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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Metam Sodium: ICI Proposal for route, dose levels, and special measures for 90 day Neurotoxicity Study

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Metam Sodium Sodium N-methyldithiocarbamate
Caswell No. 780; Shg # 039003; CAS No. 6734-80-1

The purpose of this memorandum is to respond to a proposal by ICI in a letter dated 6/15/92 concerning conduct of a 90 day Neurotoxicity Screening Battery Study of Metam Sodium.

Conclusions

1. The proposed high dose level of roughly 20 mg/kg may be too low.
2. Drinking water administration may be insufficient to administer doses high enough to satisfy the neurotoxicity guideline criteria for the high dose, i.e., "significant neurotoxic effects or other clearly toxic effects".
3. Elimination of AChE and NTE measures are not justified by inclusion of any data or references.
4. The proposed approach for conditional use of special stains and measurement of GFAP is acceptable.

Background and Rationale

1. The proposed dose levels for the 90 day Neurotoxicity study are 0, 0.02, 0.06, and 0.2 mg/ml (17-21 mg/kg).

The observed toxicity cited at 0.2 mg/ml in the rat chronic study at 90 days, was 12-16% body weight gain decrease, accompanied by decreases of 32-49% in water intake. These large reductions in water intake might well lead to reductions in dry food intake (not mentioned here) and the resulting decreased weight gain.

In the rat subchronic study, at 0.443 mg/ml, there was statistically significant reduction in food consumption of 50% initially and 20% throughout the study which accompanied decreases in water consumption and body weight.

The plausibility, then, of the unpleasant taste of the material as the cause of the reduced water and food intake contradicts the interpretation of these data as indicative of some systemic toxic effect of the material's ingestion. That is, the decreased body weight gains are confounded by reduced food and water intake.

Thus, 0.2 mg/ml cannot, on the basis of this data be regarded as a subchronic dose resulting in clearly toxic effects and would not satisfy the high dose criterion in the neurotoxicity guideline. If higher doses cannot be achieved with this route, its use may not be feasible.

2. Drinking water administration is proposed to avoid stomach ulceration associated with gavage at 50 mg/kg and above.

Causing stomach ulceration can certainly be a reasonable criterion for defining a high dose for a subchronic neurotoxicity study where oral exposure is the most relevant route of concern.

In the submitted proposal, stomach ulceration is described as occurring after 11 days of gavage at 50 mg/kg, but no data is provided or further reference given.

In the rat subchronic study, 27-31 mg/kg for 90 days was without apparent G.I. effect based on the necropsy and histopathology results. It appears, then, from these data that doses by gavage between 30-50 mg/kg might be possible.

Also, the submission notes that " Drinking water solutions are buffered to pH 8.5-9.0 with 0.5M phosphate buffer." Was this done in the gavage studies? Could it be?

Last, how else might such changes in pH of the administered material affect its toxicity, e.g., absorption, distribution?

3. No data or references are provided to support the assertion of a lack of actual or potential effect of this chemical on AchE or NTE. A revised set of recommendations for ChE measurements is being provided. Measurement of NTE is being proposed for thiocarbamates because some of these materials have been seen to cause central-peripheral neuropathies and these data would help to rule out an OPIDN type of mechanism.

4. Both special stains and GFAP measurements are recommended rather than required in the guidelines and the procedure provided here for their conditional use is generally acceptable.