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for Health and Environmental Sciences
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May 26, 2009

Via Federal Express

Document Processing Center (Mail Code 7407M)
Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, DC 20004



8EHQ-0509-17526A



DCN: 88090000250

Dear 8(e) Coordinator:

N,N-Dimethyl-p-Toluidine
CAS # 99-97-8

This letter is to inform you of the results of an eye irritation test, skin irritation test, a skin sensitization test, an acute oral toxicity study and a study to evaluate methemoglobin formation with the test substance referenced above.

Eye Irritation:

The test substance was applied undiluted at a dose of 0.1 mL to the right eye of nine New Zealand White rabbits. The untreated left eye of each rabbit served as a control for comparison purposes. The treated eye of 3 rabbits was rinsed with lukewarm water approximately 30 seconds after instillation of the test substance, while the treated eye of 6 rabbits remained unwashed after test substance administration. Rabbits were scored for irritation according to Draize at 1, 24, 48, and 72 hours and 4 and 7 days following test substance administration.

Severe conjunctival redness (score of 3) was observed in the treated unwashed eye of 1/6 rabbits at 24 and 48 hours after instillation of the test substance. Severe conjunctival redness (score of 3) was also observed in the treated washed eye of 1/3 rabbits at 1 hour after instillation. The treated eye of these rabbits was normal by 7 days.

Skin Irritation:

The test substance was applied undiluted at a dose of 0.5 mL to the shaved skin of six New Zealand White rabbits. Rabbits were scored for irritation according to Draize at 30 to 60 minutes, 24, 48, and 72 hours, and 4-14 days following test substance administration.

Very slight to well defined erythema (score of 1 or 2) persisted in all six rabbits at study termination (day 14).

Acute Oral:

The test substance was administered by oral gavage to groups of five male and five female fasted Sprague-Dawley rats at a dose of 1250, 1800, or 2500 mg/kg. The rats were observed for 14 days after test substance administration.

Mortality occurred on days 2 to 3 in 1/5, 5/5, and 5/5 male rats and in 1/5, 0/5, and 5/5 female rats dosed at 1250, 1800, and 2500 mg/kg, respectively. Decreased activity (slight to moderate) was observed up to test

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day 9 in 7 rats dosed at 1250 mg/kg, in 6 rats dosed at 1800 mg/kg, and in 8 rats dosed at 2500 mg/kg. Decreased activity (extreme) was observed up to test day 2 in 2 rats dosed at 1250 mg/kg and in 3 rats dosed at 2500 mg/kg. Hunched posture was observed on test days 5-8 in one rat dosed at 1800 mg/kg. Salivation (slight to moderate) was observed the day after dosing in one rat dosed at 2500 mg/kg. The oral LD₅₀ for male rats was 1300 mg/kg. The oral LD₅₀ for female rats was 1950 mg/kg. The oral LD₅₀ for male and female rats combined was 1650 mg/kg.

Methemoglobin Study:

The test substance was administered undiluted by oral gavage to groups of five male and five female fasted Sprague-Dawley rats at a dose of 600 or 1200 mg/kg. Total, reduced, oxidized, met- and carboxyhemoglobin levels were measured prior to test substance administration and at 6 hours and 7 days after exposure. The rats were observed for 7 days after dosing.

Increased blood methemoglobin levels were present in animals at both dose levels six hours after dosing. Mean methemoglobin levels in the 600 mg/kg group were approximately 12-13% for both males and females, while methemoglobin levels in the 1200 mg/kg group were approximately 30% in males and 14% in females, compared to normal levels of 0.2-0.5%. Methemoglobin had decreased to near baseline levels by 7 days after exposure. Salivation was observed on the day of dosing in 2 rats dosed at 600 mg/kg and in 3 rats dosed at 1200 mg/kg. Cyanosis was observed by 2 days after dosing in 3 rats dosed at 1200 mg/kg. Hypothermia was observed 2 days after dosing in one rat dosed at 1200 mg/kg.

Skin Sensitization:

The test substance was evaluated according to the modified Buehler method to determine the potential to produce dermal sensitization in the guinea pig. Dinitrochlorobenzene (DNCB) was tested concurrently as a positive control. In the induction phase, the test substance was administered once weekly over a three week period at a 50% (v/v) concentration in mineral oil to one group of guinea pigs. The positive control material was administered to a second group of guinea pigs at a 0.2% (w/v) concentration in 80% ethanol during the induction phase. In the challenge phase, the animals in the test substance group received single administrations of the test substance at approximately the maximum nonirritating concentration of 10% (v/v) in mineral oil. The animals in the positive control group received single administrations of DNCB at a 0.06% (w/v) concentration in acetone. A third group of animals (irritation controls) received, at the time of challenge only, single administrations of the same concentrations of test and positive control materials administered to the other two groups. The positive control did elicit dermal sensitization in the positive control group animals. This positive response demonstrated the susceptibility of the guinea pigs used in this study to dermal sensitization.

At challenge, the test substance produced dermal responses in 60% of the test group animals which were clearly greater than the responses observed in the irritation control group animals. Therefore, it was concluded that the test substance demonstrated the potential to produce dermal sensitization when administered by the method of Buehler to Hartley guinea pigs.

This information is submitted in accordance with current guidance issued by EPA indicating EPA's interpretation of Section 8(e) of the Toxic Substances Control Act or, where it is not clear that reporting criteria have been met, it is submitted as a precautionary measure and because it is information in which EPA may have an interest.

Sincerely,



A. Michael Kaplan, Ph.D.
Director - Regulatory Affairs

AMK/CC/SSA: clp
(302) 366-5260