



Department of Pesticide Regulation



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MEMORANDUM

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TO: Ann Prichard, Program Specialist
Pesticide Registration Branch HSM-00009

FROM: Tom Thongsinthusak, Staff Toxicologist (Specialist)
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[Original signed by T. Thongsinthusak]

DATE: November 16, 2000

SUBJECT: BRAND NAME: Metam sodium
ACTIVE INGREDIENT: Metam sodium
COMPANY NAME: Metam Sodium Task Force
TRACKING ID NUMBER: SBRA 182135 E
RECORD NUMBER (RN): 173741
DATA PACKAGE NUMBER (DPN): 50150-154
EPA REGISTRATION NUMBER: Not indicated

TITLE: METAM SODIUM: *IN VITRO* ABSORPTION THROUGH RAT AND HUMAN SKIN

Zeneca Central Toxicology Laboratory in Cheshire, UK completed the above-mentioned study on October 15, 1993. The Department of Pesticide Regulation (DPR) received the report of this study on March 1, 2000. The study method and results are summarized below.

A. Test material:

The dosing solution was prepared by mixing unlabeled and ^{14}C -labeled metam sodium in the HPLC grade water. The purity of unlabeled metam sodium was 98.5% and the radiochemical purity of ^{14}C -labeled metam sodium was 75.3%. Typically, the radiochemical purity of 95% or greater is desirable for a labeled compound used in a dermal absorption study. Two dose levels of metam sodium employed in the study were 940 and 94 $\mu\text{g}/\text{cm}^2$.

B. Rat and human skin:

This study utilized full thickness (epidermis + dermis) rat and human skin. The rat skin samples were obtained from 28-day old male rats, Wistar strain. The clipped area of dorsal and flank region was used to prepare skin samples. The skin samples were used for the study within 7 days. Human skin samples were prepared from human abdominal skin (female) obtained post mortem from subjects of varying ages. These skin samples were used within 7 days of preparation. The rat and human skin samples were checked for integrity by using tritiated water. Skin displaying coefficients greater than $25 \times 10^{-4} \text{ cm h}^{-1}$ for rat and $15 \times 10^{-4} \text{ cm h}^{-1}$ for human were regarded as "damaged" and rejected.



C. Test method:

Glass diffusion cells in which the skin forms a horizontal membrane separating donor (outer) and receptor chambers were used for measuring skin absorption. An area of 2.54 cm² of skin was available for absorption and all experiments were conducted with the diffusion cell placed in a water bath at 30 ± 1 °C. Receptor solutions were stirred for the duration of the experiment.

The aqueous solution of the dose was spread over the skin surface and the donor chambers covered with two porous carbon filter discs to trap any evaporating dose. Physiological saline (0.9% NaCl) was used as a receptor fluid. The exposure time was 10 hours. Samples of receptor fluid were taken at 0.5, 1, 2, 4, 6, and 10 hours to follow the absorption patterns for different exposure times. Each sample taken was replaced by equal volume of receptor fluid to maintain the same volume in the receptor chamber. At the end of the exposure period, the skin was rinsed with 5 mL aliquots of a detergent (3% TEEPOL L in water). Samples collected for analysis are shown in Table 1. The radioactivity from those samples was analyzed by liquid scintillation spectrophotometers.

D. Results and discussion:

It appears that the study was appropriate for the purpose of deriving the ratio of metam sodium absorption between the rat and human skin. Results of the study revealed the absorption of metam sodium in rat and human skin is time and dose dependent. Under the current convention used by DPR, the absorbed dose is the sum of recovered dose in the receptor fluid and the treated skin. This convention is similar to that used in the determination of *in vivo* dermal absorption studies where residues in the treated skin (bound skin residues) are considered absorbed unless bioavailability of the residues can be determined (Thongsinthusak *et al.*, 1993). In a recent *in vitro* absorption study, Shirai *et al.* (2000) also included skin residues of PCBs as the absorbed dose. The mean absorption values of metam sodium in rat and human skin are shown in Table 1.

Table 1. Distribution of applied dose in various samples and the mean absorption value.

1) Rat skin

Dose (µg/cm ²)	% Dose						
	Donor fluid	Skin wash	Washed skin	Donor rinse	Filter	Total recovery	Absorbed*
940	21.3	62.8	3.66	8.58	5.65	102	25.0
94	19.4	50.2	8.23	6.28	10.3	94.4	27.6

2) Human skin

Dose ($\mu\text{g}/\text{cm}^2$)	% Dose						
	Donor fluid	Skin wash	Washed skin	Donor rinse	Filter	Total recovery	Absorbed*
940	2.19	75.7	3.86	21.2	3.75	107	6.05
94	12.2	55.3	6.91	19.5	7.74	102	19.1

* not adjusted for the total recovery

Ratios of *in vitro* absorption of metam sodium in rat and human skin are as follows:

Dose ($\mu\text{g}/\text{cm}^2$)	% Dose absorbed (rat/human)	Ratio (rat/human)
940	25.0/6.05	4.1
94	27.6/19.1	1.4

The above ratios of *in vitro* dermal absorption between the rat and human skin are dose dependent. The ratio for the high dose ($940 \mu\text{g}/\text{cm}^2$) was 4.1 and that for the low dose ($94 \mu\text{g}/\text{cm}^2$) was 1.4. It is likely that the ratio could approach 1.0 when a lower dose level, e.g. $8.6 \mu\text{g}/\text{cm}^2$, was used in the *in vitro* dermal absorption study. The *in vivo* dermal absorption of 2.5%, currently used in the exposure assessment, was determined from a dose of $8.6 \mu\text{g}/\text{cm}^2$. Therefore, the human *in vivo* dermal absorption could not be derived by using the ratio of 1.4 and the dermal absorption value of 2.5% because there was about 11-fold difference in dose levels.

The following calculation is used for demonstration only. The *in vivo* dermal absorption in rats was determined to be 3.48% for the medium dose ($86.2 \mu\text{g}/\text{cm}^2$) (Thongsinthusak, 1993). The estimated *in vivo* human dermal absorption would be 2.5% ($3.48\%/1.4 = 2.5\%$). However, the exposure levels experienced by workers were much lower than dose levels used in these *in vitro* and *in vivo* dermal absorption studies.

E. Conclusions:

In vivo human dermal absorption could not be derived from this and the previous *in vivo* dermal absorption study in the rat. DPR will continue using the current *in vivo* dermal absorption of 2.5% for the exposure assessment of metam sodium.

References:

Shirai, J. H., and Duff, R., and Johnson, J. 2000. *In-vitro* dermal absorption of PCBs from a river sediment. Abstracts. 10th Annual Conference of the International Society of Exposure Analysis. October 24-27, 2000, Monterey, California. Poster number 2B-14p.

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Ann Prichard
November 16, 2000
Page 4

Thongsinthusak, T. 1993. Metam sodium: *In vivo* dermal absorption in the rat and stability determination of aqueous solutions. A memo dated July 26, 1993, to Kathy Wynn. HSM-93003. WH&S, DPR.

cc: Chuck Andrews

(Dermal/metam sodium-in vitro)