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Project Summary

Carcinogenicity Assessment of Aldrin and Dieldrin

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Evidence pertaining to the carcinogenicity of aldrin/dieldrin is reviewed and evaluated. The full 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 established neither a positive nor a negative association between cancer and aldrin/dieldrin exposure. A number of independent studies of laboratory animals, however, demonstrated that aldrin/dieldrin cause liver cancer in mice and rats. Based on the accumulated evidence, aldrin/dieldrin are classified as probable human carcinogens, Group B2, using EPA's *Guidelines for Carcinogen Risk Assessment*. The carcinogenic potency of aldrin/dieldrin is estimated by fitting mathematical models to the laboratory animal data. These estimates indicate that aldrin/dieldrin are rather potent carcinogens, ranking in the first (most potent) quartile of potential carcinogens evaluated by EPA's Carcinogen Assessment Group. Separate mutagenicity assessments of aldrin/dieldrin are attached as appendices to the full report. The full report also includes an extensive list of references pertinent to the carcinogenicity of aldrin/dieldrin.

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).

Introduction

Aldrin and dieldrin were first synthesized in the laboratory in 1948 with commercial production in the United States first reported in 1950. Aldrin and dieldrin are organochlorine pesticides extensively used in the 1960s and early 1970s for a large variety of pesticidal uses. Most uses were banned in the United States in 1974 under the Federal Insecticide, Fungicide, and Rodenticide Act. Uses were also restricted in many other countries at about the same time. The approved uses in the United States now are mainly for termite control by direct soil injection and for nonfood seed and plant treatment. Production of aldrin and dieldrin in the United States was also discontinued along with the restrictions of 1974, so that virtually all aldrin and dieldrin now used in the United States is imported. Exposure of humans has been primarily from dermal and inhalation exposure related to the application of pesticides; however, due to the persistence and bioaccumulation of dieldrin, considerable exposure has occurred through ingestion of contaminated water and food products. In contrast, little human exposure from environmental sources of aldrin occurs, as it is readily converted to dieldrin by direct expoxidation in the environment. During the early 1970s, nearly all humans sampled had measurable tissue levels of dieldrin and, due to its stability and persistence, dieldrin is still detected in humans. However, the levels are considerably low. Aldrin and dieldrin are usually considered together, as they are structurally related cyclodiene insecticides, have similar uses, and because aldrin is readily epoxidized to dieldrin in the body or the environment.

The full report reviews the currently available literature on the toxicity and carcinogenicity of both aldrin and dieldrin and conducts an assessment as to the

potential carcinogenicity risk to humans. The Carcinogen Assessment Group (CAG) conducts a "weight-of-evidence" evaluation that weighs data concerning innate biological activity including metabolism, toxic effects as related to duration and levels of exposures, results of mutagenicity and other short-term tests, long-term animal bioassays, and, where available, data derived from epidemiologic studies. Since mutagenicity is considered as one major mechanism for cancer induction, those studies are considered supportive of the *in vivo* animal or human data.

Following a review of the data, those data most appropriate for mathematical extrapolation are selected for risk assessment. Several mathematical models, as described in EPA's *Guidelines for Carcinogen Risk Assessment* are used. On the basis of the "weight-of-evidence" and risk extrapolation, the substance is classified as a potential human carcinogen according to the EPA Guidelines.

Discussion

Human Studies

Six case reports on aldrin toxicity describe neurotoxicity, including convulsions and abnormal EEGs, as the main toxic effects. Five case reports were found for dieldrin. Like aldrin, effects of the central nervous system, including convulsions, were the main signs following acute or prolonged exposure. In one of the reports, however, immunohemolytic anemia was the primary toxic effect.

Only two epidemiologic studies of humans exposed to aldrin or dieldrin were reported. One was a long-term study of 233 industrial workers at pesticide manufacturing and formulating plants in the Netherlands. However, the study focused mainly on clinical parameters and not cancer, and is considered inadequate to determine the carcinogenicity of aldrin and dieldrin. The other study included a retrospective mortality analysis of 1,155 employess at a plant that had produced aldrin, dieldrin, and endrin for 30 years prior to the analysis. There was a statistically significant ($p < 0.01$) increase in nonmalignant respiratory disease (SMR=212, $p<0.01$). While an SMR of 82 was found for all malignant neoplasms, an SMR of 235 was found for cancer of the esophagus, SMR=242 for cancer of the rectum, SMR=225 for cancer of the liver, and SMR=147 for cancer of the lymphatic and hematopoietic system. However, none of these was significnat. This study also has serious limitations. No information was presented on actual exposure levels, and exposures to other chemicals were known to occur. No attempts were made to adjust for effects of other chemical exposures, smoking, or alcohol consumption. Since the number of workers was small and vital status was unknown for 10%, the power to detect an effect was quite limited. Due to these methodological limitations and the limited data, it is difficult to draw either a negative or positive association between aldrin/dieldrin and carcinogenicity. Hence, these studies are considered inadequate epidemiologic evidence.

Animal Studies

Aldrin

Three adequately conducted long-term carcinogenicity bioassays of aldrin have been conducted with mice. The strains used were C_3HeB/Fe, C_3H, and $B6C3F_1$. In the study with $B6C3F_1$ mice, aldrin was fed at four doses of 3 to 8 ppm for 80 weeks with 10 to 13 weeks of additional observation. A statistically significant ($p < 0.001$) increase in hepatocellular carcinomas was observed in both the 4 and 8 ppm male groups but not in the females. In the other two studies, reported in 1962 and 1965, C_3H and C_3HeB/Fe mice were fed aldrin at 10 ppm for 24 months. In both, statistically significant ($p < 0.001$) increased incidences of hepatomas were diagnosed although not broken down as to incidences in males or females. Reevaluation by other pathologists diagnosed the lesions as hepatocellular carcinomas with statistically significant ($p < 0.05$) increases in both male and female groups.

While it may be true that the C_3H and $C_3H/HeB/Fe$ strains have a large percentage of their gene pool in common, we expect that $B6C3F_1$ mice have approximately half of the gene pool of the C_3H strain. Furthermore, the gene pool in these mice changes from lab to lab and, after many generations, in the same laboratory. The fact that dieldrin, a metabolite of aldrin, is carcinogenic in the C57BL/6J, CBA/J, Swiss-Webster, and CF-1 strains (highly different genetically) as well as the C_3 and $B6C3F_1$ strains argues against the C_3H strain's unique genetic susceptibility to this effect.

Seven carcinogenicity bioassays of aldrin have been conducted with rats, only one of which is considered adequate in design and conduct. Five studies used Osborne-Mendel rats, with one each using Carworth and Holtzman strains. Doses ranged from 0.5 to 150 ppm with dietary exposure generally for at least 24 months. At 50 ppm and below, good survival resulted. There was no evidence of carcinogenicity in any of the studies. However, a constant finding was liver lesions comonly referred to as "chlorinated insecticide type lesions."

In the only adequate study, the National Cancer Institute (NCI) bioassay in Osborne-Mendel rats, there were increased incidences of thyroid follicular cell adenomas and carcinomas of the thyroid in both males and females. These incidences were significant in the low-dose group but not the high-dose group when compared to pooled controls but not with matched controls. It should be noted that there were only 10 animals in the matched controls, which is not usually enough to detect all but the largest responses. Although NCI concluded that the tumors were not associated with treatment, our examination using pooled controls indicates that there was some positive response. Later evaluations by other investigators indicated that the thyroid follicular (in both sexes) and adrenal cortex tumor in female rats was suggestive evidence of carcinogenicity for aldrin.

Another study with rats was considered inadequate because as few as 62% of the treated animals in one dose group (female high-dose group) and 75% of the male controls were microscopically examined. Reevaluation of the histopathology indicated that the authors may have under estimated and underreported the incidence of malignant tumors by approximately threefold. In all, there were seven rat studies. Six of them were considered inadequate. A well-designed study on rats would be useful to answer the specific question whether the carcinogenic potential of aldrin is limited to mice or not.

Dieldrin

Twelve carcinogenicity bioassays of dieldrin have been conducted with mice; all but one were judged adequate in design. Seven strains of mice were used: C_3HeB/Fe, C_3H, CBA/J, Swiss-Webster, CF_1, $B6C3F_1$, and C57BL/6J. In all studies, either benign or malignant liver tumors were observed. The authors of six of these studies indicated that the tumors were malignant (hepatocellular carcinomas), whereas in five others the tumors were diagnosed as hepatomas.

In three of these five, a pathology reevaluation was performed by other pathologists who classified the lesions as being malignant. In three studies, all with CF_1 mice, many of the hepatocellular carcinomas had metastasized to the lung. In additon, in one study, a significant ($p < 0.05$) reduction in latency period was observed. In one of the studies with CF_1 mice, a slight but significant ($p < 0.05$) increase in the incidence of pulmonary adenomas and carcinomas, lymphoid tumors, and other tumors was seen in female mice at 1 ppm. The doses used in the bioassays ranged from 0.1 to 20 ppm with dietary administration for 18 to 24 months.

Seven long-term carcinogenicity studies were conducted with rats, three of which were considered adequate carcinogenicity assays. The others suffered mainly from too few animals, too high mortality, too short a duration, and/or inadequate pathology examination or reporting. Four strains were used: Carworth, Osborne-Mendel, Holtzman, and Fischer 344. Doses ranged from 0.1 to 285 ppm in the diet generally for 2 years or more. Although liver pathology was generally associated with exposure to the chlorinated insecticides, there was no firm evidence of a carcinogenic response in any of the studies.

Conclusion

Aldrin

For aldrin, the finding of hepatocellular carcinomas in male $B6C3F_1$ mice and the findings of the hepatomas in C_3H and C_3HeB/Fe mice, which were later diagnosed as hepatocellular carcinomas, in both males and females, constitute as a first approximation,"sufficient" evidence of carcinogenicity in animals, according to criteria in the EPA's *Guidelines for Carcinogen Risk Assessment*. However, the Guidelines call for a careful analysis of the nature of the mouse liver-tumor-only response to ascertain whether there is a sufficiently strong reason to downgrade the evidence to "limited." This downgrading was found not to be appropriate since the tumor increases were not marginal in male $B6C3F_1$ mice (which have a high spontaneous incidence of liver tumors), there was a dose-related increase in the proportion of tumors that were malignant, and the response occurred in both males and females. In addition, the response occurs in C_3H and C_3HeB/Fe mouse strains with a low spontaneous incidence of liver tumors, which is a response not subject to the downgrading factors.

One factor which would argue for a "limited" classification is that the two C_3H strains are genetically closely related and the $B6C3F_1$ strain derives half of its gene pool from these strains. However, the fact that the epoxide metabolite, dieldrin, produces liver tumors in seven different mouse strains indicates strongly that the carcinogenic effect of aldrin is not limited to a restricted genetic range of mice. Although in rats, one adequate study with aldrin and three adequate studies with dieldrin were negative or equivocal, the multiplicity of mouse strains responding is considered to be enough for classification of "sufficient" evidence in animals.

In the absence of adequate evidence in humans, the sufficient animal evidence amounts to an overall classification of B2, or "probable" human carcinogen for aldrin.

For aldrin, the carcinogenic potency, obtained by averaging estimates from most sensitive species tested (mice), is 17 per mg/kg/day. The potency using the most sensitive sex and strain is 23 per mg/kg/day. These are plausible upper bounds for the increased cancer risk from aldrin, meaning that the true risk is not likely to exceed these estimates and may be lower. These estimates have been calculated using the Agency's preferred methodology in the absence of specific physiologic, metabolic, or kinetic information: the linearized multistage model with doses scaled according to relative body surface area. Other assumptions about the dose-response model or the interspecies dose adjustment may result in lower estimates. The molecular potency index for aldrin is 6.2×10^3 per mmol/kg/day. This places aldrin in the first (most potent) quartile of suspect carcinogens ranked by the CAG.

Dieldrin

For dieldrin, the mouse liver tumor response in seven mouse strains (C_3HeB/Fe, C_3H, CBA/J, Swiss-Webster, $B6C3F_1$, and C57BL/6J) along with the appearance of pulmonary adenomas and carcinomas and lymphoid tumors in one strain (CF_1) would justify the preliminary classification of dieldrin as having "sufficient" evidence in animals. Based on the nature of the response there is no reason to downgrade the classification to "limited," since the carcinoma response is unmistakably strong, it occurs in both males and females, and at both high and low doses. The occurrence in several strains implies that it is not a genetically isolated finding. The carcinogenicity studies in rats for dieldrin were considered negative. However, the ability of most studies to detect carcinogenicity was compromised due to too few animals, too high mortality, and too short duration. Although liver pathology was associated with exposure to the chlorinated insecticides, there was no firm evidence of a carcinogenic response. In the absence of adequate evidence in humans, the sufficient animal evidence amounts to an overall classification of B2 or probable human carcinogen for dieldrin.

For dieldrin, the carcinogenic potency, obtained by averaging estimates from the most sensitive species tested, is 16 per mg/kg/day. The potency using the most sensitive sex and strain, is 55 per mg/kg/day. This estimate may, however, be misleading because 100% of the exposed animals developed cancer. The second most sensitive estimate is 28 per mg/kg/day. These are plausible upper bounds for the increased cancer risk from dieldrin, meaning that the true risk is not likely to exceed these estimates and may be lower. These estimates have been calculated using the Agency's preferred methodology in the absence of specific physiologic, metabolic, or kinetic information: the linearized multistage model with doses scaled according to relative body surface area. Other assumptions about the dose-response model or the interspecies dose adjustment may result in lower estimates. The molecular potency index for dieldrin is 6.1×10^3 per mmol/kg/day. This places dieldrin in the first (most potent) quartile of suspect carcinogens ranked by the CAG.

Although there is always uncertainty in extrapolating potency from animals to humans, our confidence in these animal potency estimates is relatively high. This confidence is based not only on the tight clustering of aldrin and dieldrin potency estimates, but on other factors as well. The potency estimates for aldrin are consistent with the potency estimates for dieldrin, one of its metabolites. In addition, aldrin's potency (and dieldrin's as well) is based in part on studies of mice with low-background tumor rates. A study of female C_3HeB/Fe mice, for example, saw the tumor incidence increase from 4% in controls to 85% in the treated group. Potencies derived from high-background strains are consistent

with potencies from low-background strains. Furthermore, potencies derived from mouse liver tumors are consistent with potencies derived from rat tumors for two other related substances, chlordane and heptachlor epoxide. Thus, mouse liver tumors can provide a basis for estimating cancer potency in humans, recognizing the current issues associated with use of this type of data and attendant uncertainties in a risk estimate based upon it.

This Project Summary was prepared by staff of Office of Health and Environmental Assessment, Washington, DC 20460.

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The complete report, entitled "Carcinogenicity Assessment of Aldrin and Dieldrin," (Order No. PB 88-139 951/AS; Cost: $19.95, subject to change) will be available only from:

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