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

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MEMORANDUM

SUBJECT: EPA Reg.241-110; 241-208, Malathion; NCI Cancer Bioassays of Malathion and Malaoxon. CASWELL#535; Accession:242903

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

FROM: William Dykstra, Toxicologist
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TO: William Miller (15)
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Recommendations:

1) Malathion was not considered carcinogenic to Osborne-Mendel rats, F344 rats or female B6C3F1 mice in the studies reported. Because of questionable liver findings in the male mice, another study in mice is required..

2) Malaoxon was not considered carcinogenic to F344 rats B6C3F1 mice in the study reported.

Review:

1) Bioassay of Malathion for Possible Carcinogenicity (NCI Carcinogenesis Technical Report Series No. 24, 1978; CAS#121-75-5; NCI-CG-TR-24)

A bioassay of technical-grade malathion for possible carcinogenicity was conducted by administering the test chemical in feed to Osborne-Mendel rats and B6C3F1 mice. Groups of 50 rats of each sex were administered malathion at one of two doses for 80 weeks, then observed for 33 weeks. Time-weighed average doses were 4,700 and 8,150 ppm. Matched controls consisted of groups of 15 untreated rats of each sex; pooled controls consisted of the matched controls combined with 40 untreated male and 40 untreated female rats from similar bioassays of four other test chemicals. All surviving rats were killed at 108-113 weeks.

Groups of 50 mice of each sex were administered malathion at one of two doses, either 8,000 or 16,000 ppm, for 80 weeks, then observed for 14 or 15 weeks. Matched controls consisted of groups of 10 untreated mice of each sex; pooled controls consisted of the matched controls combined with 40 untreated male and 40 untreated female mice from similar bioassays of four other test chemicals. All surviving mice were killed at 94 or 95 weeks.

Results:

Mortality in either rats or mice was not significantly related to the administration of malathion. Sufficient numbers of animals were at risk in the dosed and control groups of rats and mice of each sex for development of late-appearing tumors.

In female rats, three follicular-cell carcinomas and one follicular-cell adenoma of the thyroid occurred in the high-dose group, and three follicular-cell hyperplasias occurred in the low-dose group.

The incidence of three tumors showed a statistically significant (P = 0.026) dose-related trend; however, the results of the Fischer exact test for direct comparison between the dosed and control groups were not significant. More dosed males than females had either tumors or hyperplasia of the follicular cells of the thyroid; however, because of the higher incidence of tumors among the male controls, none of the results of the statistical tests were significant. These thyroid tumors were not considered to be associated with the administration of malathion.

In male mice, hepatocellular carcinoma occurred at the following incidences: matched controls 2/10, pooled controls 5/49, low-dose 7/48, high-dose 11/49. In addition, neoplastic nodules occurred in 3/49 pooled-controls and 6/49 high-dose animals. When the combined incidence of these neoplasms in the dosed animals was compared with that of the pooled controls, the dose-related trend was P = 0.019 and the direct comparison of the high-dose group with the control group was P = 0.031. Thus, when NCI compared this high dose group with the control group using Bonferroni criteria, the difference was not significant since a P of 0.025 was required. Although NCI did not consider these liver tumors to be associated with the administration of malathion, the Agency has concerns about acceptability of this study as a negative study to fulfill our registration requirement for a mouse oncogenic study. Since there was a dose-related trend (P = 0.019) and an increase of tumors at the high dose (P = .031) at levels which the Agency normally considers to be significant, we believe that there is sufficient justification to require another mouse oncogenic study.

Conclusion:

Under the conditions of this bioassay, there was no clear evidence of the association of the tumor incidence with the administration of malathion to Osborne-Mendel rats or B6C3F1 mice. However the questionable increases of liver tumors limit its usefulness as a negative oncogenic study to fulfill a regulatory requirement.

Classification: Core-Minimum Data

2. Bioassay of Malaoxon for Possible Carcinogenicity (NCI Technical Report Series No. 135, 1979; Cas. No. 1634-78-2; NCI-CG-TR-135)

A bioassay of malaoxon, the oxygen analog of malathion, for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were fed diets containing 500 or 1,000 ppm malaoxon for 103 weeks and were then observed for up to an additional 2 weeks. Matched controls consisted of groups of 50 untreated rats and 50 untreated mice of each sex. All surviving animals were killed at 103 to 105 weeks.

Results:

The only effects that could be related to administration of malaoxon at the doses used were increased mortality among male mice, decreased mean body weights of female mice, gastric ulcers in male and female rats, and possibly C-cell adenomas or carcinomas of the thyroid among treated female rats. The incidence of C-cell adenomas or carcinomas among historical controls, however, precluded relating the administration of the chemical to the incidence of these tumors.

Conclusion:

Under the conditions of this bioassay, malaoxon was not carcinogenic for F344 rats or B6C3F1 mice.

Classification: Core-Minimum Data

3. Bioassay of Malathion for Possible Carcinogenicity (NCI Carcinogenesis Technical Report Series No. 192, 1979; Cas. No. 121-75-5; NCI-CG-TR-192)

A bioassay of malathion for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats.

Groups of 49 to 50 rats of each sex were fed diets containing 2,000 or 4,000 ppm malathion for 103 weeks and were then observed for an additional 2 or 3 weeks. Matched controls consisted of 50 untreated rats of each sex. All surviving rats were killed at 105 or 106 weeks.

Results:

No tumors occurred in the dosed groups of rats of either sex incidences that could be related clearly to administration of the test chemical. Compound-related toxic effects were not observed in female rats at the doses used, but in males decreased mean body weights, increased mortality, gastritis, and gastric ulcers were dosed related.

Conclusion:

Under the conditions of this bioassay, malathion was not carcinogenic in male or female rats, but the females may not have received a maximum tolerated dose.

Classification: Core-Minimum Data

TS-769:th:LCHITLIK:12-2-80