclude that the impurity in the test did not contribute significantly to the observed carcinogenic response for HxCDD.

78. Comment: The use of corn oil gavage may have introduced other confounding factors.

Response: In the Kociba et al. TCDD rat study the compound was given in diet, whereas, in the NTP TCDD rat study, the compound was administered by gavage using the corn oil as vehicle. In both of these studies TCDD produced a clear positive carcinogenic response; therefore, it appears that corn oil has no obvious effect on the induction of carcinogenic response.

HxCDD, which is structurally related to TCDD, also produced a positive carcinogenic response in rats when the compound was administered by gavage using the corn oil as vehicle. The Carcinogen Assessment Group (CAG) considers that the observed carcinogenic response may not be mediated by corn oil.

79. Comment: The selection of liver tumor data for the HxCDD unit risk estimate is inappropriate. The EPA used the male rat liver tumor data from the NTP study, and female rat liver tumor data from a re-evaluation by Hildebrandt to calculate the unit risk for HxCDD. However, there is no mention of the 1983 Squire re-evaluation of the NTP study, although the EPA saw fit to use the Squire re-evaluation of the Kociba TCDD study as the most "sensitive" evaluation of TCDD oncogenesis. This highly selective use of data by the EPA is unscientific and inappropriate.

Response: The reasons for selecting the rat liver tumor data for the unit risk estimation of TCDD and HxCDD was discussed in Health Assessment Document for Polychlorinated Dibenzo-p-dioxins dated May 1984. The EPA's selection of histopathologic data is based on sound scientific judgment, and not based on who read the histopathologic slides.

80. Comment: Kociba et al. (1978) TCDD study. There was also a significant decrease incidence of endometrial hyperplasia, subcutaneous mammary tumors, pituitary adenomas, adrenal medullary hyperplastic nodules, pheochromocytomas, pancreatic acinar adenomas; all should be discussed. (This document is "chronically" one-sided and stresses the positive response data.)

Response: The CAG agrees that the Kociba et al. (1978) study on 2,3,7,8-tetrachlorodibenzo-p-dioxin shows a significant decreased incidence of endometrial hyperplasia, subcutaneous mammary tumors, pituitary adenomas, adrenal medullary hyperplastic nodules, pheochromocytomas, pancreatic, and acinar

Liver Tumor Response for HxCDD (Observed)
and TCDD Contaminant (Calculated)

Animal	HxCDD Dose ($\mu\text{g/kg/wk}$)	Liver Cancer Response Observed	0.09% TCDD Contaminant Dose ^a ($\mu\text{g/kg/wk}$)	Liver Cancer Response Calcu- lated 95% Upper Limit
Rat (OM)				
Male	5	4/48 ^b	0.0045	TCDD has shown no effect in NCI study
Female	5	18/50 ^c	0.0045	0.02/50 ^d
Mouse (B6C3F1)				
Male	5	24/48 ^e	0.0045	0.20/48 ^d
Female	10	10/47 ^f	0.009	0.22/47 ^e

^a It is assumed that all of the contaminant is 2,3,7,8-TCDD.

^b NTP reviewed.

^c Re-evaluation by Heldebrandt (see table 11-34).

^d Based on response in NCI 2,3,7,8-TCDD study-see table B-10.

^e see table B-11.

^f see table B-12.

adenomas. These results were not described in the Health Assessment Document because these findings have no bearing on the clear positive carcinogenic evidence observed by Kociba et al.

81. Comment: HxCDD and TCDD cause tumors through non-genetic mechanisms, and, therefore, should be considered "weak carcinogens."

Response: Currently no data exist on mutagenicity of HxCDD and available information concerning the mutagenicity of TCDD is inconclusive. HxCDD and TCDD both have been shown to be carcinogenic in long-term cancer bioassay studies. Although TCDD has been shown to be a promoter for rat liver cancer, it also induces a carcinogenic response in lung, tongue, and nasal turbinate for which a promotion effect is not demonstrated. The CAG considers that evidence is insufficient for suggesting the mechanism of carcinogenesis for HxCDD and TCDD.

The relative carcinogenic potencies of HxCDD and TCDD are presented in Table 11-36, Health Assessment Document. Relative Carcinogenic Potencies Among 54 Chemicals Evaluated by the Carcinogen Assessment Group. Quantitatively, in terms of low-dose response, 2,3,7,8-TCDD and the 1:2 mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD rank respectively, as the most potent and second most potent carcinogens that the CAG has evaluated.

82. Comment: The negative Ott study of an industrial cohort is discounted because dioxin exposures were "exceedingly low" although such exposures were likely to be as high as some of those in reported positive studies and are actually higher than dioxin exposures to the general population.

Response: As with most studies by Gerald Ott, this study is a cohort mortality study of a very small number of workers (204) that reported altogether only 11 deaths and as such is unlikely to provide enough power, given a latent period of 15-20 years, to detect even two or three fold excess risk of the relatively rare STS. This is true also with respect to total cancer in workers followed for the same length of time. (Only one of Ott's eleven deaths was due to cancer).

83. Comment: A British government report critical of the Hardell studies is discussed as "overly optimistic".

Response: The British government report entitled "Advisory Committee on Pesticides: Report on Advisory Committee on Phenoxy Acid Herbicides" was criticized by the Carcinogen Assessment Group (CAG) because of its too willing dismissal of the evidence of STS in the Hardell and Erikssen's studies while concurrently accepting as valid without critical comment the non-positive studies although questions have been raised concerning limitations in these studies. The British Report concluded that no evidence exists to alter their earlier conclusion that

formulations of phenoxy acid herbicides and related wood preservatives as "presently cleared" are safe and may continue to be used. Such as a blanket endorsement of the use of a substance for which sufficient questions have been raised concerning its health implications, seems a bit premature.

84. Comment: The section on cancer epidemiology is unfairly weighted in favor of the reported positive studies, especially Hardell.

Response: We have made every effort to present all the data from the epidemiologic studies in a careful and unbiased manner based upon all available information at the time. Advantages and limitations of each study were presented in a balanced manner. Where it appears that the author made an extra effort to explain or measure the impact of potentially limiting factors in his study such as was done by Hardell in his case control study utilizing color cancer controls (Hardell, L. 1981), we felt obligated to report on his efforts. It appears that Hardell took extra precautions to show that the presence of certain potential confounders could not have caused the statistically significant excess of STS and non-Hodgkins lymphomas among phenoxy acid and/or chlorophenol exposed persons. However, we do agree that selective recall is still present to some extent in the study. Observer bias could be kept under control by the researchers and it appears evident Hardell took suitable measures to eliminate it. On the other hand, selective recall would have been much more difficult to control. A credible argument could be made that persons with STS would be more likely to connect their cancer somehow with exposure to phenoxyacetic acid and/or chlorophenols than would non-STS persons because of the publicity and attention given to that possibility by the news media and the medical community. However, it does not seem likely that with the statistically significant risks ranging from a low of 5.3 to a high of 6.6 in Hardell's study, selective recall alone could have produced the significant risks seen.

85. Comment: Hardell included the seven sarcomas found in his observation study in the first STS case control study. This tends to make the results a "self-fulfilling" prophecy and is scientifically unsound.

Response: This argument has no meaning. The literature is replete with studies very similar in initial development. There is nothing unscientific about it. If a cluster of cases of an unusual type of cancer occurs in a given area, it is only natural that epidemiologists would want to know if the incidence of this cancer differs markedly from the incidence in the background population from which it came, hence, it may be necessary to conduct a rigorous epidemiologic investigation which would determine if a significant excess risk of that type of cancer exists. If it appears that this risk is

associated with exposure to a particular substance such as the mentioned herbicides, then separate independent studies should be accomplished to confirm or deny the association.

86. Comment: A recent publication by Dr. Marilyn Fingerhut of the National Institute of Occupational Safety and Health reports that of the seven sarcomas found in cohort studies of industrially exposed workers from Dow and Monsanto Chemical only two of the seven could be possibly associated with dioxin exposure, three of the workers were found to have had no occupational exposure to dioxins, and that 2 of the 4 purported sarcomas were found to be carcinomas. Dr. Fingerhut also pointed out difficulties in classifying sarcomas and relying on death certificate classifications of sarcomas. Furthermore, since the number of sarcomas have been reduced from seven to two (and one would have been classified as a skin cancer), these cohort studies do not supply confirmatory evidence on dioxin as a cause of soft tissue sarcoma (STS). Two cohort studies of (relatively) heavily dioxin exposed workers did not show a significant elevation for cancer mortality.

Response: First, the CAG could not have included a critique of the Fingerhut paper prior to the May 1984 draft of the polychlorinated dibenzo-p-dioxin document because its existence was not known at the time. However, a review of this paper will be included in the document before it is published in final form.

We have had an opportunity to review this paper subsequently and it does not support the commentators claim. What it indicates is that of the seven soft tissue sarcomas alluded to above that were pathologically shown to be soft tissue sarcomas, a subsequent review by the Armed Forces Institute of Pathology and a review by one of the authors of the Fingerhut paper confirmed five of the seven as soft tissue sarcomas while the remaining two were determined to be carcinomas although the subtypes differed in three.

In terms of occupational exposure, Dr. Fingerhut proposed a strict definition of exposure as follows: a record must exist somewhere that shows an assignment to either a 2,4,5-T department or to a trichlorophenol department at sometime in the past. If such a record did not exist then the individual would not have been considered to have a confirmed exposure. Four of the seven who had a confirmed exposure in this manner were also members of cohorts that had been studied previously while the remaining three who could not be confirmed as having been assigned to any 2,4,5-T department or trichlorophenol department. The latter three were not identified as having been part of a study previously but were case reports of Johnson et al. (1981) and Moses et al. (1981). Individuals who were members of a study cohort might be expected to have better documentation of exposure, based upon an employment record, than would cases turning up in a medical prac-

tice. However, Dr. Fingerhut did point out that of these 3 cases, one worked 32 years in production, clerical, truck-driving, and maintenance jobs, in a chemical manufacturing site which produced trichlorophenol and 2,4,5-T, the second worked two and one half years as a production worker in a plant that made 2,4,5-T, while the last was a production and maintenance worker for 29 years at the same facility as the former.

One must question the usefulness of a classification scheme that relies on documentation of an assignment to a specific area of a plant as proof of exposure to dioxin without real evidence substantiating that exposure. While at the same time assignment to all other areas of the same plant is considered insufficient evidence of exposure although nothing is offered to substantiate the presence or lack of exposure to 2,3,7,8-TCDD in either case. It is ironic that in most occupational epidemiologic studies, employment at a plant where the agent is produced or found is generally considered enough to call such a person "exposed" and thus included in a cohort for study. On the other hand, if Dr. Fingerhut's definition were retrospectively applied to the already small occupational cohorts from which the first four STSs came, even two of these relatively rare STSs might probably constitute an excessive risk in the much smaller cohorts circumscribed by her definition.

With respect to the difficulties involved in the classification of sarcomas and problems with death certificate classifications, this topic is discussed in detail on pages 11-62 and 11-63 in the HAD.

87. Comment: The Environmental Protection Agency (EPA) discounts the negative case control study of agricultural workers in New Zealand. The EPA takes Smith to task for failing to confirm exposure data but does not analyze the same weakness in the Hardell exposure data. Smith's exposure data is more reliable than Hardell's exposure data and uses sounder methodology than the Hardell studies.

Response: The EPA disagrees with the commentor regarding his characterization of our interpretation of the Smith study. First, the authors data was not completely negative. Smith found elevated but nonsignificant relative risks of exposure ranging from 1.3 in individuals who were "probably exposed" for a minimum of 5 days not in the previous 10 years prior to cancer registration, to a high of 1.6 in individuals "probably exposed" for a minimum of 1 day not in the previous 5 years prior to cancer registration. No power calculations are provided with either of these statistics. However, the author concluded that his findings did not support the hypothesis that exposure to phenoxyacetic acid herbicides causes STS which CAG faithfully reported on Page 11-77 of the HAD. But, as we stated in our critique of his study,

documentation of actual exposure is not that good although we did say that his documentation was at least as good as that of Hardell in his study. In fact Smith reported the possibility that TCDD contamination may be lower in the New Zealand study compared to that of the Swedish studies.

Smith's patients were considered "exposed" if they had definite, probable, or possible exposure to phenoxyacetic acids through spraying or hand contact. Smith said that the actual chemical was identified only in some instances. They concluded in all remaining situations that if the member sprayed "gorse" or "blackberries" this was tantamount to potential exposure to phenoxyacetic acids. Such designations are not supported by concrete evidence of actual exposure to phenoxyacetic acid and consequently to the dioxin impurities within.

Another problem with the Smith data is the short period of time that one had to have "sprayed" the phenoxyacetic herbicides to be considered as an "exposed" person i.e., 5 days or 1 day. Perhaps a longer exposure time requirement might have helped to insure better specificity of exposure to the herbicide.

Furthermore, the time interval of 10 years and/or 5 years from exposure to registration may not have been long enough to allow latent effects to become evident. If very few persons in New Zealand, especially among the 2000 professional sprayers alluded to by Smith, received their potential exposure more than 15 years prior to registration than not enough time has elapsed for the detection of the relatively rare STS.

Both studies use case control methodology and both have no evidence of actual real exposure to dioxin contaminated phenoxyacetic acids. It is difficult to imagine that the Smith study has "sounder methodology" than the Hardell study. Both have limitations but Hardell seems to have paid more attention to potential confounders and the degree of contribution of each.

88. Comment: Hardell failed to find a predominate type of STS from the wide variety of soft tissue sarcomas which is contrary to evidence for the known carcinogens.

Response: As was discussed in the EPA document, STS may be classified at several different sites. Furthermore, they may not have their origin in only predominate mesenchymal tissue but may also arise in non-mesenchymal tissues as well. However, in terms of identifying a predominate type of STS that may be affected, it may be that all or only certain types of STS may be subject to an increased tumorigenic response. Furthermore, exposure to a carcinogen may not be specific to one site only but may affect several sites i.e., asbestos has

been shown to cause lung cancer independent of the risk of mesotheliomas and vinyl chloride has been found to be associated with increased risks of brain cancer and lung cancer as well as angiosarcomas of the liver.

89. Comment: Chapter 14. This chapter does not clearly present major concerns nor criteria used to determine what is or is not discussed. No mention of the observation of species difference is made and this would seem to be an important consideration in trying to make a human health hazard assessment. Again, however, no criteria are presented and fortunately no conclusion or health hazard assessment appear to have been made.

Response: This chapter concurs with the approach followed in other Health Assessment Documents. No change is warranted.

90. Comment: Given the many sources of combustion in the country, the listing and regulation of dioxin under Section 112 of the Clean Water Act would be unworkable should EPA mistakenly find that our exposure to dioxin presents a hazard.

Response: It does appear that dioxin is formed and released to the atmosphere when wastes containing chlorinated organics are combusted at certain temperatures. However, the listing of dioxin under Section 112 of the Clean Air Act would not dictate that all sources of combustion would have to be regulated; combustion sources can be regulated by source category and all source categories need not be included for regulation after a listing under Section 112. At the time of listing as a hazardous air pollutant, OAQPS would have determined all sources and done dispersion modeling to determine which source categories are the most important, what technologies might be most appropriate for mitigation of atmospheric release, and what the economic factors involved would indicate. A decision on source category regulation would be based on these and other factors.

The slope factor for the dose response data (q_1^*) for inhalation exposure has been determined to be 3.3×10^{-5} (pg/m³). If this is multiplied by maximum annual ground levels of dioxin in air, OAQPS anticipates that maximum human lifetime risk can be on the order to 10^{-4} risk in same area. It is a risk management decision as to whether 10^{-4} risk represents a hazard, but this would be the level that Dow would be referring to as the one where EPA would "mistakenly" find that air exposure is a hazard.

91. Comment: The workshop cannot be considered an independent review of EPA's work. The panel was selected by EPA, and the proceedings were orchestrated and dominated by Agency personnel.

Response: The peer review panel consisted of independent scientists of international repute, most of whom have contributed extensively on dioxins issue. Considering this the peer review workshop reflects an independent review of the document.