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April 21, 2008

US EPA Office of Pollution Prevention and Toxics
EPA East Building Room 6428
Attn: Section 8(e)
1201 Constitution Avenue, NW
Washington, DC 20004

SUBJECT: TSCA 8(e) Notice

8EHQ-07-16906

Dear 8(e) Coordinator:

This letter is to inform you of the results of a developmental oral OECD 414 study conducted with p-toluenesulfonamide (CAS #70-55-3) by Notox, the Netherlands, on behalf of Axcentive SARL, France. The test article was administered to New Zealand White rabbits in the diet at dose levels of 0, 1000, 3000 or 11,000 ppm (equivalent to 0, 41, 114, and 367 mg/kg/day) during gestation days 7 to 29. Interim results, from the study, were previously submitted to US EPA (8EHQ-07-16906).

Prior to treatment, there was a low pregnancy rate within all groups including controls. Thirty-three out of ninety-six females were not pregnant (7/24, 9/24, 7/24 and 10/24 in groups designated for control, low, mid and high dose treatment, respectively). The low pregnancy rate was not attributed to treatment as test article administration was initiated after implantation but rather considered due to environmental stress from significant construction noise. Due to low pregnancy rates additional animals were added to the study (referred to as Part I and Part II, respectively).

Out of eighteen Part II females, three were not pregnant. These were in the group designated for low dose treatment.

Intrauterine growth and survival were not affected by treatment in either Part I or Part II groups.

Part I dams in the 11000 ppm group exhibited a non statistically significant reduction in body weight and weight gain on days 7-10 post-coitum. After this period body weight gain increased. However, it remained lower when compared to concurrent controls. Body weight gain was reduced at necropsy after correction for uterus weight.

There was a slight reduction in body weight and weight gain in the Part I 3000 ppm group dams from days 7-10 post-coitum. Values returned to normal following this period.

Part II dams in the 11000 and 3000 ppm group exhibited slightly reduced body weight and weight gain on days 7-10 post-coitum. Values returned to normal following this period. Body weight gain was reduced, in the 11000 ppm group, at necropsy after correction for uterus weight.

There was an initial reduction in food and water consumption which returned to control values by the end of treatment in 11000 ppm Part I and Part II dams. Similar effects on food and water consumption were also noted in the 3,000 ppm groups. No such findings were reported in the 1000 ppm group.

There were no treatment related effects on pre- and post implantation loss, litter size and sex ratio in either Part I of Part II animals.

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Combining data from Parts I and II, there was a trend toward reduced body weight of fetuses in the 11000 ppm group which was not statistically significant and considered related to the decreased maternal body weights.

Developmental delays, in the form of vertebral centra anomalies, were reported in the cervical vertebral region and were observed in 0(0), 1(1), 2(1), and 3(3) fetuses (litters) in Part I and Part II control, 1000, 3000 and 11000 ppm dose groups, respectively.

Part I

Vetebral centra anomalies of the cervical region were observed in 0(0), 0(0), 2(1) and 3(3) fetuses (litters) in the control, 1000, 3000 and 11000 ppm groups, respectively. Fetuses in the 11000 ppm group had an absent and/or smaller than normal half of one cervical centrum and the fetuses in the 3000 ppm group had an absent half of one cervical centrum. The mean litter proportion of vertebral centra anomalies was 0%, 0%, 1.5% and 3.4%, respectively. The differences were not statistically significant but were outside the historical control data ranges for this laboratory (0.0% to 0.3% per litter). However, vertebral centra anomaly had been observed previously in a historical control fetus. Furthermore, all except one of the fetuses, with vertebral centra anomaly, had fetal weights below the reduced mean fetal body weight at 110000 ppm (fetal weights ranged from 34.1 to 44.5 grams). Therefore, in the absence of any corroborative effects, this finding was considered indicative of a developmental delay that has no significant biological effect on body conformity, rather than a malformation.

Part II

One fetus in the 1000 ppm group had an absent half of one cervical centrum. This finding was considered a developmental delay.

The total number of malformations reported in this study in fetuses (litters) were 3(3), 0(0), 4(3) and 11(8) in Part I and Part II control, 1000, 3000 and 11000 ppm groups, respectively. The only malformation considered treatment related were vertebral anomalies with or without associated rib anomaly.

Part I Fetuses

The percent of fetuses with vertebral anomalies with or without associated rib anomaly was 0%, 0%, 0% and 3.9% for the control, 1000, 3000 and 11000 ppm groups, respectively. In the 11000 ppm group, this anomaly was noted in 4 (4) fetuses (litters) and consisted of absent half of lumbar centrum, absent thoracic rib, arch and half of centrum and absent lumbar arch and half of centrum.

Although concurrent control fetuses did not exhibit vertebral anomalies with or without associated rib anomaly, historical control data revealed that these anomalies had occurred at a fetal incidence of up to 1.2%.

Part II Fetuses

There were no test article related effects on skeletal fetal morphology.

Dose Range Finding Fetuses

To determine the significance of vertebral anomalies with or without associated rib anomaly observed only in Part I fetuses, all fetuses of the dose range finding study were skeletally examined.

Vertebral anomalies with or without associated rib anomaly were not observed with dose levels up to 20000 ppm.

The table below includes the incidence of the vertebral anomalies with or without associated rib anomaly in Part I, Part II and Dose Range Finder portions of the study.

Part I	Fetuses (Litter) with Finding	Total # Fetuses	Total # Litters
Control	0(0)	93	17
1000 ppm	0(0)	96	15
3000 ppm	0(0)	104	17
11000 ppm	4(4)	88	14

Part II and Ranger Combined	Fetuses (Litter) with Finding	Total # Fetuses	Total # Litters
Control	0(0)	52	8
1000 ppm	0(0)	14	3
3000 ppm	0(0)	17	3
5000 ppm	0(0)	44	6
10000/11000 ppm	0(0)	66	12
20000 ppm	0(0)	32	4

As the table illustrates, only those fetuses from dams in the group subjected to environmental stress (Part I) exhibited this malformation. Therefore, a definitive conclusion, that the vertebral anomalies with or without associated rib anomaly, resulted from a direct effect of the test article cannot be made. Maternal stress may have contributed to this finding.

The NOAEL for this study was considered 3000 ppm for embryo/fetal developmental toxicity and maternal toxicity.

Please contact me at (312) 544-7061 if you have any questions regarding this letter.

Sincerely,

Louette Rausch

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