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TXR # 0051898

DATA EVALUATION RECORD

STUDY TYPE: *in vitro* Dermal Absorption - (human and rat)

P.C. CODE:035001 DP BARCODE: D290024 SUBMISSION NO: S635214

TEST MATERIAL (RADIOCHEMICAL PURITY): Dimethoate 96%

SYNONYMS: [other names and code names]

CITATION: Davis, D.J. December 7, 1999, Dimethoate; *In Vitro* Absorption from a 400 g/L EC formulation through human and rat epidermis. Central Toxicology Laboratory. Study No JV1591. MRID 45922602

SPONSOR: Dimethoate Task Force

EXECUTIVE SUMMARY: In an *in vitro* dermal penetration study (MRID45922602) Dimethoate (99.5% a.i., batch #291-BSe-75B) was administered to the isolated epidermal membrane from human and rat skin in 400 g/L EC formulation and a 1/200 v/v water dilution thereof. Exposure durations were 8 and 24 hours at the end of which time a sample of the receptor fluid was taken, the application site was washed and the epidermal membrane collected. Samples analyzed were; skin wash, membrane, skin strippings (from human samples) and receptor fluid.

The Agency has received adequate comparative dermal absorption data on chemicals tested *in vivo* in the rat and *in vitro* with this preparation of rat epidermis to conclude that the preparation does not accurately model *in vivo* dermal absorption. Errors range from 2 to 6 fold. They usually overestimate penetration but may underestimate and appear to be random. The errors of the

procedure do not appear to be correctable.

There is an additional problem with the species comparison data. The human epidermal was obtained from human , female, whole skin samples. "The skin samples were immersed in water at 60ºC for 40-45 seconds and the epidermis teased away from the dermis." For the rat "The skins were soaked for approximately 20 hours in 1.5 M sodium bromide then rinsed with distilled water. The epidermis was carefully peeled from the dermis." Scott, R.C. et al (1986) presented the rational for the use of 1.5 M sodium bromide for effectively removing an epidermal membrane from both rat and human skin. However, in this study, and in all similar studies using human skin submitted to the Agency, heat separation has been used. No explanation has been given for using this method. Heat processing can be expected to denature the protein matrix of the epidermis (of the stratum corneum) resulting in an unpredictable decrease in permeability.

This *in vitro* study using the isolated epidermal membrane of the human and the rat is unacceptable/nonguideline and does not satisfy any guideline requirement. The Agency has sufficient experimental information to show that this methodology does not accurately predict human or rat *in vivo* absorption and that the methodology cannot be corrected.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

Reference

Scott, R.C. ; M., Walker; Dugard P.H. 1986 In vitro percutaneous absorption experiments: A technique for the production of intact epidermal membranes from rat skin. J. soc. Cosmet. Chem. 37, J/F 35-41