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RE: FYI Submission

To Whom It May Concern:

Evonik Corporation is submitting information regarding one study under TSCA FYI for **1,4-Butanediol dimethacrylate** CAS no. 2082-81-7. The effects of 1,4-Butanediol dimethacrylate after repeated dosing and on reproductive function such as gonadal function, mating behavior, conception, parturition and development of offspring up to Day 4 *post partum* were evaluated in rats. The study concluded that the NOAEL (No observable adverse effect level) for reproductive effects was 300/mg/kg/day in both male and female rats.

With kind regards,

Tiana M. Rosamilia



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1. SUMMARY

1.1 Study design

The effects of 1,4-Butanediol dimethacrylate after repeated dosing and on reproductive function such as gonadal function, mating behaviour, conception, parturition and development of offspring up to Day 4 *post partum* were evaluated in rats.

The test item, suspended in corn oil, was administered by oral gavage to 3 groups of 10 males and 10 females each as indicated below. A similar constituted control group (Group 1) received the vehicle alone during the treatment period.

Group Number	Treatment (mg/kg/day)	Level	Number of animals
1	0	Control	10M+10F
2	100	Low	10M+10F
3	300	Medium	10M+10F
4	1000	High	10M+10F

Males were treated for a total of 33 days including 2 weeks prior to pairing and continuously thereafter, up to the day before necropsy.

Females were dosed throughout the study including 2 weeks before pairing, thereafter during pairing, gestation and lactation periods until Day 3 *post partum*.

The following parameters were evaluated in parental animals: body weight, clinical signs (including neurotoxicity assessment, motor activity and sensory reaction to stimuli), food consumption, oestrous cycle, mating performance, clinical pathology investigations (haematology, clinical chemistry and urinalysis only males), litter data, macroscopic observations, organ weights and histopathological examination.

Check of body weight, clinical signs and macroscopic observations of pups were also performed.

1.2 Mortality and fate of females

No mortality occurred in the study.

A total of 8 females were found not pregnant at necropsy: one each in the control and low dose groups and 6 in the high dose group.

The number of females with live pups on Day 4 *post-partum* were: 9 in the control group, 9 in the low dose group, 10 in the mid-dose group and 4 in the high dose group.

1.3 Clinical signs and neurotoxicity assessment (Functional Observation Battery Tests)

No clinical signs of toxicological significance were reported.

1.4 Body weight and body weight gain

Body weight and body weight gain were lower in the high dose group compared to controls throughout the study.

1.5 Food consumption

Food consumption was reduced in the high dose group compared to controls.

1.6 Motor activity and sensory reaction to stimuli

No relevant differences were noted in all parameters investigated between control and treated groups.

1.7 Haematology

No changes of toxicological significance were found.

1.8 Clinical chemistry

The main relevant change was an increased value of bile acids in treated groups compared to controls with a clear dose-relation in males.

1.9 Urinalysis

No changes were recorded.

1.10 Oestrus cycle, reproductive parameters, pairing combination and mating performance

Measurements of oestrus cycle, pre-coital intervals and copulatory index did not show differences between treated and control groups. On the contrary, fertility index was markedly reduced in the high dose group (40% compared to 90% of the control group).

1.11 Implantation, pre-birth loss data and gestation length of females

No significant differences were observed in the number of implantation, corpora lutea, total litter size, pre-implantation loss, pre-birth loss and gestation length between control and treated groups.

1.12 Litter data and sex ratios

Reduced litter and mean pup weights were found in the high dose group compared to controls. The percentage of cumulative pup loss on Day 4 *post partum* starting from the total litter size at birth, was increased in the high dose group.
No differences were found in sex ratio between the groups.

1.13 Clinical signs of pups

Small pups were generally observed in all groups including the control group. Cold to touch and apparently no food intake were the signs noted in pups of the treated groups only.

1.14 Necropsy findings in decedent pups and in pups sacrificed on Day 4 *post partum*

No relevant differences were recorded in decedent pups between the groups.
No abnormalities were observed in pups sacrificed at term.

1.15 Terminal body weight and organ weights

Terminal body weight was lower in the high dose group compared to controls and this difference was statistically significant in females.

Statistically significant higher kidneys weight was observed in high dose males and females compared to controls. In addition, thymus weight was significantly decreased in high dose males.

1.16 Macroscopic and microscopic observations

Macroscopic observations

No treatment-related changes were noted at macroscopic examination.

Microscopic observations

Treatment-related findings were limited to the high dosed animals and were seen in the stomach of both sexes and in the liver of the females only.

Stomach (non-glandular)

The treatment-related change seen in the high dosed animals (1/10 and 5/10, respectively in males and females), consisted of mild diffused hyperplasia of the squamous epithelium in the non-glandular stomach, which was associated with mild thickening (i.e., hyperkeratosis) of the keratin layer. This change was not associated with any indication of inflammation and/or ulceration

Liver

In 3/10 high dose animals (females), minimal degree of multifocal perlobular hepatocytic vacuolation, which is suggested to be consistent with fatty change, was noted. The vacuoles were of mixed type (i.e., micro- and macrovesicular) and no presence of inflammation and/or necrosis was noted.

Spermatogenic cycle

Evaluation of the spermatogenic cycle did not show differences between the groups. Regular layering in the germinal epithelium was noted.

1.17 Conclusions

On the basis of the results obtained in the study, the NOAEL (No Observed Adverse Effect Level) for both for general toxicity and reproduction/developmental toxicity could be considered 300 mg/kg/day for males and females.

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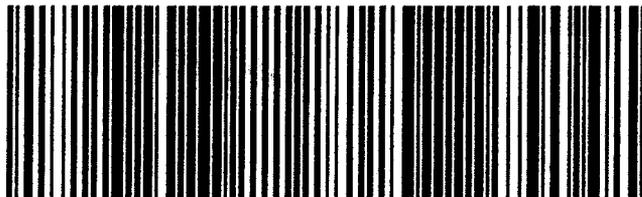
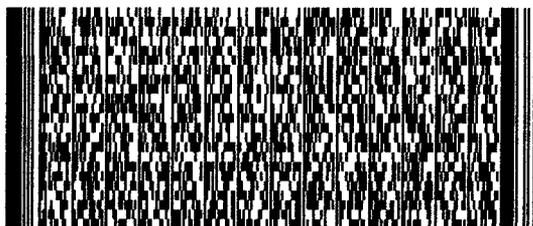
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