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DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ-10-18155	88110000039	10/22/10

COMMENTS:

DOES NOT CONTAIN CBI

mR# 330706

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10 OCT 22 AM 11:20

October 21, 2010

8EHQ-10-18155

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, ICC Building
1201 Constitution Ave., NW
Washington, DC 20004

8EHQ-1010-18155A
DCN:88110000039

88110000039

Dear 8(e) Coordinator:

Benzenesulfonyl isocyanate, 2-chloro-
CAS # 64900-65-8

This letter is to inform you of the results of several toxicity studies with the above reference test substance in xylene.

Acute Oral Toxicity Study

An acute toxicity study was conducted in male and female SD rats with the test substance in xylene after a single oral gavage administration. In preliminary tests, 2 animals/sex/dose received 644, 1329 or 2643 mg/kg. Since low mortality (one of two females) was seen at 2643 mg/kg, a limit test was conducted at this same dose using 5 males and 5 females. Three of 5 males, but no females died in this study. Additional testing was conducted with 5 animals/sex/dose at doses of 0, 2960, 3322, 3730 or 4696 mg/kg. In all cases, animals were observed for a 15 day period.

In the limit test, all animals showed subdued behavior and prostration from 1 hour to day 2. In some cases snorting, subdued behavior, excessive salivation, red colored urine and dirty fur were observed from 1 hour after dosing to day 6.

At 2960 mg/kg, 1 female and 2 males died on day 5 or 6. All animals showed subdued behavior and prostration from 1 hour to 4 hours after treatment. In some cases snorting, subdued behavior, abdominal distension and lethargy were observed from 2 hours after dosing to day 6. At 3322 mg/kg no males died and only one female died on day 3. All animals showed subdued behavior and prostration from 15 minutes to day 2. In some cases snorting, subdued behavior, excessive salivation, and abdominal distension were observed from 1 hour after dosing to day 7. At 3730 mg/kg, 3 males and 2 females died from day 2 to 6. All animals showed subdued behavior and prostration from 15 minutes to 4 hours after treatment. In some cases snorting, subdued behavior, prostration and abdominal distension were observed from 1 hour after dosing to day 10. At 4696 mg/kg 4 males and 2 females died from day 2 to 4. All animals showed subdued behavior and prostration from 15 minutes to 6 days after treatment. In some cases snorting, excessive salivation, piloerection, dirty fur and paleness were observed from 1 hour after dosing to day 11. For male rats the LD50 was 2513 mg/kg and for female rats was 3560 mg/kg (active ingredient).

Acute Dermal Toxicity

The test substance in xylene was applied as received to the intact clipped skin of 8 (2 in the range-finding study and 6 in the approximate lethal dose, ALD study) male New Zealand White rabbits at a dose rate of 4.9 g/kg of body weight. The test material was applied to a clipped area of the back and covered with surgical gauze. Following

approximately 24 hours of exposure, the wrappings and gauze were removed and the test sites gently wiped free of excess test material. Animals used in the range-finding screen were observed for viability twice daily for 7 days and deaths were recorded. In the ALD study observations were made at 1, 2 and 4 hours after dosing and daily thereafter for 14 days.

One of the two animals in the range-finding study was found dead on Day 3 and one animal in the ALD study was found dead on Day 5. The animal found dead on Day 5 had its head caught in the cage door. It is not clear if this death can be attributed to the test material administration. However, this animal did exhibit signs of toxicity (hypoactivity, decreased food consumption, substantial weight loss ~ 29% of its pretest weight) prior to death. All surviving animals lost weight for 7 days after dosing but gained weight between Days 7 and 14. Hypoactivity was seen in one or two animals from one hour after dosing through Day 4. Most animals exhibited decreased food consumption on Days 2 and 3, and all survivors had severe dermal effects (extensive necrosis with eschar formation, fissuring and exfoliation) from Day 4 to study termination. Other abnormalities occurred sporadically, generally in single animals. Under the conditions of this study, the skin absorption LD50 was greater than 4.9 g/kg.

Eye Irritation

An eye irritation study was conducted using 6 rabbits. Test material in xylene (0.1 ml) was applied to one eye of each rabbit without rinsing. The mean Draize scores for the 24, 48 and 72 hour readings were 3.50 for chemosis, 2.22 for conjunctival redness, 1.0 for congestion of the iris and 2.28 for corneal opacity. Ulceration of the cornea was observed in all animals from 24 hours onward. By day 7 the readings were not resolving. Depilation of the hair around the lids of the treated eyes was noted in all animals. The animals were sacrificed for humane reasons after taking the day 7 readings.

Skin Sensitization Test

When attempting the maximization test in guinea pigs, which requires that the test substance be injected, the injection of 0.1 ml solutions at 50%, 20% or 10% in xylene caused "a severe irritation with burnt aspects" noted at 28 and 48 hours. The severity of the response was similar to xylene alone injection. No other suitable solvent was found. Due to this problem, the Buehler method was employed to test the sensitization potential of the compound. No sensitization was demonstrated using the Buehler test.

A 4-week gavage study

A 4 week oral toxicity study was conducted in male and female SD rats with the test substance in xylene. A solvent control consisting of xylene alone was also conducted. Five rats/sex/dose were used. The doses were 0 (water control), 0 (solvent control), 50, 200 or 800 mg/kg. Animals were gavaged daily for 28 days.

All rats dosed at 800 mg/kg group were sacrificed due to morbidity on day 2 or 3. All females and one male from the 200 mg/kg group died or were sacrificed due to moribundity between days 4 and 16. Salivation and markedly subdued behavior were observed in the 800 mg/kg group. Subdued behavior with staggering and ptosis were observed in the 50 and 200 mg/kg groups, with a dose-dependant relationship. Lower body weight gain was observed in the 50 and 200 mg/kg group males, and in the 200 mg/kg females; a decrease in food consumption followed the same dose pattern. Lower body weight gain and lower food consumption were also observed in the male xylene control group but the effect was not as striking as in the 50 and 200 mg/kg groups. No such an effect was seen in females treated with xylene only.

In animals found dead or sacrificed from the 200 and 800 mg/kg dose groups, the platelet count was increased. Some females also showed an increase in red blood cell count, hemoglobin and packed cell volume. At week 4, the same effect was found in one male and female rat from the 50 mg/kg group. Changes in some clinical chemistry parameters were observed at 50 and 200 mg/kg. A similar trend was noted in the xylene treated group, but changes were not statistically significant compared to controls and the magnitude of changes was lower compared to 50 or 200 mg/kg groups. The following mean values were increased to a statistically significant level in the 50 and 200 mg/kg males: chloride, calcium, inorganic phosphorus and alanine amino transferase; in addition cholesterol and albumin were statistically elevated at 200 mg/kg only. In females, the following mean values were increased to a statistically significant level in the xylene and 50 mg/kg groups: protein and globulin; in addition at 50 mg/kg only calcium, inorganic phosphorus and cholesterol were statistically elevated and the albumin/globulin ratio was

decreased. Reducing substances were present in the urine of the xylene, 50 and 200 mg/kg treated males and in the xylene and 50 mg/kg females. Specific gravity was slightly, but statistically significantly increased in the xylene and 50 mg/kg groups.

Organ weight changes and the macroscopic observation of thickening of the non-glandular stomach were related to treatment with xylene. Microscopically, treatment-related changes (lymphoid atrophy of the white pulp) were observed in the spleen at the 200 and 800 mg/kg dose level. Liver changes (minimal to moderate hypertrophy) and gastric changes (acanthosis with hyperkeratosis in the non-glandular portion often associated with inflammatory infiltration of the squamous mucosa) were related to treatment with xylene, but were also seen in the test substance treated groups. In 800 mg/kg males and 200 and 800 mg/kg females, acantholysis of the non-glandular stomach, with submucosal edema and/or hemorrhage were observed.

In Vitro Chromosomal Aberration Test

An in vitro assay was conducted with the test substance in xylene to evaluate its ability to induce chromosomal aberrations in cultured whole human lymphocytes, with and without metabolic activation. A stock solution was prepared by dissolving the test substance in dimethylsulfoxide at a concentration of 502 mg/ml. Based on the cytotoxicity in the range-finding test, concentrations up to 502 µg/ml were used in the main study with and without metabolic activation.

Without metabolic activation, three concentrations were used (251, 377 and 502 µg/ml) for the 22 hour test and one concentration (502 µg/ml) for the 44 hour test was used. The mitotic indices for the 22 hour concentrations were depressed by 17, 31 and 41% as compared to the solvent control, respectively. The mitotic index at 44 hour was depressed by 69%. A statistically significant increase in cells with chromosome aberrations was observed only at the 44 hour time point. This response was further investigated by testing 377, 503 or 654 µg/ml in the 22 hour assay and 654 µg/ml in the 44 hour assay. The mitotic indices were decreased by 34, 59 and 72%, respectively, at the 22 hour time point and by 76% for the one concentration tested at 44 hours. Toxicity was manifested on the slides prepared from cultures treated with 654 µg/ml by the poor morphology of many of the metaphases. A statistically significant increase in cells with chromosome aberrations was observed in the 654 µg/ml cultures for both the 22 and 44 hour time points.

With metabolic activation, cultures treated with 251, 377 and 502 µg/ml in the 22 hour test had mitotic indices depressed by 13, 40 and 10%, respectively, as compared to the solvent control. Though the mitotic index was not significantly depressed at 502 µg/ml, toxicity was manifested on the slides prepared from cultures at this concentration, as seen by the presence of dead and unhealthy cells, and sparse numbers of cells and metaphases. No significant increase in cells with chromosomal aberrations or in polyploid or endoreduplicated cells were observed at the concentrations tested. In the 44 hour assay cultures treated with 502 µg/ml had a reduction in mitotic index of 46%, but no significant increase in cells with chromosomal aberrations or in polyploid or endoreduplicated cells were observed. Evidence that the activation system was working was seen in the increased incidence of cells with chromosomal aberrations in the cultures treated with cyclophosphamide.

According to the report, the test substance was considered positive for inducing chromosomal aberrations in cultured whole blood lymphocytes at a single high dose under conditions lacking metabolic activation, but was negative when metabolic activation was present. Positive results were only observed concurrent with high cytotoxicity (approx. 70% or greater reduction in mitotic index) and most likely was caused by excessive cytotoxicity rather than by a genotoxic mechanism.

In Vivo Micronucleus Study

A range finding study and a micronucleus test were conducted in male and female SD rats with the test substance in xylene administered by gavage in a dosing volume of 2 ml/kg xylene as a solvent carrier.

In the range finding study, animals were tested with doses of 0 (solvent carrier), 197, 351, 627 1120 or 2000 mg/kg using 3 animals/sex/dose. Animals were observed for mortality and clinical signs for 3 days. All animals in the 2000 mg/kg group showed clinical signs starting on day 1 which were noted as subdued behavior. One male was found dead on day 2. In addition to subdued behavior, ptosis and respiratory distress were seen in both sexes on day 2. On day 3 prostration was observed among the females, and subdued behavior and respiratory distress in both

sexes. No other deaths were observed. A dose-related decrease in the ratio of polychromatic to normochromatic erythrocytes was observed in the range of 351 to 1120 mg/kg.

For the main study, animals were tested with doses of 0 (solvent carrier), 845, 1300 or 2000 mg/kg body weight using 10 animals/sex/dose. A positive control with cyclophosphamide at 60 mg/kg by i.p. injection had 5 animals/sex. All of the cyclophosphamide animals and half of all animals in the other groups were sacrificed on day 2 (24 hours after dosing). The remaining animals were sacrificed on day 3 (48 hours after dosing).

Mortality was observed between 24 and 48 hours of dosing at 1300 mg/kg (2 males) and 2000 mg/kg (1 male & 1 female). Clinical signs were noted in all test substance-treated groups and were still present at 2000 mg/kg 48 hours after dosing. On the day of dosing, subdued behavior and ptosis were noted in all males at all doses and all females except 4 females at 845 mg/kg; on the 2nd day at 845 mg/kg subdued behavior and staggering gait were noted in one male and respiratory distress in one female, but the other 9 males and 9 females were symptom free; at 1300 mg/kg subdued behavior and lateral decubitus were noted in 2 males, but 7 males and all females were free of signs; at 2000 mg/kg all except 2 males showed respiratory distress and all except 2 females showed respiratory distress or subdued behavior; on the 3rd day at 2000 mg/kg all males and females displayed clinical signs noted as subdued behavior, piloerection and respiratory distress and one male at 1300 mg/kg showed lateral decubitus, hypothermia and respiratory distress before dying. Ventral decubitus was noted for one female in the xylene treated control group only on the day of dosing.

The groups treated with test substance did not show significant bone marrow toxicity at 24 or 48 hours. Cyclophosphamide induced a clear and statistically significant increase in micronucleated polychromatic erythrocytes (MPCE). A statistically significant increase in MPCE was noted at 2000 mg/kg in males, and in both sexes combined at 48 hours after dosing, but not at other doses or at 24 hours. In this regard, the mean frequencies of MPCE observed after dosing at 2000 mg/kg in males at 48 hours was 3.54 and in the sexes combined it was 4.04; the individual male values did not exceed the highest value noted in the vehicle control (3.98), but one female's value was high (9.20). In the absence of a clear positive response, the report considered the result to be equivocal at 2000 mg/kg.

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

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

AMK/MB: clp
(302) 366-5260

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