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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

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OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Re-evaluation of the Oncogenicity of Lindane

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TO: Anne Barton
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In response to your July 3, 1985 letter requesting the Carcinogen Assessment Group (CAG) to re-evaluate the carcinogenicity of Lindane using the current proposed Carcinogen Risk Assessment Guidelines, we held a joint meeting on July 12, 1985 between the Carcinogen Assessemnt Group and members of your staff along with Dr. Donald Barnes of the Office of Pesticide Toxic Substances staff. At this meeting we discussed the four points in your July 3, 1985 request, and arrived at the following conclusions.

1) Are additional mouse studies necessary to assess oncogenic effects in this species?

Currently there are positive or marginally positive studies on four strains of mice, in which lindane has induced liver tumors. An additional mouse study would not markedly change the nature of the evidence for carcinogenicity, although a positive result would confirm the current studies. A negative result would not negate the current positive findings.

However, another mouse study with a sufficient number of animals per group (perhaps 50) done on an appropriate strain at high doses (up to 40 ppm) with more than one dose group, preferably more than two, would give a much more solid basis for quantitative risk evaluation. Currently the only two studies with adequate group size give extremely limited dose-response information: the NCI study at 80 and 160 ppm on B6C3F1 mice gave no response at the highest dose but was positive at the low dose; and the Tunstall lab study at the single dose of 400 ppm in CF-1 mice in which males had greater than 90% incidence of liver tumors.

2) Do the studies available now provide a satisfactory assessment for tumor sites other than the liver in mice?

The four studies reviewed in the 1979 CAG report, which currently form the basis for the evidence of carcinogenicity, reported statistically significant increases in tumors only of the liver. There is no evidence that Lindane induces tumors at other sites. The authors of all four studies examined other sites to search for the possibility of tumor induction but found no such evidence.

3) Based on the currently available evidence, including the mutagenicity information summarized by Dr. Mauer, what is the appropriate classification of lindane according to the current proposed EPA guidelines?

In the attached April 1985 memorandum to the Drinking Water Office, the CAG classified lindane as B2 in its evaluation of 37 compounds potentially present in drinking water, However, in our July 12 meeting the evidence was re-evaluated using the EPA proposed guideline factors for evaluation chemicals having evidence of liver tumors alone. Our attention centered on the two larger sized carcinogen studies (NCI and Tunstall). The guidelines take the postion that a mouse liver tumor only response should be considered as "sufficient" evidence of carcinogenicity unless factors such as the following are observed, in which case the classification could be changed to "limited". These factors are listed below along with our collective evaluation of whether the corresponding factor increases (+) the concern that Lindane may be carcinogenic.

Downgrading Factor	Occurrence of Factor NCI Study	Tunstall Study	Summary
1a) Tumors occur only at high dose or at end of study	No+	No Information	+
1b) Lack of systematic dose-response relationship	Yes+	No Information	+
2) No dose-related increase in the proportion of tumors that are malignant	Yes+	No Information	+
3) Tumors are predominantly benign	(No)+	(No)	(+)
4) No dose-related shortening of time-to-tumor	No Information	No Information	
5) Negative short-term test		Yes(+)	+
6) Occurring in single sex only	Yes+	No+	+

Additional considerations in the overall evaluation were that: 1) there is a carcinogenic metabolite of Lindane (namely 2,4,6-trichlorophenol) which increases concern for carcinogenicity and that 2) there was adequate testing in a second species (rat) with no positive result, this would decrease concern and 3) there are four positive mouse strains, which increases concern.

2

After these factors were discused and displayed the group was asked to vote on what classification is appropriate for Lindane. Eighteen people plus the chairman were preset. The results of the vote was: For B2, 0; for C, 6 people, for a range of B2 to C, 8 people. The conclusion is that a range from B2 to C is the appropriate classification for Lindane.

4) What is the appropriate value for the upper-bound slope of the dose-response relationship for Lindane?

The upper-bound slope appropriate for quantitative estimation for carcinogenic risk is $q_1^* = 1.1\ (mg/kg/day)^{-1}$ which is consistent with the value of $0.03\ (ppm)^{-1}$ for Lindane in the diet which we stated in the 1982 memorandum. The older evaluation derived in the Water Quality Criteria Document (1980) and later quoted in the Health and Environmental Assessment Document from ECAO/Cincinnati is $1.33\ (mg/kg/day)^{-1}$ and was derived from males alone, under the policy at that time that the data set with the highest potency should be used. However, we now believe that in the case of the Lindane data, the data sets from both sexes should be combined, since there is no evidence to indicate that males and females in this study are different.

cc: J. Cotruvo