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# DBE

## Dibasic Esters Group

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Attention: 8(e) Coordinator

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The Dibasic Esters (DBE) Group is submitting the following information based upon EPA guidance regarding the reportability of toxicity data under TSCA Section 8 (e). The DBE Group, comprised of Aceto Corporation, E.I. duPont de Nemours & Company, and Solutia, Inc., is informing you of the results of a 90-day inhalation study conducted in male and female rats with butanedioic acid, dimethyl ester (DMS, CAS # 106-65-0); pentanedioic acid, dimethyl ester (DMG, CAS # 1119-40-0); and hexanedioic acid, dimethyl ester (DMA, CAS # 627-93-0). The DBE Group is conducting the study under a TSCA Section 4(a) Consent Agreement (Docket No. OPPTS-42190) and is copying this letter to our ECA Coordinator George Semeniuk."

Groups of 36 male and 36 female rats were exposed via inhalation to 0, 10, 50, or 400 mg/m<sup>3</sup> DMG, 400 mg/m<sup>3</sup> DMS, or 400 mg/m<sup>3</sup> DMA over a 90-day period for 6 hours per day. The exposure period was followed by a 1-month recovery period. Rats were weighed once per week and clinical signs were taken daily. Food consumption was determined on a weekly basis. Samples for hepatic, lung, and nasal (levels II and III) cell proliferation (CP) were collected from rats approximately two weeks after initiation of the study and approximately 90 days after study initiation. A clinical pathology evaluation was conducted on rats approximately 45 and 90 days after initiation of the study. Approximately 90 days after study initiation, rats designated for the clinical pathology evaluation were sacrificed for pathological examination and evaluation of male reproductive endpoints including sperm motility and sperm morphology. A neurobehavioral test battery, consisting of functional observational battery assessments and motor activity, was conducted prior to test substance administration to obtain baseline measurements, and during test weeks 4, 8, 13, and 17 (recovery). Approximately 90 days after study initiation and after approximately 1 month of recovery, rats designated for neuropathological evaluation were sacrificed for evaluation of this endpoint. The estrus cycle of female rats was determined for the last 21 days of exposure. Following 90 days of exposure, blood was collected via the tail vein from 10 rats/sex/group and serum was prepared for hormonal analyses. In males rats, serum luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone concentrations were measured. In female rats, serum estradiol and progesterone concentrations were measured.

No compound-related effects were observed on body weight or food consumption parameters, clinical signs, clinical pathology, neurobehavioral endpoints, neuropathology, male reproductive endpoints, or estrus cycle.

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Compound-related effects were observed in the noses of male and female rats exposed to 400 mg/m<sup>3</sup> of DMG, DMS, and DMA for 90 days. These effects consisted primarily of degeneration/atrophy of the olfactory mucosa of the dorsal meatus and of the dorso-medial aspect of the dorsal endoturbinates. Less commonly, focal respiratory metaplasia of the olfactory mucosa of the dorsal meatus was also present. Lesions were minimal to mild in severity and occurred in higher incidences in the DMG group. Degeneration/atrophy of the olfactory mucosa occurred in recovery animals in the same locations as was apparent at the 90-day sacrifice in animals exposed to DMG, DMS, and DMA. The lesions were usually focal and minimal in severity. The incidence of lesions in female recovery groups was higher in the DMG and DMS groups compared to the DMA group, while in male recovery groups, incidences were somewhat higher for the DMA group. The nasal lesions observed in this study were expected findings based on two 90-day inhalation studies conducted on a dibasic ester mixture containing these three test substances at comparable concentrations. The data from these studies have previously been published in the literature.

Male rats exposed to 400 mg/m<sup>3</sup> DMS and DMA showed significant increased CP in the liver at day 14 compared to controls. No significant effects were observed in the liver from males evaluated at 90 days or from females evaluated at either time point. Female rats exposed to 400 mg/m<sup>3</sup> DMA had significantly greater CP in the lung relative to controls at days 14 and 90. No effects on CP were observed in the lung from male rats. Male rats exposed to 400 mg/m<sup>3</sup> DMG and DMA showed significantly greater CP in the nose level II compared to controls at day 90. Female rats exposed to 400 mg/m<sup>3</sup> DMG had significantly greater CP in the nose level II at day 14. Male rats exposed to 400 mg/m<sup>3</sup> DMG had significantly greater CP in the nose level III at day 90. CP in the nose level III of female rats exposed to 400 mg/m<sup>3</sup> DMG was significantly greater than controls on day 14. Female rats exposed to 400 mg/m<sup>3</sup> DMS had significantly greater CP in the nose level III compared to controls on day 90. The increased CP in the noses of rats evaluated at day 90 was expected based on pathological evaluations conducted on rats sacrificed at this time point. No pathological evaluations were conducted on rats sacrificed at day 14. The biological significance of the CP criteria for lung and liver is questionable due to a lack of pathological findings in these tissues at 90 days.

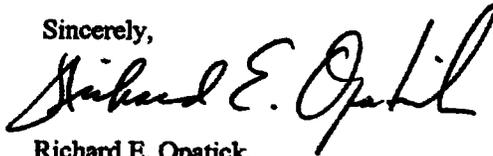
In male rats exposed to DMG, serum testosterone concentrations were decreased in a dose-dependent manner and were statistically significantly decreased at concentrations of 50 and 400 mg/m<sup>3</sup> (59 and 50% of control, respectively). Similarly, serum LH concentrations were decreased in a dose-dependent manner and were statistically significantly decreased at 400 mg/m<sup>3</sup> (71% of control). Serum concentrations of FSH were not affected by DMG treatment. In female rats, DMG exposure did not alter serum estradiol or progesterone concentrations. In male rats exposed to DMS or DMA, no significant alterations in serum hormone concentration were observed. In female rats, DMS caused a statistically significant decrease in serum estradiol concentrations (43% of control); serum progesterone concentrations were not affected. In female rats, DMA exposure did not alter serum estradiol or progesterone concentrations.

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Inhalation exposure to DMG caused decreases in serum testosterone and LH concentrations in male rats. Due to the lack of concordant changes in organ weights or histopathology of the male reproductive organs, the biological significance of the hormonal alterations is unclear. In female rats, DMS caused a statistically significant decrease in serum estradiol levels; however, due to the small number of animals and the variability associated with estrous cyclicity of the female rats, it is not possible to conclude that the alterations in serum estradiol were compound-related.

Under these experimental conditions, the findings with respect to the reproductive hormones described above appear to be reportable, based upon EPA guidance regarding the reportability of such data under TSCA Section 8(e) criteria.

Sincerely,



Richard E. Opatick.  
Executive Director

cc: TSCA Section 4 (Dr. Semeniuk)  
DBE Group

**CERTIFICATE OF AUTHENTICITY**

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