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TSCA Confidential Business Information Center (7407M)
EPA East - Room 6428 Attn: Section 8(e)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

8EHQ-1010-18156A



Re: TSCA Section 8(e): Tier I Endocrine Disruptor Screening Program Assays-
Isophorone

Dear Sir or Madam:

The Isophorone EDSP Consortium (Consortium) of the American Chemistry Council submits this letter describing the results of 3 range-finding studies to select dose levels of isophorone for use in subsequent Tier I endocrine disruptor screening program (EDSP) assays. The Consortium has not made a determination as to whether a significant risk of injury to health or the environment is presented by these findings.

Further evaluation of the data presented by the range-finding studies is presented below:

1. Initial Oral Gavage Probe Study:

Due to discrepancies in previous toxicity reports for rats given 1000 mg/kg isophorone, a small study was conducted in which 4 CD rats (2 males and 2 females) were exposed to 1000 mg/kg/day isophorone by gavage (Marty and Marshall, in progress). By test day (TD) 3 (after 2 doses of isophorone), both male and female rats had lost weight (17 and 20 g, respectively). Feed consumption ranged from 0.7-6.8 g/day in these animals. Clinical signs included decreased activity, slow respiration, incoordinated gait and perineal/perioral soiling. These animals were euthanized for humane reasons on TD 3.

2. Oral Gavage Range-finding Study:

An oral range-finding study was conducted in which male CD rats (5/group) were given 0, 100, 400 and 700 mg/kg/day isophorone in corn oil by gavage for 2 weeks (postnatal days 30-44). There were no significant effects on body weight; however, liver and adrenal weights were increased in a dose-dependent manner (preliminary data: at the high dose (700 mg/kg/day), absolute and relative adrenal weights were increased 23 and 30%, respectively; absolute and relative liver weights increased 20 and 22%, respectively). Concurrent with liver weight changes, aspartate aminotransferase was decreased slightly (10%) at 700 mg/kg/day. Effects on liver weight and histology (hepatocellular hypertrophy) have been reported in previous toxicity studies with isophorone.

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3. Subcutaneous Injection Range-finding Study:

For the subcutaneous range-finding study, CD rats (2-3/sex/dose) were injected with isophorone in corn oil (3 ml/kg body weight) at doses of 0, 400, 700 and 1000 mg/kg/day; however, these animals were removed from study after the first dose was administered due to adverse clinical signs (i.e. decreased activity, incoordinated gait, partially closed eyelids, labored and/or shallow respiration, hemorrhage and swelling at the injection site). These clinical observations were observed in all exposure groups with only minimal differences in severity. A subset of these animals underwent gross necropsy; these animals exhibited an acute irritation response to subcutaneous isophorone treatment at these dose levels; thus, the maximum tolerated dose had been exceeded. A second range-finding study was initiated that included dose levels of 0, 25, 75 and 250 mg/kg/day isophorone. Rats given 75 mg/kg/day struggled and vocalized during dosing, suggesting irritation due to subcutaneous isophorone administration at this dose level; therefore, the 250 mg/kg/day dose was not administered. For the second and third days of dosing, the 75 mg/kg/day animals were given 50 mg/kg/day; these animals did not vocalize at 50 mg/kg/day. Due to apparent acute irritation reaction to the test material, a high dose level of 50 mg/kg/day isophorone was selected for subcutaneous dosing in order to meet animal welfare policies of the laboratory.

Final reports from these studies will be submitted to EPA when they are available. Please contact me with any questions at (202) 249-6714 or at bill_gulledge@americanchemistry.com.

William P. Gulledge
Manager, Isophorone EDSP Consortium

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