DER #15

Malathion: Dermal Absorption Analysis

10/6/1994

MEMORANDUM October 6, 1994

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Subject: Malathion, EPA Technical Report, Protocol for Dermal Exposure Assessment, Part 6. Percutaneous Skin Absorption Study in Humans

TO: Joanne Edwards PM 74 Reregistration Branch Special Review and Reregistration Division (7508C)

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Action Requested

. Evaluate Part 6. Phase I: Percutaneous Absorption Study Task 5, pages 61-84 and Appendices A and B of the Following Report;

Protocol for Dermal Exposure Assessment: A Technical Report. M. Castles and V. Reddy. Midwest Research Institute, Kansas City MO, Contract No. 68-DO-0137, Jan 1993, for Environmental Monitoring Systems Laboratory, ORD, USEPA, Las Vagas, Nevada.

Conclusions

The study was designed to determine the human percutaneous absorption of malathion (neat), ortho Malathion 50 (50% malathion in xylene), Orthro malathion diluted to 1% in water and Orthro malathion diluted to 10% in water when applied to the forearm. Proposed doses were 5.4, 5.6, 0.0342 and 1.2 mg/cm2 respectively. Due to errors in dose application the mean doses applied were 0.8, 0.9, 0.032 and 1.13 mg/cm2 respectively. Mean absorption, based on urinary excretion of label, for a 24 hour exposure was 7.2, 5.6, 15.0 and 5.5 percent respectively.

Maiback et. al. (1971) reported a mean absorption of 6.8(+2.3)% of a 0.004 mg dose of malathion in acetone to the human forearm. Subsequently Feldman and Maiback (1974) reported a mean absorption of 8.2(+2.7)% of a 0.004 mg dose in acetone to the human forearm. While the study reviewed did not achieve its designed purpose, its agreement with the published studies indicates that a dermal absorption of 10% can be reasonably used as an upper limit of absorption for human risk assessment. However, if significant toxicological issues are raised concerning

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malathion and the MOE or risk calculation based on 10% absorption is unacceptable a guideline dermal absorption study should be performed.

Experimental Design

Malathion was administered to an area of 4.6 cm^2 on the forearm of human subjects.

Table A. Intended dosing information.

		Nominal Dose			
Formulation	No. of Subjects	^{14}C (Uci)	Malathion (mg)	Malathion (mg/cm2)	volume (ul)
Malathion (neat)	6	7.24	24.6	5.4	20
Orthro malathion 50	6	7.25	25.7	5.6	50
1% Malathion from formulation	6	2.45	0.1571	0.0342	15
10% malathion from formulation	6	5.70	5.5	1.2	100

The dose formulation was applied to an area, after a soap and water wash, on the forearm of 4.6 cm^2 marked with a graphite pencil. After dose application the subject was observed in the laboratory for 4 hours. The application site was then covered with a sterile pad and impervious surgical tape and the subjects released. The subjects returned approximately 24 hours after dose application, the cover was removed and the application site washed with soap and water. Subjects collected total urine for three days following application. The amount absorbed was based directly on the amount of radioactivity excreted and the percent absorbed was calculated from the actual dose applied.

Results

Upon application the dose of neat malathion and Orthro Malathion 50 was observed to spread beyond the measured area as seen by a surface 'sheen'. The area of the sheen was measured and the dose/cm^2 recalculated based on this area.

The dose and absorption data from Table 14 of the report are summarized in Table B.

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Table B. Summary of actual dose and absorption data. Values are the mean of the six subjects per dose group. Twenty four hour exposure. ±S.D.

Formulation	Dose (mg)	Area (cm^2)	Dose (mg/cm^2)	Absorbed (%)	Absorbed mg
Malathion (neat)	21.5	39.04	0.8	7.2	0.89 ±6.2
Orthro Malathion 50	21.2	28.38	0.9	5.6	0.93 ±3.1
1% Malathion from formulation	0.149	4.6	0.032	15.0	0.02 ⁺4.8
10% Malathion from formulation	5.20	4.6	1.13	5.5	0.28 ±2.7

Discussion

This study was planned to compare the dermal absorption of malathion administered in four dosage forms. As planned the study would have been only partially successful in detecting formulation related differences. Dermal penetration of a chemical is effected by a variety of factors in addition to its own physical/chemical properties. For chemicals which are not volatile or do not damage the skin, the major factor is the dose per unit area. The amount absorbed per unit area increases at a decreasing rate with increasing dose until absorption is saturated. Concurrently the percent absorbed decreases, asymptotic to zero, with increasing dose. The planned doses of Malathion neat and Orthro Malathion 50 were essentially identical. Differences in absorption between the two could have been reasonably attributed to the xylene in the Orthro formulation. The 1% and 10% solutions of the Orthro formulation as planned would have had doses per cm^2 that were sufficiently different such as to be expected to produce dose-related differences in percent absorbed.

Failure to physically restrict the area of the application site resulted in spreading of the neat and formulation dosages so that the resultant mean doses 'per unit area were essentially identical to each other and to the 10% solution. The resultant percent absorptions were essentially identical when one considers the overlap of standard error of the means. However, the dose of the 1% solution was approximately an order of magnitude less than the other three and the resultant greater percent absorption can be attributed to the difference in dose per unit area.

References

Maibach, H.I., M.D. Feldman, Milby, T.H. & Serat, W.F., Regional variation of percutaneous

penetration in man, Archives of Environmental Health, 23, No. 3, (1971), 208-211

Feldman, R.J., & H.I. Maibach, Percutaneous penetration of some pesticides and herbicides in man., Toxicology and Applied Pharmacology, 28, 126-132 (1974)