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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dimethoate - Carcinogenicity in Animals

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2-6-95

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Dimethoate; CAS Registry No. 60-51-5; Chemical No. 035001

The Health Effects Division (HED) Carcinogenicity Peer Review Committee met on May 22, 1991 to evaluate the carcinogenicity data for dimethoate. Full details and references are found in the Peer Review files.

A. Carcinogenicity in Animals

After a full evaluation of all the data and supporting information regarding animal carcinogenicity, it is concluded that exposure to dimethoate results in the induction of combined spleen hemangioma/hemangiosarcoma in male rats. The increase was driven primarily by the malignant hemangiosarcoma component of the tumor response. There was also an induction of lymph angiosarcoma in the male rats albeit only at the lowest dose tested. In male mice, dimethoate induced an increase in combined hemolymphoreticular tumors (although this increase was determined to be equivocal). Dimethoate is regarded to have genotoxic activity based on the weight of all the mutagenicity evidence and this supports the carcinogenicity concern. The relevance of these data to an evaluation of dimethoate's potential for human carcinogenicity is discussed in the Peer Review document for Dimethoate (August 29, 1991).

B. Animal Carcinogenicity Studies

Male and female Wistar SPF rats were fed 0, 5, 25, or 100 ppm (equivalent to 0, 0.25, 1.25, or 5.0 mg/kg/day, respectively) of dimethoate for 24 months. The dosing levels in this study were

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considered appropriate for assessing carcinogenicity based on significantly decreased plasma, RBC and brain cholinesterase activity in both sexes. Also, body weight and body weight gain were significantly decreased in highest dose tested (HDT) males during the first year of the study and body weight gain depression in HDT females during the first eight months of the study. Male rats had no significant mortality with incremental doses of dimethoate, whereas female rats had a significant dose related trend, but no significant pair-wise comparison with controls at any dose, for mortality.

In male rats, there were dose related trends for (i) spleen hemangiosarcomas, (ii) combined spleen hemangioma and hemangiosarcoma, (iii) combined spleen hemangioma, hemangiosarcoma, and skin hemangiosarcoma. Furthermore, there were significant pair-wise comparisons between control and the high dose (100 ppm) for combined spleen hemangioma/hemangiosarcoma. While the incidence for spleen hemangiosarcoma by itself was borderline significant ($p = 0.057$), this malignant tumor type was the driving determinant in the significant incidence for combined spleen tumors. There was also a significant difference by pair-wise comparison between the control and low dose (5 ppm) for lymph angiosarcoma and combined lymph angioma and angiosarcoma. The Peer Review Committee felt it was appropriate to combine the tumor types in the male rats (from spleen, lymph, and skin). Although there was no dose response, there were significant pair-wise comparisons ($p < 0.05$) at the low and high doses for all these tumors combined. The Committee agreed that these tumors in male rats are compound related despite the absence of a dose response. The female rats did not have any biologically significant tumor increases with dose increments of dimethoate.

Male and female B6C3F1 CrlBR mice were fed 0, 25, 100, or 200 ppm (equivalent to 0, 3.75, 15, or 30 mg/kg/day, respectively) of dimethoate for 78 weeks. The dosing levels in this study were considered appropriate for assessing carcinogenicity based on significantly decreased plasma and RBC cholinesterase activity in both sexes. Also, body weight gain was significantly decreased in male mice (at all doses) and in HDT females during the first five weeks of the study. The body weight differences persisted in the HDT males up to week 50. Organ weight changes were prevalent in dosed females, especially lower relative liver weights, ovary weights and other organ weights. Male mice had no statistically significant mortality with incremental doses of dimethoate. Female mice had a statistically significant dose related mortality trend as well as a statistically significant difference between control and the mid-dose group (100 ppm).

In male mice there were significant dose related increased trends for (i) combined lung adenoma and/or adenocarcinoma, (ii) lymphoma, and (iii) combined group of lymphoma, reticularsarcoma, and leukemia. A significant difference ($p < 0.05$) in the pair-wise

2

comparison of control and the HDT was found for the combined tumor group of lymphoma, reticularsarcoma, and leukemia. The Committee did not believe that the lung tumors seen in males were biologically significant tumors related to dimethoate administration. For the hemolymphoreticular tumors, the Committee agreed that the lymphoma incidence was the main determinant in the group, but could only describe this incidence for the combined group as equivocal.

In the female mice, significant dose related trends for liver carcinoma and for combined liver adenoma/carcinoma were found. However, the Committee agreed that although the liver appears to be a target organ, not much weight was put on the combined tumor incidence. There were no significant pair-wise comparisons to control for adenomas, carcinomas, or combined liver tumors.

The National Cancer Institute (NCI) conducted carcinogenicity studies in B6C3F1 mice and Osborne-Mendel rats (1977 report). In the mouse study, male and female mice were fed doses of 250 or 500 ppm. Female mice received the diet for 60 weeks, low dose males for 69 weeks, and high dose males for 60 weeks; animals were kept for a total of 90 weeks. In the rat study, male rats were fed time weighted doses of 155 or 310 ppm (7.75 or 15.5 mg/kg/day) and female rats were fed time weighted doses of 192 or 384 ppm (9.6 or 19.2 mg/kg/day) for 80 weeks, followed by an observation period of 35 weeks.

No increases in tumor incidence was associated with administration of dimethoate in rats or mice in the NCI studies. However, significant deficiencies in the studies were identified and the Agency required the above described tests in rats and mice to be performed.

C. Additional Information

A series of mutagenicity studies testing dimethoate has been submitted to the OPP. Acceptable negative studies include a Salmonella assay, aberrations in rat bone marrow, a mouse micronucleus assay, and a mouse dominant lethal assay. Equivocal results were obtained from two further acceptable assays, an E. coli WP2 uvrA gene mutation assay and a Chinese hamster ovary (CHO)/hprt gene mutation assay.

Other mutagenicity studies from published sources have been reviewed by the OPP. Hanna and Dyer (Mutat. Res. 28: 405-420, 1975) obtained positive results for gene mutation in two E. coli strains WP2 uvrA and WP67, and negative results in other E. coli strains and several Salmonella tester strains. Mohn (Mutat. Res. 20: 7-15, 1973) found dimethoate to induce a dose-responsive effect in an E. coli K-12/galRS18 gene mutation assay. Positive results for mitotic gene conversion in S. cerevisiae were reported by

Fahrig (Naturwissenchaften 60: 50-51, 1973). Induction of unscheduled DNA synthesis (UDS) with metabolic activation (negative without activation) in transformed human cells was reported by Ahmed et al. (Mutat. Res. 42: 161-174, 1977; MRID #00131720). Usha Rani et al. (Bull. Environ. Contam. Toxicol. 25: 277-282, 1980) report that dimethoate induced positive results for gene mutations in a host-mediated assay and for micronuclei in a mouse bone marrow micronucleus assay. The latter result was reviewed by the Gene-Tox Panel of experts for the micronucleus assay and judged the result to be a single point positive (i.e. a single dose-time point in one experiment). The OPP's Position Document 4 (PD 4) on dimethoate mentions two 1975 studies that report positive effects in a mouse dominant lethal study and for aberrations in mouse bone marrow (Gerstengarbe, Arch. Sci. J., Univ. Halle, M Series, 1975 (German) and Bhunya and Behera, Cur. Sci. 44(23): 859-860, 1975, respectively; no other reviews available).

Other published studies with dimethoate are available. The National Toxicology Program concludes dimethoate is a mutagenic compound based on their testing: positive in Salmonella strain TA100 with and without activation, positive for sister chromatid exchanges (SCEs) in CHO cells, and equivocal for aberrations in CHO cells (reported in Shelby and Stasiewicz, Environ. Mutagen. 6: 871-878, 1984). SCE induction is also found in V79 Chinese hamster fibroblast cells with activation (Chen et al., Environ. Mutagen. 4: 621-624, 1982 and Mutat. Res. 88: 307-316, 1981) and in cultured human lymphoid cells - positive with and without activation, but enhanced with activation (Sobti et al., Mutat. Res. 102: 89-102, 1982). Ishidate et al. (Mutat. Res. 195: 151-213, 1988) report dimethoate is positive for aberrations in cultured CHL cells without activation. Dzwonkowska and Hubner (Arch. Toxicol. 58: 152-256, 1986) report that dimethoate is weakly clastogenic in bone marrow of Syrian hamsters. On the other hand, Degraeve and Moutschen (Mutat. Res. 119: 331-337, 1983) report negative results in the mouse for aberrations in bone marrow and spermatogonia and for dominant lethal effects. However, these results were submitted in 1981 to the OPP and were found unacceptable as dose levels were not high enough, among other deficiencies.

Based on the total weight of the evidence, dimethoate presents a mutagenicity concern. It is a bacterial mutagen and equivocal for gene mutations in mammalian cells, and it produces clastogenic effects in several studies in vitro and in vivo (as well as negative results it is noted). The overall mutagenicity concern supports a concern for carcinogenicity.

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