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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 Repot - 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 & 4000 ppm for 103 weeks showed

no carcinogenic effects. No adverse effect in females. 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 ~~adulted~~ toxic effect to chick via eggs. Corn oil vehicle enhanced chick teratogenicity; acetone vehicle did not.

2.) All mammalian studies involved i.p. injection except the following, which was gastric intubation: Wistar rats, pregnant females were gavaged on days 6-15 with 50 mg/kg, 100, 200 & 300 mg/kg malathion. No change in litter size, fetal weight, # 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. - Khera, K.S., Toxicol. Appl. Pharm. 45: 435-444 (1978) Teratogenicity studies with Linuron, 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 females. Animals bred at 5 mo. No adverse effect were seen. Litter size was not statistically significantly differes from control, except for susceptibility to infection.

4. Repsd. Study - U. Missouri. Trace Substances in Environmental Health. Pt. III. 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 tests - generally (−)
exceptions:
a.) Kawachi et al 1980 - S. typhimurium TA 100 (+)
S. typhimurium TA 98 (+)
Rec assay (±)

b.) (Shirai - 1980 - similar results to our table.)
c.) Shirasu, 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 (−) results w. Malathion. (I added it to the attached table.)
Yoshie

Summary -

Mutagenicity Results for Malathion

Study No.	Test + System	Results	Comments	Reference
1.	Mouse Dominant lethal	–	–	Simmons et al 1977
2.	S. typhimurium strains His^+	–	with MA and without MA*	"
3.	E. coli WP2 TRP^+	–	" " "	"
4.	S. cerevisiae D3	–	" " "	"
5.	DNA Repair - E. coli W 3110	–	–	"
6.	" " B. subtilis H17 + M45	–	–	"
7.	Unscheduled DNA synthesis in cultured human Fibroblasts WI 38	–	with and without MA.	"
8.	E. coli - 5-MT resistance forward mutation	–	NOT validated because data were not reported	Fahrig 1973
9.	S. marcescens spot test back mutation	–	" "	"
10	E. coli - forward mutation	–	" "	"
11	E. coli Streptomycin resistance	–	" "	"
12.	S. cerevisiae - gene conversion	–	" "	"
13	E. coli Lac^- - reverse mutations	–	Too few details for validation	Ficsor + Lo-Piccolo 1972
14.	E. coli Cis^- - reverse mutations	–	"	"
15.	S. typhimurium G46 and TA 1530 reverse mutation plate test	–	"	"
16	S. typhimurium - reverse mutation	+	Weak positive; less than 0.05 revertants per nanomole	McCann et al 1975

*MA = metabolic Activation

Summary -
Mutagenicity Tests for Malathion Page 2

Study No.	Test and System	Results	Comments	Reference
17	E. coli WP-2 TRP⁻	−		Nagy, 1975
18	B. subtilis - DNA Repair	±	Results are not validated because repair system is newly developed	Shiau et al 1980
19	B. subtilis forward mutation	+		
20	B. subtilis forward mutation	+		
21	B. subtilis forward mutation	−		
22.	B. subtilis DNA damage H17 and M45 strains	−		Degreave et al 1978
23**	Sister chromatid exchange - cultured human fibroblast cells	+	Not of primary significance - mechanism not elucidated	Nicholas, 1979
24	Drosophila 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