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Subject: Malathion Mutagenicity and Teratogenicity
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Oak Ridge people consulted, among other literature sources, Gene Tox data, Medline, IARC, Tox Line, EMIC, EDIC and NCI data banks. The following information was transmitted to me by telephone:

A Malathion Carcinogenicity:

- 1) NCI Report - negative for carcinogenicity - tumor formation occurred only when malathion was administered in rodent ~~with~~ together with a known carcinogen, such as dimethylbenzanthracene
- 2) Carcinogen program Report PB 278527 (1977) no clear evidence of tumors with malathion fed Osborn-Mendel Rats or B6C3H/F1 mice.
- 3) NCI Tech Report 192, 1979. Fisher 344 male & female rats fed malathion at 2000 or 4000 ppm for 103 weeks showed

no carcinogenic effect. No adverse effect in female.
Males had gastro-intestinal symptoms, weight loss & a dose-dependent increase in mortalities.

B. Teratology

1) of 45 papers, 4 dealt with mammalian studies (rest were on chickens). Malathion is not toxic to chicken. Chickens fed malathion did not transfer ~~adverse~~^{toxic} effect to chicks via eggs. Corn oil which enhanced chick terata; acetone vehicle did not.

2) All mammalian studies involved i.p. injection except the following, which was gastric intubation: Wistar rats, pregnant female, were gavage on days 6-15 with 50 mg/kg, 100, 200 & 300 mg/kg malathion. No change in litter size, fetal weights, # abnormalities per litter were seen. No fetotoxicity at highest dose. No sign of maternal toxicity except reduction in weight at highest dose. No significant resorption.

Ref. - Khara, K.S., Toxicol. Appl. Pharm. 45: 435-444 (1978)
Teratogenicity studies with Zenuron, Malathion and Methoxychlor in Rats.

3. Reproduction Study.

Wistar rats. Second Generation Toxicity

of Malathion in Rats. Nature, 192: 464-5 (1961)
Kalow, W.

Wistar rats administered malathion (95% tech. grade) in corn oil at 240 mg/kg/b.w. diet. Animals aged 70-100 d., (40 male, 40 female). Animals bred at 5 mo. No adverse effect were seen. Litter size was not statistically significantly different from controls, except for susceptibility to infection.

4. Reprod. Study. U. Missouri. Trace Substance in Environmental Health. Pt. II. Hemphill, D.D. pp. 183-209. Effects of pesticides on Rat and Chick embryos. Green, Vernon A.

Sprague-Dawley rats used. Fed diet with malathion (no dosage given). Of 25 female, 12 pregnancies resulted, 86 pups born, 7.1 average litter size. None survived past 21 days.

c. Mutagenicity -

Literature presented without citations although based on such. Findings presented were peer-reviewed by EPA Gene Tox Panel. Each statement is a definitive group assessment for that test.

1. Hordeum plant (barley) (+) chromosomal aberrations

2. D. Melanogaster (-) sex-linked recessive lethal

3. E coli Repair deficient WP2 UVRA⁻ (-)
4. Human Lung fibroblast (+) SCE, confirmed dose-response relationship
5. Yeast - chromosomal effects (-) includes S. cerevisiae and Schizosaccharomyces pombe
6. Ames test - generally (-)
exceptions:
 - a) Kawachi et al 1980 - S. typhimurium TA100 (+)
S. typhimurium TA 98 (+)
Rec assay ($\pm$)
 - b) (Shiau - 1980 - similar results to our table.)
 - c) Shiau, 19 - Vol. 40, Mut. Research pp. 19-30
Salmonella (-)

Kawachi et al found SCE in human cultured cells to be negative.

Oak Ridge people are sending us a brief report of our phone conversation and copies of pertinent table-data including Kawachi's 1980 SCE (-) result w. Malathion. (I added it to the attached table.)

Summary - Mutagenicity Results for Marathion

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Study No.	Test + System	Results	Comments	Reference
1.	Mouse Dominant lethal	-	-	Simmons et al 1977
2.	<u>S. typhimurium</u> strains His ⁺	-	with MA and without MA ⁺	"
3.	<u>E. coli</u> WP2 TRP ⁺	-	" " "	"
4.	<u>S. cerevisiae</u> D3	-	" " "	"
5.	DNA Repair - <u>E. coli</u> W3110	-	-	"
6.	" " <u>B. subtilis</u> H17 + M45	-	-	"
7.	Unscheduled DNA synthesis in cultured human Fibroblasts WI 38	-	with and without MA	"
8.	<u>E. coli</u> - 5-MT resistance forward mutation	-	not validated because data were not reported	Fahrig 1973
9.	<u>S. marcescens</u> spot test back mutation	-	" "	"
10.	<u>E. coli</u> forward mutation	-	" "	"
11.	<u>E. coli</u> Streptomycin resistance	-	" "	"
12.	<u>S. cerevisiae</u> - gene conversion	-	" "	"
13.	<u>E. coli</u> Lac ⁻ - reverse mutations	-	Too few details for validation	Ficson + Lo Piccolo 1972
14.	<u>E. coli</u> Cis ⁻ - reverse mutations	-	"	"
15.	<u>S. typhimurium</u> 646 and TA 1530 reverse mutation plate test	-	"	"
16.	<u>S. typhimurium</u> - reverse mutation	+	Weak positive; less than 0.05 revertants per nanomole	McCann et al 1975

* MA = metabolic Activation

Study No.	Test and System	Results	Comments	Reference
17	<u>E. coli</u> WP-2 TRP ⁻	-	Results are not validated because repair system is newly developed	Nagy, 1975
18	<u>B. subtilis</u> - DNA Repair	±		Shiau et al 1980
19	<u>B. subtilis</u> forward mutation	+		
20	<u>B. subtilis</u> forward mutation	+		
21	<u>B. subtilis</u> forward mutation	-		
22	<u>B. subtilis</u> DNA damage H17 and M45 strains	-		Degreave et al 1971
23**	Sister chromatid exchange - cultured human fibroblast cells	+	Not of primary significance - mechanism not elucidated	Nicholas, 1979
24	<u>Drosophila</u> sp. sex-linked recessive	-		Valencia (no date)
25**	Plasmid DNA breakage	+	Unvalidated; questionable significance to humans	Griffin & Hill 1978
26	Sister chromatid Exchange Human cell cultures †	-		Kawachi et al 1980

** These two studies are directly referred to by Kalman

† Kawachi et al. (1980). IARC Science Publ. Vol. 27, pp. 323-330