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Document Processing Center (Mail Code 7407M)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue
Washington, DC 20460-0001

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Re: TSCA 8(e) Submission of Reproductive Toxicity Findings from a Screening Study on Isobutane

Dear Madam or Sir:

The American Petroleum Institute (API), on behalf of the Petroleum HPV Testing Group (Testing Group), is submitting this notice pursuant to Section 8(e) of the Toxic Substances Control Act for the substance, isobutane, CASRN 75-28-5. The Testing Group is an unincorporated group of petroleum substance manufacturers and importers affiliated by contractual obligation to establish and fund a voluntary data disclosure and testing program, in response to EPA's HPV Chemical Challenge Program. The Testing Group program is administered by API (membership list attached).

The Testing Group has received a draft study report entitled "Isobutane: Combined Repeated-Exposure Toxicity Reproduction and Neurotoxicity Screening in Rats via Whole-Body Inhalation Exposures." This study followed the OECD 422 testing guideline. The test substance was administered at target concentrations consisting of 0, 900, 3000 and 9000 ppm to Sprague Dawley® CD rats (12 per sex per group in the Main Study and 12 females per group in the Satellite Study) for 6 hours per day, 7 days a week. Main Study male rats were exposed for two weeks prior to mating, during mating, and until euthanized for a minimum exposure of 4 weeks. Main Study female rats were exposed for a minimum of 4 weeks. Satellite female rats were exposed for two weeks prior to mating, during mating, and during gestational days 0-19. Main study females were evaluated for subchronic effects and satellite females for reproductive effects only. The highest exposure level (i.e., 9000 ppm), which is one-half the lower explosion limit of

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this gas, was considered the highest level that could be tested without posing a safety hazard to laboratory personnel.

The draft report noted a statistically significant ($p<0.05$) higher post-implantation loss among females exposed to 9000 ppm (mean 1.8±0.8) compared to concurrent control females (mean 0.8±0.9). The draft also reported that male and female fertility indices in the 9000 ppm group (75%) were below the concurrent control (100%) and the testing facility historical control values (mean 96.4%, range of 87.5% - 100%). Based on these findings, the no-observed-adverse effect level (NOAEL) for reproductive endpoints was judged by the investigators to be 3000 ppm.

A summary of the reproductive and offspring draft study results, including the potentially reportable findings, are provided below:

Endpoint	**Concurrent Control**	**900 ppm**	**3000 ppm**	**9000 ppm**
A – No. Pairs Cohabited	12	12	12	12
B – No. Pairs Mated	12	12	12	12
C – Mating Index (%)	100	100	100	100
D – No. Females Pregnant	12	11	11	9
E – Male and Female Fertility Index (%)	100	91.7	91.7	75
F – No. Females with Live Litters	12	11	11	9
G – Gestation Index (%)	100	100	100	100
H – Mean Time to Mating (days)	2.8	2.4	4.1	2.9
I – Mean Gestation Length (days)	21.8	21.7	21.8	21.7
J – No. of Females Completing Delivery with Stillborn Pups/All Stillborn Pups	0/0	0/0	1/0	0/0
K – Mean Pre-implantation Loss	1.8	1.0	1.0	1.3
L – Mean Post-implantation Loss	0.8	0.6	0.7	1.8*
M – Mean Pups Delivered	13.8	13.5	13.4	13.4
N – Live Birth Index (%)	100	100	98.6	100
O – Viability Index (%)	97	98	98.6	99.2

*$p<0.05$

A NOAEL of 9000 ppm was reported for all systemic and neurotoxic endpoints among the parental rats in this study. The NOAEL for pup endpoints was 9000 ppm based on the lack of effects on postnatal survival, body weight, and development up to postnatal day 4. Because of the small group sizes employed in this study and the small differences reported between isobutane-exposed and control animals, the Testing Group believes the subject reproductive findings are equivocal. However, the study authors considered the decreased fertility index and the increased post-implantation loss at the high exposure level to be exposure-related.

In accordance with EPA's published TSCA Section 8(e) guidance we are submitting the reported draft reproductive findings, as well as the attached Summary section of the draft study report, for your review.

If you have any questions or require further information regarding this submission please contact Thomas Gray at API (202-682-8480 or grayt@api.org).

Sincerely,

Howard J. Feldman

Attachments: Petroleum HPV Testing Group Membership List
Summary section of the study draft report

cc: Oscar Hernandez, USEPA
Diane Sheridan, USEPA
Mark Townsend, USEPA

SUMMARY

This study was designed to screen the potential toxicity, including neurotoxicity and reproductive performance in male and female rats when isobutane was administered by whole-body inhalation exposure. It also was designed to permit detection of effects in both sexes on mating behavior and on gonadal function that may not be evident from histological examination of the reproductive organs. In addition, for female rats, this study design can detect effects on conception, development of the conceptus and parturition and pup survival to postnatal day 4.

The test substance was administered as a gas to Sprague Dawley CD rats (12/sex/main study group and 12 females/satellite group) at target concentrations of 900, 3000 and 9000 ppm (note: highest dose is 50% of the lower explosive limit) for 6 hours/day, 7 days/week for 2 weeks prior to mating initiation. Exposure levels were determined using an infrared spectrophotometer (IR) 4 times per chamber per day. Main study male rats were exposed during the mating and post-mating periods until euthanized for a minimum exposure of 28 days. Main study female rats (12/group) were exposed once daily (6 hours/day), 7 days/week for 4 weeks (minimum of 28 days). Satellite female rats were exposed once daily (6 hours/day), 7 days/week for at least two weeks prior to mating initiation. Satellite female rats continued to be treated once daily (6 hours/day) during mating. Once mated, satellite female rats were treated once daily (6 hours/day) during gestation days 0-19. Main study females were evaluated for subchronic effects and satellite females for reproductive effects only. The following parameters were evaluated in all animals: viability, clinical observations, body weights, feed consumption, functional observational battery (FOB), motor activity, clinical pathology (termination), organ weights, and macroscopic observations. Microscopic pathology was conducted in the main study control and high-exposure groups only.

The test substance, purchased from MG Industries, was assayed by GC versus an analytical standard before and after the study to demonstrate the purity and stability of the test substance. The test substance was determined to be 99.84% isobutane before the study and 99.53% isobutane after the study demonstrating the purity and the stability of the test substance. Chamber distribution analyses showed that the test substance was evenly distributed within each chamber. The mean (± standard deviation) analytical (IR) concentrations for the control and the respective exposure groups were as follows: 0 ± 0, 930.0 ± 27.8, 3122 ± 83 and 9148 ± 201 ppm. Chamber environmental conditions averaged 24°C temperature and 55% relative humidity. Mean particle size distribution measurements for the exposures indicated that the atmospheres were gas only, as expected, since there was no substantial difference between the test substance chambers and the air control chambers.

SUMMARY

exposed animals compared to the air control animals. There was no apparent exposure-related effect on FOB or motor activity parameters for either sex in this study. There were no exposure-related differences in hematology or coagulation values or clinical chemistry values in test substance exposed animals compared to the air control animals at the terminal interval. There were no exposure-related differences in macroscopic postmortem evaluations or organ weights in the test substance exposed animals compared to the air control animals. There were no microscopic findings considered to be related to exposure to isobutane.

Almost all mated female animals were found pregnant and delivered live pups. In the 9000 ppm group, 25% of the mated females did not become pregnant, and this reduction in the male and fertility indices (75%) was considered exposure-related. Mating index for the male rats treated with the test substance were comparable to the air control group. Mating and gestation indices for the female rats treated with the test substance were comparable to the air control group. Almost all females in each group mated at the first opportunity. There were also no treatment-related differences in the other reproductive parameters up to the time of parturition including the percent of females completing delivery and the duration of gestation, when compared to the air control group. An exposure-related increase in post-implantation loss was also observed for the 9000 ppm group of exposed female rats. Otherwise, there were no exposure-related differences in any of the parturition parameters including pre-implantation loss, the total number of pups delivered, the number of pups dying, the viability (4 day survival) index, the pup sex ratio and the number of live pups/litter, when compared to the air control group. There were no exposure-related differences in body weights or weight gains in the pups feeding from females exposed to test substance during gestation compared to the pups feeding from air control animals. There were no exposure-related differences in macroscopic postmortem evaluations in the pups feeding from females exposed to test substance during gestation as compared to the pups feeding from air control animals.

In conclusion, exposure of male and female rats to target concentrations of 900, 3000 or 9000 ppm of isobutane by whole-body inhalation for 4-6 weeks resulted in no general systemic/neurotoxic effects. A no-observed-adverse effect level (NOAEL) of 9000 ppm was determined for all general systemic/neurotoxic endpoints in this study. Based on decreased male and female fertility and increased post-implantation loss in the 9000 ppm group, the fertility and reproductive endpoints NOAEL was determined to be 3000 ppm. The NOAEL for pup endpoints was 9000 ppm based on no effects in offspring survival, body weight and development up to post-natal day 4.

The Petroleum HPV Testing Group

Alcoa Inc.

Big West Oil LLC

BP

Calcasieu Refining Company

Chevron Corporation

CHS Inc.

CITGO Asphalt Refining Company

CITGO Petroleum Corp.

Coffeyville Resources, Refining and Marketing, LLC

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The Goodyear Tire & Rubber Company

The Premcor Refining Group Inc.

Total Petrochemicals USA, Inc.

Tricor Refining, LLC

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