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

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MAR - 1 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Malathion, Metabolism Study in Rats

TO: J. Edwards, PM-74
Registration Division (H7505C)

FROM: Robert P. Zendzian Ph.D. 2/27/90
Senior Pharmacologist
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THROUGH: Albin Kocialski Ph.D. ABK 2/28/90
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Compound; Malathion | Tox Chem #535 | MRID #413677-01

Registration #241-208 | Registrant; Malathon Task Force | Tox Project #0-0606

Action Requested

Review the following study;

Disposition and metabolism of ^{14}C-labeled malathion in rats (preliminary and definitive study), V. Reddy, T. Freeman & M. Cannon, Midwest Research Institute, MRI Project No. 9354-B, Dec 20, 1989, MRID 413677-01

Conclusion

Guideline study

^{14}C-labeled malathion was dose orally at 40 and 800 mg/kg and 40 mg/kg following 14 daily doses of 40mg/kg/day. 90+ percent of the dose was excreted in 72 hrs with 80-90% excreted in the urine. Females excreted slightly more in the urine than males. Between 4 and 6 % of the dose was converted to the active inhibitor, malaoxon.

Attachment
DER
cc
Gardner

Data Evalaution Report

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Compound Malathion

Citation

Disposition and metabolism of ^{14}C-labeled malathion in rats (preliminary and definitive study), V. Reddy, T. Freeman & M. Cannon, Midwest Research Institute, MRI Project No. 9354-B, Dec 20, 1989, MRID 413677-01

1/17/90

Reviewed by Robert P. Zendzian Ph.D.
Senior Pharmacologist

Core Classification Guideline

Conclusion

^{14}C-labeled malathion was dose orally at 40 and 800 mg/kg and 40 mg/kg following 14 daily doses of 40mg/kg/day. 90+ percent of the dose was excreted in 72 hrs with 80-90% excreted in the urine. Females excreted slightly more in the urine than males. Between 4 and 6 % of the dose was converted to the active inhibitor, malaoxon

Materials

Malathion, CAS 121-75-5
O,O-Dimethyl-S-(1,2-dicarboxyethyl)phosphorodithioate
Deep Brown to yellow liquid
Nonlabeled
Product No. W 60930-6038
Purity 94.6%
^{14}C-Labeled malathion (labeled in the carbons of the dicarboxy)
Lot No. C4
Purity 98%
specific activity 90.0 uCi/mg

Adult male and female Sprague-Dawley (Crl:CD BR) rats 7 to 10 weeks old from Charles River

Experimental Design

Doses were administered orally by gavage in a volume of 4 ml corn oil/kg as follows;

Study	Sex	No. of Animals	Nominal Dose (mg/kg)	Actual Dose[a] (mg/kg/)
Preliminary	M	1	40	36.9
	F	1	40	37.4
	M	1	800	796.4
	F	1	800	765.9

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Study	Sex	No. of Animals	Nominal Dose (mg/kg)	Actual Dose[a] (mg/kg/)
Definitive Single Dose	M	5	40	36.4
	F	5	40	37.1
	M	5	800	755.3
	F	5	800	751.8
Multiple[b] Dose	M	5	40	35.1
	F	5	40	36.3

a. mean of dosed animals.
b. following 15 daily single doses of 40mg/kg/day.

Doses were prepared by adding sufficient quantity of 14C malathion and sufficient nonlableled malathion to corn oil to produce final concentrations of 10 or 200 mg/ml for the 40 and 800 mg/kg dose groups, respectively. Prepared dosing solutions were analyzed and actual doses calculated.

Preliminary study.

Animals were dosed as above and placed individually in metabolism cages. Urine, feces and epired air were collected and analyzed for radioactivity at 4, 8, 12, 24, 48 and 72 hours after dosing. "At 72 hours, the animals were anesthetized with ether and esanguinated by withdrawal of blood from the abdominal aorta."

Definitive study.

Animals were dosed as above and placed in individual metabolism cages. "Following the administration of the radio-labeled dose (low, high and multiple dose groups), urine and feces were collected and measured for ratioactivity content at 4, 8, 12, 24, 48 and 72 hr. At 72 h, all animals were killed as described previously for tissue sampling." The following tissues were collected weighed and analyzed;

Liver	Splee	Muscle (thigh)
Kidneys	Adrenals	Fat (retroperitoneal)
Lungs	Testes	Bone (femur)
Brain	Uterus	Skin
Heart	Ovaries	GI tract plus contents
		Residual Carcass

Whole blood, plasma and RBC were analyzed.

Individual and pooled urine and fecal samples from the dosed animals were analyzed for biotransformation (malathion and metabolites).

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Results

Preliminary study.

Dose excretion, as percent of applied dose, was as follows;

Route	40 mg/kg		300 mg/kg	
	Male	Female	Male	Female
Expired Air	0.92	0.33	0.44	0.32
Urine	93.92	93.81	83.38	89.31
Feces	8.59	4.05	14.55	15.25
Total	103.43	98.19	98.37	104.88

Definitive study.

Excretion (urinary, fecal and total) are presented as percent of dose per collection period and cumulative percent of dose in Table 1 (males) and 2 (females) from the report. Data are summarized as follows;

Route	40 mg/kg		800 mg/kg		40 mg/kg X 15	
	Male	Female	Male	Female	Male	Female
Urine	83.83	88.03	76.17	85.24	84.56	88.36
Feces	10.95	5.95	13.68	6.61	6.81	5.81
Total	94.78	93.97	89.85	91.85	91.38	94.17

Dose distribution in blood, tissues and excreta is presented, as ug Equivalants/g tissue and percent of dose, in Table 3 (males) and 4 (females) from the report. The highest concentration and percent of dose was observed in the liver. No indication of bioaccumulation was observed.

Metabolic profiles, as percent of total radioactivity, are presented in Table 5 (urine) and 6 (feces). Of the eight radiolabeled metabolites identified, the diacid (DCA) and mono acids (MCA) represented greator than 80 % of the recovered radioactivity. The remaining 5 radiolabeled metabolites were identified in peaks A and B. Based on the metabolites of malathion that were identified, a possible metabolic pathway is presented in Figure 6 from the report. This figure has been modified as noted below.

Discussion

Malathion must be converted to malaoxon in order to inhibit cholinesterase. Therefore, determination of the percent of malathion converted into malaoxon is critical.

Figure 6 shows the conversion, by oxidation, of malathion to malaoxon but the figure, as presented in the report, omits a critical metabolic step which is indicative of the inactivation of malaoxon and/or its reaction with cholinesterase. Malaoxon can be inactivated by removal of the 2-mercaptosuccinic acid group or malaoxon can react with cholinesterase a step which also releases 2-mercaptosuccinic acid. However, 2-mercaptosuccinic acid was not identified as a metabolite but rather its metabolites 2-mercaptosuccinic acid disulfide and fumaric acid. This metabolic process is shown in the modifications of Figure 6 which indicate malaoxon metabolism. The maximum possible conversion of malathion to malaoxon is the total of malaoxon, 2-mercaptosuccinic acid disulfide and fumaric acid, given as minor metabolites constituting between 4 and 6 percent of the dose of malathion. Maximum cholinesterase reacted enzyme is given as the total of 2-mercaptosuccinic acid disulfide and fumaric acid, between 2 and 4 percent of the dose of malathion.

This conclusion is supported by data on the intraperitoneal LD_{50}s of malathion and malaoxon in the rat. The respective values are 900 and 25 mg/kg, indicative of 2.8% malathion converting to malaoxon and reacting with the enzyme.

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RIN 1244-00

Malathion Tox Review # 7791

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