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MEMORANDUM

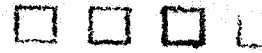
SUBJECT: *FENTHION: RE-EVALUATION OF THE DERMAL ABSORPTION FACTOR* - Report of the Hazard Identification Assessment Review Committee.

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On September 16, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) reevaluated the dermal absorption factor because of the use pattern information provided by the occupational and residential exposure assessor which indicated the need for a re-evaluation of dermal absorption. The Committee's conclusions are presented in this report.

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Committee Members in Attendance

Members present were: David Anderson, William Burnam, Virginia Dobozy, Karen Hamernik, Pamela Hurley, Mike Ioannou, Tina Levine, Sue Makris, Nicole Paquette, Kathleen Raffaele, PV Shah, Jess Rowland and Pauline Wagner.

Also in attendance were William Hazel, Jeff Dawson, and Mike Metzger.

Data was presented by Elizabeth Mendez.

I. BACKGROUND

In 1996, the Toxicology Endpoint Selection Committee (TESC) extrapolated a dermal absorption factor of 20% based on the results of an oral developmental toxicity study in rabbits (MRID No. 40462701) and a 21-day dermal toxicity study with rabbits conducted in 1979 in which fenthion was applied as a dilute solution in Cremophor (MRID No. 40808601). The TESC did not use another 21-day dermal toxicity study in rabbits conducted in 1988 in which fenthion was applied as "neat" (MRID No. 40329501) because the TESC considered the Cremophor-diluted fenthion to more closely resemble the potential for dermal exposure than the fenthion technical applied neat. The rationale provide in the TES document (HED Doc. No. 013205) is as follows:

No dermal absorption data are available. Therefore, an estimate of dermal absorption was made using the comparison between a developmental toxicity study in rabbits (MRID No.: 40462701, refer to Executive Summary below) and a 21-day dermal toxicity study in rabbits (MRID No.: 40808601, refer to Executive Summary below). Two 21-day dermal studies in rabbits are available. In the older study (MRID No.: 40808601), fenthion was applied in a Cremophor vehicle; in the more recent study (MRID No.: 40329501), fenthion technical was applied neat. The NOEL from the older study was selected to develop a dermal absorption factor because the committee viewed this study as more representative of a formulated product. Based upon the ChE/AChE NOEL from the developmental toxicity study in rabbits (1.0 mg/kg/day) and the LOEL from the dermal toxicity study in rabbits (5 mg/kg/day, the lowest test dose in the study) the dermal absorption is estimated to be $\approx 20\%$. (The comparison of the NOEL from the developmental study to the LOEL from the dermal study is considered valid because the degree of RBC AChE inhibition at the low dose in the dermal study was considered to be relatively low, suggesting that this dose is close to a NOEL.

The HIARC was requested to re-evaluate the dermal absorption factor due to additional information available regarding the use pattern provided by the occupational and residential exposure assessor. Fenthion is used (sprayed) as the technical grade and the mode of application indicates that the compound is applied as an ultra low volume (ULV) primarily in the technical grade form (95%) for short and intermediate term exposure scenarios. Based on this new information, it is evident that the use of the 21-day dermal study conducted with the "neat" material would be more appropriate since the vehicle used in the 1979 study (Cremophor) may have enhanced the dermal absorption of the test article.

II. Selection of Dermal Absorption Factor

A dermal absorption factor is required since an Oral NOAEL (0.07 mg/kg/day) established in a study with monkeys was selected for Short and Intermediate-Term dermal risk assessments and a dermal absorption study is not available in the database. The HIARC determined that the 21-day dermal toxicity studies are not appropriate for dermal risk assessments since the species tested was rabbits and rabbits have a number of unique physiological and biochemical characteristics which can lead to a potential underestimation of dermal toxicity, particularly true for organophosphates which require biological activation to the oxon. In humans, activation of S=organophosphates takes place in the liver upon the exchange of oxygen for the sulfur atom. However, this process does not occur to the same extent in the rabbit due to the high levels of arylesterases present in the rabbit blood stream. Arylesterases can rapidly detoxify organophosphates before they reach the liver and are activated. As a result, basing the dermal

toxicity of an organophosphate solely on rabbit dermal toxicity studies may underestimate the toxicity (Zendzian memo, 1997).

The HIARC used an oral and dermal toxicity studies in the same species (rabbits) based on the same endpoint (cholinesterase inhibition) to extrapolate a dermal absorption factor. Based on the ratio of the LOAELs in the oral developmental toxicity study in rabbits (MRID No. 40808601) and in the 21-day dermal toxicity study where the test article is applied neat (MRID 40329501), a dermal absorption factor of 3% was extrapolated.

In the oral developmental toxicity study in rabbits, the **LOAEL was 2.75 mg/kg/day** based on plasma, RBC and brain cholinesterase inhibition.

In the 21-day dermal toxicity study in rabbits, the **LOAEL was 100 mg/kg/day** based on plasma, RBC and brain cholinesterase inhibition.

$$\text{Dermal Absorption Factor} = \frac{2.75 \text{ mg/kg/day (oral LOAEL)}}{100 \text{ mg/kg/day (dermal LOAEL)}} \times 100 = 3\%$$

This dermal absorption factor should be used in Short and Intermediate-Term dermal risk assessments. Based on the current use pattern there is no potential for Long-Term dermal exposure, therefore, this risk assessment is not required.