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Project Summary

Carcinogenicity Assessment of Chlordane and Heptachlor/ Heptachlor Epoxide

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Evidence pertaining to the carcinogenicity of chlordane and heptachlor/ heptachlor epoxide is reviewed and evaluated. The final report covers studies completed before 1985. Case reports and epidemiologic studies of pesticide applicators and pesticide manufacturing workers are reviewed, but because of methodologic limitations, these studies establish neither a positive nor a negative association between cancer and chlordane or heptachlor/heptachlor epoxide exposure. A number of independent studies of laboratory animals, however, demonstrates that chlordane and heptachlor/ heptachlor epoxide cause liver cancer in mice and rats. Based on the accumulated evidence, chlordane and heptachlor/heptachlor epoxide are classified as probable human carcinogens, Group B2 using EPA's Guidelines for Carcinogen Risk Assessment. The carcinogenic potency of chlordane and heptachlor/heptachlor epoxide is estimated by fitting mathematical models to the laboratory animal data. These estimates indicate that chlordane and heptachlor/heptachlor epoxide are rather potent carcinogens, ranking in the second quartile of potential carcinogens evaluated by EPA's Carcinogen Assessment Group. A separate mutagenicity assessment of chlordane and heptachlor/heptachlor epoxide is attached as an appendix to the final report. The report also includes an extensive list of references pertinent to the carcinogenicity of chlordane and heptachlor/heptachlor epoxide.

This Project Summary was developed by EPA's Office of Health and Environmental Assessment, Washington, DC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Discussion

Qualitative Data

Human Studies

Case Reports

There were 11 case reports involving CNS effects where the author looked at the toxic effects of chlordane/heptachlor, eight case studies involving blood dyscrasias, and five case studies of neuroblastomas in children with pre-/ postnatal exposure to chlordane or heptachlor. The blood dyscrasias in children included four cases of aplastic anemia and one case each of refractory megaloblastic anemia, acute lymphoblastic leukemia, acute stem-cell leukemia, and acute myelomonocytic leukemia.

Epidemiologic Studies

Three epidemiologic studies of workers exposed to chlordane and/or heptachlor have been reported. One of these studies, conducted in chlordane/heptachlor applicators, was considered inadequate in sample size and duration of follow-up since initial exposure. However, this study showed increased mortality from bladder cancer (SMR = 277, $p < 0.05$). A second study showed an increased mortality from lung cancer (SMR = 134), but the increase was not statistically significant. The mortality from cerebrovascular disease

was statistically significant (SMR = 183, $p \leq 0.05$). Of the 1,043 men involved in the study, only one liver cancer was reported. The third study involved 2,141 workers exposed to organochlorine pesticides. One of the four plants involved in pesticide manufacture produced chlordane and one produced heptachlor. The SMR for malignant neoplasms was 69 at the chlordane plant and 91 at the heptachlor plant. There was an excess risk for cancer in various tissues; none was statistically significant. The last two studies were carried out in chlordane/heptachlor manufacturing plants.

All of these studies have several limitations. Neither the quantitative nor length of exposure histories are available for chlordane/heptachlor for the populations studied. The workers were also exposed to other pesticides and chemicals. Adjustments for these other chemical exposures and other confounding factors, like smoking and alcohol consumption, were not considered in any of these studies. All of the study populations were small. In the pesticide applicator study, individual follow-up was not undertaken and the data were missing on 10.3 percent of the decedents reported by the Social Security Administration.

Because of these methodological limitations and the limited data, it is difficult to establish either a negative or positive association between chlordane/heptachlor and carcinogenicity. Hence, these studies are considered inadequate epidemiologic evidence.

Animal Studies

Chlordane

Mice. Four chlordane carcinogenesis bioassays in mice have been reported. The strains tested include C57B1/6N, CD-1, B6C3F1, and ICR. In C57B1/6N mice fed 25 or 50 ppm for 18 months, hepatocellular carcinomas were observed in 27 percent (16) of the survivors. This mouse strain rarely develops spontaneous liver lesions. For CD-1 mice fed 5, 25, or 50 ppm for 18 months, liver nodules/hepatocellular carcinomas were observed in the 25 and 50 ppm groups. In B6C3F1 mice fed approximately 30 and 60 ppm for 80 weeks and then held for 10 weeks, hepatocellular carcinomas were observed in both males and females. For ICR mice fed 1, 5, or 12.5 ppm for 24 months, hepatocellular adenomas and hemangiomas were significantly increased ($p < 0.001$) in males receiving 12.5 ppm and nonneoplastic liver lesions were present in males fed 5 ppm and in females fed 5 or 12.5 ppm.

Rats. Four chlordane carcinogenesis bioassays in rats have been reported. The strains tested include albino, Osborne-Mendel, and Fischer 344. Three of these studies were considered adequate, and one was inadequate. In albino rats fed 10, 20, 40, 80, 160, 320, 640, or 1280 ppm for 400 days, there were no treatment-related tumors. In Osborne-Mendel rats fed 5, 10, 30, 150, or 300 ppm for 2 years, hepatic toxicity was noted at 150 and 300 ppm, but no liver tumors were noted. In Osborne-Mendel rats fed 203.5 or 407 ppm (males) or 120.8 or 241.5 ppm (females), respectively, for 80 weeks and held for an additional 29 weeks, no liver tumors were noted, but thyroid tumors were significantly increased. In light of historical data for Osborne-Mendel rats, the thyroid tumors were not considered to be treatment-related. In Fischer 344 rats fed 1, 5, or 25 ppm for 130 weeks, there was a statistically significant increase in hepatocellular adenomas, which was considered by the authors as weak evidence for carcinogenicity in males fed 25 ppm. Hepatocellular swelling was significant in females fed 25 ppm. The hepatocellular adenomas occurred only in males surviving longer than 104 weeks.

Heptachlor/Heptachlor Epoxide

Mice. Three heptachlor/heptachlor epoxide carcinogenesis bioassays in mice have been reported. The strains studied include C3H, B6C3F1, and CD-1 mice. In C3H mice fed 10 ppm of both heptachlor and heptachlor epoxide for 2 years, benign liver tumors/hepatocellular carcinomas were reported in both male and female mice. Hepatocellular carcinomas in treated groups were generally large and frequently multiple tumors, especially in the epoxide group in respect to the controls. For B6C3F1 mice fed technical grade (containing 22 percent chlordane) at concentrations of 6.1 or 13.8 ppm (males) or 9 or 18 ppm (females), respectively, for 80 weeks and held for an additional 10 weeks, hepatocellular carcinomas were significantly ($p < 0.001$) increased in both male and female mice. In CD-1 mice fed a mixture of heptachlor epoxide/heptachlor (75:25) at concentrations of 1, 5, or 10 ppm for 18 months, nodular hyperplasia/hepatocellular carcinomas were noted at 5 and 10 ppm in both male and female mice.

Rats. Five heptachlor/heptachlor epoxide carcinogenesis bioassays in rats have been conducted. The strains of rats studied include Wistar, Osborne-Mendel, CD, and CFN. In Wistar rats given 5 doses of 10 mg/kg bw of heptachlor and held for 106 to 110 weeks, no treatment-related tumors were observed. For Osborne-Mendel rats fed technical grade heptachlor at concentrations of 38.9 or 77.9 (males) or 25.7 or 51.3 (females) ppm, respectively, for 80 weeks and held for 30 weeks, no liver tumors were noted, although neoplastic nodules were found in both treated and control rats. In CD rats fed a mixture of heptachlor/heptachlor epoxide (75:25) at concentrations of 5, 7.5, 10, or 12.5 ppm for 2 years, no liver tumors were noted, although nonneoplastic lesions were noted in the livers of rats fed 7.5, 10, or 12.5 ppm. In one study using CFN rats fed 1.5, 3, 5, 7, or 10 ppm of heptachlor for 110 weeks, the incidence of liver tumors was not statistically different in treated and control animals. In a second study using CFN rats fed 0.5, 2.5, 5, 7.5, or 10 ppm of heptachlor epoxide for 108 weeks, treatment-related liver carcinomas were noted by several pathologists.

Supporting Evidence

Mutagenicity

The published literature on mutagenicity tests of chlordane and heptachlor/heptachlor epoxide is quite similar, with most studies reporting results on both chemicals. Generally, the results have indicated that these chemicals are not mutagenic in bacteria or in mammalian cells in culture, and do not induce DNA repair, as measured by unscheduled DNA synthesis in rodent hepatocytes. While dominant lethal tests in mice have been negative for both chemicals, the absence of direct cytogenetic tests in both germinal and somatic cells precludes a conclusion as to their potential for causing chromosomal aberrations.

Structural Relationship

Three compounds, structurally related to chlordane/heptachlor/heptachlor epoxide, have induced malignant liver tumors in animals. Aldrin, dieldrin, and chlorendic acid have produced liver tumors in mice and chlorendic acid has also produced liver tumors in rats.

Quantitative Analysis

In the absence of information on human absorption, tissue distribution, metabolism, and excretion, this assessment

makes no adjustment for potential differences between animals and humans.

Chlordane

Five data sets involve chlordane: male and female CD-1 mice, male and female B6C3F1 mice, and male F344 rats. The most sensitive sex and strain tested is male CD-1 mice. From these, the potency is estimated at 4.7 per mg/kg/day.

The most sensitive species tested is mice. There are four potency estimates, ranging from 4.7 down to 0.25 per mg/kg/day, with a geometric mean of 1.3 per mg/kg/day. This geometric mean from mice is consistent with potency estimate from rats of 1.1 per mg/kg/day. Because humans may be as sensitive as the most sensitive animal species, the potency for the general population is estimated at 1.3 per mg/kg/day.

These estimates are plausible upper bounds for the increased cancer risk from chlordane, meaning that the true risk is not likely to exceed these estimates and may be lower. These estimates supersede the potency of 1.61 per mg/kg/day previously calculated by the EPA.

The molecular potency index, which is the potency expressed in terms of molecular weight, has been used to rank suspect carcinogens according to potency. The index is computed by multiplying the general-population potency by the molecular weight. The molecular potency index for chlordane is 5.2×10^2 per mmol/kg/day. This places chlordane in the upper middle quartile of suspect carcinogens ranked by the Carcinogen Assessment Group (CAG)

Heptachlor

Four data sets involve heptachlor: male and female C3H mice, and male and female B6C3F1 mice. The most sensitive sex and strain tested is female C3H mice. From these, the potency is estimated at 14.9 per mg/kg/day.

The most sensitive species tested is mice. There are four potency estimates, ranging from 14.9 down to 0.83 per mg/kg/day, with a geometric mean of 4.5 per mg/kg/day. Because humans may be as sensitive as the most sensitive animal species, the potency for the general population is estimated at 4.5 per mg/kg/day.

These estimates are plausible upper bounds for the increased cancer risk from heptachlor, meaning that the true risk is not likely to exceed these estimates and may be lower. These estimates supersede the potency of 3.37 per mg/kg/day previously calculated by EPA.

The molecular potency index for heptachlor is 1.7×10^3 per mmol/kg/day. This places heptachlor in the upper middle quartile of suspect carcinogens ranked by the CAG.

Heptachlor Epoxide

Five data sets involve heptachlor epoxide: male and female C3H mice, male and female CD-1 mice, and female CFN rats. The most sensitive sex and strain tested is female C3H mice. From these, the potency is estimated at 36.2 per mg/kg/day.

The most sensitive species tested is mice. There are four potency estimates, ranging from 36.2 down to 1.0 per mg/kg/day, with a geometric mean of 9.1 per mg/kg/day. This geometric mean from mice is consistent with the potency estimate from rats of 5.8 per mg/kg/day. Because humans may be as sensitive as the most sensitive animal species, the potency for the general population is estimated at 9.1 per mg/kg/day.

These estimates are plausible upper bounds for the increased cancer risk from heptachlor epoxide, meaning that the true risk is not likely to exceed these estimates and may be lower. These estimates supersede the potency of 57.86 per mg/kg/day previously calculated by the EPA.

The molecular potency index for heptachlor epoxide is 3.5×10^3 per mmol/kg/day. This places heptachlor epoxide in the most potent quartile of suspect carcinogens ranked by the CAG.

Conclusions

Based on the accumulated evidence, chlordane is a probable human carcinogen, classified in Group B2 under the EPA's Guidelines for Carcinogen Risk Assessment. Animal studies provide sufficient evidence for carcinogenicity: chlordane increased the incidence of liver carcinomas in C57B1/6N, CD-1, and B6C3F1 mice; liver adenomas and hemangiomas in ICR mice; and liver adenomas in Fischer 344 rats. Epidemiologic studies provide inadequate evidence due to methodology and data limitations.

According to the criteria in the guidelines, the above evidence puts chlordane in Group B2. However, the guidelines allow for the possibility of downgrading the classification from Group B2 to Group C when the only tumor response is that of mouse liver tumors in strains with high background rates, or when warranted by a number of other factors. In the case of chlordane these conditions do not apply, since chlordane caused tumors in C57B1/6N mice — which do not have a high background rate — and caused tumors in rats as well. Other pertinent evidence includes highly significant tumor responses, up to 77 percent increased incidence over controls, increased incidence in both males and females, increased incidence at medium and high doses, a dose-related increase in the proportion of malignant tumors, and induction of tumors by structurally related chemicals. In light of these factors, downgrading is clearly not warranted, and chlordane remains in Group B2.

For chlordane, the carcinogenic potency, averaging estimates from the most sensitive species tested, is 1.3 per mg/kg/day. The potency using the most sensitive sex and strain is 4.7 per mg/kg/day. These are plausible upper bounds for the increased cancer risk from chlordane, meaning that the true risk is not likely to exceed these estimates and may be lower. The molecular potency index for chlordane is 5.2×10^2 per mmol/kg/day. This places chlordane in the second (upper middle) quartile of suspect carcinogens ranked by the Carcinogen Assessment Group (CAG).

Heptachlor/heptachlor epoxide is a probable human carcinogen, classified in Group B2 under the EPA's Guidelines for Carcinogen Risk Assessment. Animal studies provide sufficient evidence for carcinogenicity: heptachlor/heptachlor epoxide increased the incidence of liver carcinomas in C3H, CD-1, and B6C3F1 mice and in CFN rats. Epidemiologic studies provide inadequate evidence due to methodology and data limitations.

The guidelines consider this evidence sufficient for Group B2, but they allow downgrading from Group B2 to Group C when the only tumor response is that of mouse liver tumors in strains with high background rates, or when warranted by a number of other factors. The evidence, however, shows highly significant tumor responses, increased incidence in both males and females, increased incidence at medium and high doses, and induction of tumors by structurally related chemicals. In light of these factors, downgrading is clearly not warranted, and heptachlor/heptachlor epoxide remains in Group B2.

For heptachlor, the carcinogenic potency, averaging estimates from the most sensitive species tested, is 4.5 per mg/kg/day. The potency using the most sensitive sex and strain is 14.9 per mg/kg/day. These are plausible upper bounds for the increased cancer risk from heptachlor, meaning that the true risk is not likely to exceed these estimates and

may be lower. The molecular potency index for heptachlor is 1.7×10^3 per mmol/kg/day. This places heptachlor in the second quartile of suspect carcinogens ranked by the CAG.

For heptachlor epoxide, the carcinogenic potency, averaging estimates from the most sensitive species tested, is 9.1 per mg/kg/day. The potency using the most sensitive sex and strain is 36.2 per mg/kg/day. These are plausible upper bounds for the increased cancer risk from heptachlor epoxide, meaning that the true risk is not likely to exceed these estimates and may be lower. The molecular potency index for heptachlor epoxide is 3.5×10^3 per mmol/kg/day. This places heptachlor epoxide in the most potent quartile of suspect carcinogens ranked by the CAG.

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The complete report entitled "Carcinogenicity Assessment of Chlordane and Heptachlor/Heptachlor Epoxide," (Order No. PB 87-208 757/AS; Cost: $24.95, subject to change) will be available only from:

National Technical Information Service
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