UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-EHC-91-002

OFFICE OF
THE ADMINISTRATOR

November 26, 1990

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of issues relating to the health effects of ingested pentachlorophenol

Dear Mr. Reilly,

The Science Advisory Board's Environmental Health Committee met in Miami Beach, Florida, on February 15-16, 1990, to review issues relating to the health effects of ingested pentachlorophenol. The review was performed at the request of four offices in the Agency: Office of Drinking Water, Office of Research and Development, the Office of Pesticide Programs and Office of Solid Waste. In addition, the Board considered this matter further at the July 9-10, 1990 Executive Committee meeting and held a public teleconference on August 29, 1990 to allow further opportunity for public comment. As a result of these two meetings, the Committee found no reason to revise the substance of its report.

Four issues were considered in this review of the health effects of ingested pentachlorophenol. The first issue concerned interpretation of the observed relationship between mouse liver toxicity and tumor incidence and, in particular, the choice of the experimental evidence that should be used to describe the carcinogenic potential of pentachlorophenol. The Committee recommended that the dose-dependent increase in the incidence of hepatocellular carcinomas and adenomas that was observed should be considered a valid indicator of oncogenicity.

In regard to the second issue, the relevance of the observed increase in the incidences of mouse pheochromocytomas to humans, the Committee concluded that the incidence and dose-response pattern of such tumors in mice suggest that their

increased rate of occurrence was clearly related to the administration of the test agent; however, the fact that the increase was limited to benign and not malignant pheochromocytomas led the Committee to question whether these tumors are related to human cancer.

The third issue concerned the selection of the data set(s) that should be used in formulating quantitative estimates of human cancer risk. The Committee recommended the use of the observed dose-incidence data on hemangiomas and hemangiosarcomas as the basis on which to assess the cancer risk for humans, since these tumors are more likely than the others to be known human cancers.

As concerns the final issue, whether a toxicity-equivalence-factor approach should be considered for the liver tumors, the Committee recommended that it not be used.

Based on the evidence presented the Committee concluded that pentachlorophenol should be classified as a B2 carcinogen, according to the EPA's weight-of-evidence scheme in its carcinogen guidelines.

We appreciate the opportunity to conduct this particular scientific review. We request that the Agency formally respond to the scientific advice provided herein.

Sincerely,

Raymond C. Loehr

Raymond C. Loehr
Chairman
Executive Committee

Arthur C. Upton

Arthur Upton
Chairman
Environmental Health Committee

REPORT OF SCIENCE ADVISORY BOARD'S REVIEW OF ISSUES CONCERNING THE HEALTH EFFECTS OF INGESTED PENTACHLOROPHENOL

1.0 EXECUTIVE SUMMARY

The Science Advisory Board's Environmental Health Committee reviewed issues relating to the health effects of ingested pentachlorophenol. The review was performed at the request of four offices in the Agency: Office of Drinking Water, Office of Research and Development, Office of Pesticide Programs, and Office of Solid Waste.

Four issues were considered in this review of the health effects of ingested pentachlorophenol. The first issue concerned interpretation of the observed relationship between mouse liver toxicity and tumor incidence. The Committee recommended that the observed dose-dependent increase in the incidence of hepatocellular carcinomas and adenomas be considered a valid indicator of the oncogenicity potential of the chemical.

In regard to the second issue, the relevance of the observed increase in incidence of mouse pheochromocytomas to humans, the Committee concluded that the incidence and dose-response pattern of such tumors in mice suggest that their increased rate of occurrence was related to the administration of the test agent to mice.

The third issue concerned the selection of the data set(s) that should be used in formulating quantitative estimates of human cancer risk. The Committee recommended the use of the observed dose-incidence data on hemangiomas and hemangiosarcomas as the basis for the cancer risk for humans.

The final issue, whether a toxicity-equivalence-factor approach should be considered for the liver tumors, the Committee recommended that such a factor not be used.

2.0 Introduction

The Environmental Health Committee of the Science Advisory Board of the U. S. EPA met in Miami Beach, Florida on February 15 and 16, 1990 to discuss the overall weight-of-evidence classification appropriate for pentachlorophenol. In addition, the Board considered the matter further at the July 9-10, 1990 Executive Committee meeting and held a public teleconference on August 29, 1990 to allow further opportunity for public comment. The Science Advisory Panel was represented at the February review by Dr. Edward Bresnick (see list at the end of this report). The

review was performed at the request of four offices in the Agency: Office of Drinking Water, Office of Research and Development, Office of Pesticide Programs, and Office of Solid Waste. The major emphasis was on data, reported in 1989, of studies conducted in male and female B6C3F1 mice by the National Toxicology Program. These studies examined both technical grade pentachlorophenol and Dowicide EC-7 pentachlorophenol given in the feed for two years.

From these studies the NTP concluded that there was clear evidence of carcinogenic activity for male mice fed diets containing the technical grade pentachlorophenol as evidenced by increased incidences of adrenal medullary and hepatocellular neoplasms. There was also some evidence of carcinogenic activity in female mice administered the technical grade pentachlorophenol as evidenced by increased incidences of hemangiosarcomas and hepatocellular neoplasms. There was clear evidence of carcinogenic activity for male mice exposed to EC-7 pentachlorophenol, as shown by increased incidences of adrenal medulla and hepatocellular neoplasms. There was clear evidence of carcinogenic activity for female mice given the EC-7 pentachlorophenol, as shown by increased incidences of adrenal medullary and hepatocellular neoplasms and hemangiosarcomas. Based on the above evidence the Committee concluded that pentachlorophenol should be classified as a B2 carcinogen, according to the EPA's weight-of-evidence scheme in its carcinogen guidelines. The guidelines were issued September 24, 1986 by the U.S. Environmental Protection Agency.[1]

Four issues were presented to the Committee for comment and recommendations. Issue 1 concerned whether the liver toxicity found in virtually all of the exposed mice may have contributed to the incidence of liver tumors and thus compromised the validity of the study for extrapolation to low dose levels where toxicity is greatly reduced or absent. The question was whether or not there was evidence to demonstrate a causal relationship between the liver toxicity and the liver tumors.

Issue 2 concerned the possibility that the pheochromocytomas seen in rats may have reflected a reaction to stress and therefore may not be relevant to the carcinogenicity at low dose levels. The question asked was whether there was sufficient evidence to support the same conclusion in mice and thus to discount the relevance of the mouse pheochromocytomas to humans.

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[1] These guidelines can be found in the Federal Register, 51 FR 33992 or in a separate EPA publication "The Risk Assessment Guidelines of 1986", EPA/600/8-87/045, U.S. Environmental Protection Agency, Washington, D.C., 20460.

Issue 3 concerned the selection of the data set that should be used in the quantitative assessment of cancer risk; i.e., which tumor types should be included, which sexes should be included, which grades of pentachlorophenol should be considered, and whether it was appropriate to take averages across the sexes or grades of pentachlorophenol. Four options were presented, including 1) taking an average of unit risks from female mice exposed to technical grade pentachlorophenol and female mice exposed to EC-7 pentachlorophenol, 2) using the unit risk from female mice exposed to EC-7 pentachlorophenol, 3) using the unit risk from male mice exposed to technical grade pentachlorophenol, and 4) taking an average of the unit risks across both sexes and both grades of pentachlorophenol.

Issue 4 concerned the question of whether a toxicity-equivalence-factor approach should be considered for the liver tumors, in view of the fact that the principal impurities identified in the pentachlorophenol preparations used (namely chlorinated dibenzo-p-dioxins, dibenzofurans and hexachlorobenzene) were those for which such an approach has been used in the past. This approach might seem desirable since hexachlorobenzene and some dioxins cause liver tumors in mice, but these chemicals have not been associated with the other two tumor types observed in the studies on pentachlorophenol.

3.0 Issue 1

In regard to Issue 1, on the relationship between mouse liver toxicity and tumor incidence, the Committee recommends that the dose-dependent hepatocellular carcinomas and adenomas be considered as valid indicators of the oncogenic potential of pentachlorophenol, especially since they were accompanied by the presence of tumors in other organs. In regard to hepatotoxicity, since the liver normally has a low rate of cell turnover, usually the Committee considers that it must usually undergo a toxic reaction prior to the development of neoplasia. An exception to this generalization may exist, however, in the case of the peroxisomal proliferators. Although most hepatocarcinogens may be hepatotoxins, not all hepatotoxins are necessarily hepatocarcinogens[2]. The Committee also wishes to point out the unusual sensitivity of the B6C3F1 mouse to hepatocarcinogenesis, which suggests that its liver may already conceivably be primed for tumor development. For this reason, the Committee recommends that the incidence of hepatocellular carcinomas and adenomas in these mice be considered less important than the appearance of hemangiosarcomas.

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[2]Hoel, D.G., Haseman, J.K., Hogan, M. D., Huff, J., and McConnell, E., The impact of toxicity on carcinogenicity studies: implications for risk assessment, Carcinogenesis, 9:2045-2052, 1982.

4.0 Issue 2

As concerns Issue 2, whether there was sufficient evidence to discount the relevance of mouse pheochromocytomas to humans, the Committee finds that the increased incidence and dose-response pattern of pheochromocytomas in these studies suggest that the tumors were related to the administration of the test agents, even though there was no increase in the number of malignant pheochromocytomas.

5.0 Issue 3

In regard to Issue 3, as to which data set(s) should be used in the quantitative estimate of the cancer risk, the Committee recommendsthe use of the hemangiomas and the hemangiosarcomas as the tumors on which to base the risk assessment. These tumors were related to the administration of the pentachlorophenol formulations tested, occurred in a dose-response manner in the treated animals, and are morphologically related to known fatal human cancers that are induced by xenobiotics. It should also be noted that the development of hemangiosarcomas was related to the incidence of multifocal hematopoietic proliferation in control animals (TG-controls, male 6%, females 14%; EC-F controls, male 3%, females 59%).

Ample consideration was given to the questions of the liver tumors and the pheochromocytomas. The Committee's recommendation of using the data on hemangiosarcomas in preference to the data on the other tumors does not negate the association of the liver tumors and pheochromocytomas with the administration of the formulations of pentachlorophenol. However, the committee recognizes the controversies surrounding the pathogenesis of these lesions and the difficulty in extrapolating these results in order to estimate human risk.

In the case of the liver tumors, it was recognized that the concurrent hepatotoxicity may have played a key role in the formation of the tumors. As noted above, to the best of our knowledge, few rodent hepatocarciogens (with the notable exception of peroxisome proliferators) induce their effects without hepatotoxicity. In point-of-fact, what may actually be occurring is promotion and progression of spontaneous tumors in the liver. The committee recommends that EPA address the generic issue of promotion of liver tumors as soon as possible. It should be noted that the classic rodent liver promotion models utilize hepatotoxicity as the means to enhance development of tumors.[3]

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[3] Solt, D.B. and Farber, E., Nature, 263:701, 1976.

The Committee had similar reservations about utilizing the pheochromocytomas as the underpinning of the classification of pentachlorophenol containing formulations. There is genuine disagreement in the interpretation of the meaning of these tumors in rodents and, in addition, there is controversy in the diagnosis of the lesions. The lesions in mice and in rats may or may not be similar in pathogenesis but in neither case is it fatal nor does it invade other tissue. The Committee recommends that EPA support research on the biogenesis of this lesion in mice, including the study of similarities between pheochromocytomas in mice and rats.

The Committee further recommends that the q_1^*, for pentachlorophenol be estimated from derivations using the linearized multistage model (LMS) as well as the time-to-tumor model. The reason for this recommendation is that most, if not all, other q_1^*s have been developed using LMS and the Agency is urged to be consistent. In so recommending, the Committee is not saying that other models are not appropriate. It further recommends that the Agency continue to examine alternative models for estimating risk.

In summary, the Committee recommends that the q_1^* be based on the development of tumors most relevant to human cancer and to the most unique tumors in this study, namely the hemangiosarcomas. Under these circumstances it is reasonable to average across grades of pentachlorophenol as tested, but averaging across tumors types and genders (no hemangiosarcomas in males) should not be done. The Committee agreed that, using the weight-of-evidence scheme from the EPA's carcinogen guidelines, pentachlorophenol should be classified as a B2 carcinogen.

Further the Committee recommends:

a that EPA and other interested parties initiate research on the biogenesis and interpretation of pheochromocytomas in mice,

b that other toxicity studies be conducted to determine the shape of the dose-response curve for hepatotoxicity of pentachlorophenol in rats and mice,

c) that EPA address the questions of hepatic tumor promotion with agents that are both hepatotoxic and contain contaminants that are structurally related to tumor promoters,

d) that EPA (perhaps through NIEHS/NTP programs) refine its definition of MTD in light of the difficulty of inducing hepatocarcinogenicity without hepatotoxicity,

e) that NTP design its studies to be used in

risk assessment, rather than to take the position that NTP studies stand alone and are not designed for risk assessment.

6.0 Issue 4

In regard to Issue 4, whether or not a toxicity-equivalence-factor approach should be considered for the liver tumors, the Committee recommends that toxicity-equivalent factors not be applied to assessing the carcinogenic potential of pentachlorophenol, for several reasons:

a) Bioassay data are available for two mixtures which are similar in purity but differ somewhat from mixtures marketed today in regard to their specific impurities. Toxicity estimates for the two tested mixtures are likely to bracket those for the mixtures to which the public is currently exposed,

b) Individuals are exposed to mixtures and if data are available for the same or similar mixtures they should be used to estimate toxicity. For more details see the Risk Assessment Guidelines for Chemical Mixtures,

c) Toxicity-equivalent-factors for dioxin are likely to change and are currently based, among other things, on induction of the Ah receptor associated with acute toxicity data in rat liver; the pentachlorophenol data are based on their response data in mice,

d) The Committee recommends that quantitative risk estimates be based upon the hemangiosarcoma data for female mice. There is little difference between mixtures in risk for this effect, suggesting that the risk estimate varies relatively little with variability in mixture formulations. Moreover, these tumors have not been associated with the identified impurities in pentachlorophenol.

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