



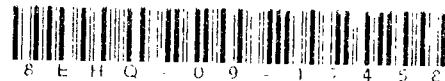
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March 26, 2009

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



Dear 8(e) Coordinator:

3-Sulphonylisocyanato-2-thiophene carboxylate  
CAS # 79277-18-2

This letter is to inform you of the results of several mutagenicity studies and a 28-day oral toxicity study with the test substance referenced above.

Ames Assay:

The test substance (85.4% w/w in xylene) was evaluated for mutagenic activity in the Salmonella Reverse Mutation Assay (Ames Assay) in the absence and presence of an exogenous metabolic activation system of mammalian microsomal enzymes derived from Aroclor™ – induced rat liver (S9). The tester strains used in this study were TA98, TA100, TA1535 and TA1537. Six doses of the test substance (100, 333, 667, 1000, 3330, and 5000 µg per plate) were used in assay.

The test substance caused a positive increase in the numbers of histidine revertants per plate with tester strain TA100 at 5000 µg per plate (2.2 and 2.0-fold) in the presence of S9 and with tester strain TA98 at ≥ 1000 µg per plate (2.9 and 3.5-fold) and TA1537 at ≥ 667 µg per plate (12.3 and 6.7-fold) in the absence of S9. With TA100 at 5000 µg per plate, in the absence of S9, a 1.9-fold increase was observed in the initial trial but the confirmatory assay gave a 2.1-fold increase with TA100 in the absence of S9.

*In Vitro* Chromosomal Aberration Study:

The test substance was evaluated in an *in vitro* chromosomal aberration study in human whole blood lymphocytes with and without metabolic activation

The test substance (85.4% w/w in xylene) was heated to 60°C to liquefy and then dissolved in dimethylsulfoxide. The preliminary range-finding study was run at concentrations ranging from 4.40 to 4400 µg/ml with and without metabolic activation. Severe cytotoxicity was observed at 1470 and 4400 µg/ml and more than 50% reduction in the mitotic index was observed at 440 µg/ml without activation but no reduction with metabolic activation.

Concentrations of 225 µg/ml to 1300 µg/ml of the test material were tested in a 22 hour aberrations assay and 450 µg/ml to 1300 µg/ml were used in a 44 hour aberration assay with metabolic activation. Cultures treated under nonactivation conditions with 225, 450, and 675 µg/ml from the 22 hour assay and with 675 µg/ml from the 44 hour assay were analyzed for chromosomal aberrations. Cultures treated under

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conditions of metabolic activation with 325, 975, and 1300 µg/ml from the 22 hour assay and with 975 µg/ml from the 44 hour assay were analyzed.

A significant increase in cells with chromosomal aberrations was observed in the cultures treated with 450 and 675 µg/ml in the 22 hour assay and in the cultures treated with 675 µg/ml in the 44 hour assay under non-activation conditions and in the cultures treated with 975 and 1300 µg/ml in the 22 hour assay with metabolic activation. While the study authors called the findings positive, the positive findings were only observed at concentrations that caused cytotoxicity.

#### *In Vivo* Rat Bone Marrow Micronucleus Test:

The test substance (85% w/w in xylene) was evaluated *in vivo* in a rat bone marrow micronucleus test. In the preliminary study, 3 male and 3 female rats were dosed at 1241, 1862, and 2482 mg/kg of body weight and the rats dosed at 2482 mg/kg were noted to have “subdued behavior” on the day of dosing. In the main study, the test substance was administered at 1241, 1862, and 2482 mg/kg of body weight to groups of 10 male and 10 female rats, and the bone marrow collected 24 or 48 hours after dosing. The test substance did not induce micronuclei in the rat bone marrow erythrocytes micronucleus test at dose levels up to and including 2482 mg/kg. Subdued behavior was not observed in the main study at 2482 mg/kg.

#### Unscheduled DNA Synthesis Assay:

The test substance (92.85% in xylene) was evaluated for its ability to induce unscheduled DNA synthesis (UDS) in the liver of orally dosed male rats using an *in vivo/in vitro* procedure.

Treatment with 800 or 2000 mg/kg did not produce a positive response in the UDS assay; however, the only clinical sign observed was piloerection in animals dosed with 2000 mg/kg of body weight.

#### 28-Day Oral Toxicity Study:

The test substance (39.4% w/w in xylene; equivalent to 427 mg/ml) was evaluated in a 28-day oral toxicity study in rats following daily oral gavage administration. Groups of 5 male and 5 female rats were dosed with 0 (water), 0 (vehicle control – xylene), 50, 150 or 800 mg/kg/day of the test substance for 28 days. Clinical exams were performed daily and full clinical examinations were performed weekly. Food consumption and individual body weights were recorded weekly. Clinical pathology evaluations were performed at termination (day 29). All surviving animals were sacrificed and necropsied at termination on day 29. Selected organs were weighed and tissue samples were fixed and preserved. Selected tissues from all groups were examined histopathologically.

One low dose male, 2 intermediate dose rats (1 male and 1 female) and 8 high dose rats (4 male and 4 female) were found dead or sacrificed in extremis during the first 10 days of the study. Clinical signs observed in all treated groups, including the vehicle, included salivation, subdued behavior (or prostration) and noisy or labored breathing were dose related. Body weight gains were reduced in male and female rats given the test substance or vehicle, and were more marked in males than females.

Mean relative adrenal weight in females (including vehicle) were slightly higher as was mean relative kidney weight in males treated with the vehicle and at the intermediate dose level. Mean relative testis weight of males treated with the vehicle was slightly higher than controls. Relative and absolute liver weight of treated animals (including vehicle) was slightly higher than controls with a slightly higher severity in intermediate dose males in comparison with rats treated with the vehicle.

Hepatocellular hypertrophy was noted in all treatment groups (including vehicle) with a higher frequency and/or severity in high dose males and intermediate and high dose females. Lymphoid atrophy of the white pulp of the spleen was noted in several animals from all dose groups but with a higher frequency in high dose animals. None of the rats treated with the vehicle seemed to show this abnormality. Gross pathologic changes of the stomach (induration, pale or dark areas, thickening of the mucosa) were found in all treated groups (including vehicle) at necropsy. Acanthosis and hyperkeratosis of the non-glandular portion of the stomach were observed in all treated groups (including vehicle) but ulcerations of the mucosa were only noted in some intermediate and high dose animals.

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 handwritten signature in black ink that reads "A. Michael Kaplan". The signature is written in a cursive, flowing style.

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

AMK: clp  
(302) 366-5260