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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

001421

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: February 5, 1982

SUBJECT: Review of Rat and Rabbit Inhalation Teratology Studies of VIKANE (Sulfuryl fluoride)
Acc. No. 246489 Tox. Chem. 816A

FROM: Gary J. Burin, Toxicologist
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Registrant: Dow Chemical USA
Midland, MI 48640

Chemical Name: VIKANE, sulfuryl fluoride (SO_2F_2)

Registration Number: 464-236

Physical State: Odorless, colorless gas

Recommendations: The inhalation teratology study of VIKANE in rabbits is classified as Core-Minimum. The NOEL for maternal and fetotoxicity is 75 ppm.

The inhalation teratology study in rats is also classified as Core-Minimum. The NOEL for maternal and fetotoxicity is 225 ppm.

Neither study suggests a teratogenic potential for VIKANE.

Review of Data

1) Inhalation Teratology, Rabbits. Conducted and submitted by Dow Chemical USA, October 26, 1981.

New Zealand white rabbits were artificially inseminated using the method of Gibson et al*. Groups of 28 or 29 inseminated rabbits were then exposed to 0, 25, 75 or 225 ppm of test compound, via inhalation, on days 6-18 of gestation. Exposure was for 6 hours a day under dynamic conditions in a 4.3 cubic meter Rochester-type chamber with an airflow of approximately 800 liters per minute. Temperature was maintained at approximately 22°C and relative humidity was maintained between 55-70%. Test material concentration was determined 1-2 times per hour by infrared spectrophotometry. Animals were observed daily for indications of toxicity. Body weights were recorded on days 6, 9, 12, 15, 19 and 29 of gestation.

Animals were sacrificed on day 29 of gestation by carbon dioxide asphyxiation. The uterine horns were removed and the following data was recorded: number and position of fetuses, number of live and dead fetuses, number and position of resorption sites, number of corpora lutea; sex, body weight and length of fetuses and external alterations. The uteri of animals not showing evidence of pregnancy were stained with a 10% solution of sodium sulfide and examined for evidence of implantation sites. One half of each litter was randomly examined for soft tissue alterations, using the technique of Staples**. The heads of these fetuses were removed, fixed and serial sectioned. All fetuses were then eviscerated, preserved in alcohol, cleared and stained with alizarin-S. All fetuses were examined for skeletal alterations.

*Gibson, J.P., Staples, R.E. and Newberne, J.W. (1966) "Use of the Rabbit in Teratogenicity Studies", Tox. Appl. Pharmacol. 9:398-408.

**Staples, R.E. (1974) Detection of visceral alterations in mammalian fetuses. Teratology 9:37.

Results: (Time weighted average actual concentrations were found to be 0, 25 ± 1, 76 ± 1 and 225 ± 2 ppm).

Two dams of 25 ppm group, one dam of the 75 ppm group and 3 dams of the 225 ppm groups died during the course of the study. One of the deaths at 25 ppm and two of the deaths at 225 were attributed to pneumonia (Pasteurellosis), the cause of the other deaths was not known.

Maternal body weight and maternal body weight gain were both significantly less than control values for the 225 ppm dose group.

Three females (one each from the 25, 75 and 250 ppm dose levels) were found to have litters which had completely aborted early in pregnancy and each of these animals also had mucopurulent exudates indicative of uterine bacterial infections. Evidence of early resorption sites were also found in one 25 ppm rabbit.

Three control animals and two high dose animals delivered litters prior to cesarian section.

No compound related effects on litter size, incidence of resorptions, incidence of major malformations or the incidence of most minor variations were apparent. The most common fetal alterations included satellite vessals off major arteries, pale livers, extra ribs, 8 lumbar vertebra and delayed ossification of the sternebrae, all of which are considered to be variations. Fetal body weight was significantly decreased in the 225 ppm dose group and crownrump length was slightly decreased in this group. No effects on these parameters were observed at 25 or 75 ppm.

Core Classification: Core-Minimum. A positive control group was not used in this study and historical control data was not submitted. The NOEL for maternal and fetotoxicity was found to be 75 ppm. Teratogenicity was not demonstrated at 225 ppm (highest dose tested).

2. Inhalation Teratology, Rats. Conducted and submitted by Dow Chemical USA, October 26, 1981.

Fischer 344 female rats were bred with males of the same strain. The finding of sperm in a vaginal smear was considered to be day 0 of gestation. Groups of 35 and 36 animals were exposed to 0, 25, 75 or 225 ppm of test material, via inhalation, on days 6 through 15 of gestation. Exposure was for 6 hours per day under dynamic conditions

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in a 4.3 meter Rochester-type chamber with an airflow of approximately 800 liters per minute. Temperature was maintained at approximately 22°C and relative humidity was maintained between 55-70%. Test material concentration was determined 1-2 times per hour by infrared spectrophotometry. Animals were observed daily for indications of toxicity. Body weights were recorded on days 6, 9, 12, 16 and 21 of gestation. Maternal food and water consumption were recorded at 3 day intervals beginning on day 6 of gestation.

Animals were sacrificed on day 21 of gestation by carbon dioxide asphyxiation. The uterine horns were removed and the following data were recorded: number and position of fetuses, number of live and dead fetuses, number and position of resorption sites, number of corpora lutea; sex, body weight and length of fetuses and the incidence of external alterations. The uteri of animals not showing evidence of pregnancy were stained with a 10% solution of sodium sulfide and examined for evidence of implantation sites. One half of each litter was randomly examined for soft tissue alterations using the technique of Staples*. The heads of these fetuses were then eviscerated, preserved in alcohol, cleared and stained with alizarin-S. All fetuses were examined for skeletal alterations.

Results: (Time weighted average actual concentrations were found to be 0, 25 ± 1, 76 ± 1 and 225 ± 2 ppm.)

No mortalities occurred during the course of the study. No maternal signs of toxicity were noted at any dose level, although it is noted that maternal body weight and body weight gain were slightly less than controls in the high dose group. Although food consumption was not affected by treatment, water consumption was significantly increased in the high dose group on gestation days 6-17.

No compound-related effect on incidence of pregnancy, pre-implantation loss, mean litter size or incidence of resorptions was observed at any dose level. At 225 ppm, fetal body weight and crown-rump length were significantly increased compared to controls. No compound related effects on major malformations were apparent. A significant increased bilobed centra of the vertebrae was observed in the 25 and 225 ppm groups. However, the incidence did not appear to be dose-related and the magnitude of the increase was not large. A significant increase in unfused centra was observed in the 75 ppm group compared to controls. These variations are shown in the following table:

*Staples, R.E. (1974) Detection of visceral alterations in mammalian fetuses, Teratology 9:37.

Table: Incidence of Bilobed or Unfused Sternebrae*

	0 ppm	25 ppm	75 ppm	225 ppm
Unfused Centra	2(2)	2(2)	7(1)**	2(2)
Bilobed Centra	1(10)	22(16)**	12(6)	24(17)**
TOTAL***	13(10)	24(18)	19(7)	26(17)

*Fetuses effected (litters effected)
**Significant at $p < .05$.
***Total fetuses effected either by variation (total litters effected by either variation)

The possibility that the increases in either unfused or bilobed centra were due to chance can not be eliminated. No other possible effects on skeletal development were apparent.

Core Classification: Core-Minimum. Although maternal toxicity was not demonstrated, it is probable that the high dose level was approaching a level which would have demonstrated maternal toxicity based on the results of the "probe" study which demonstrated maternal toxicity (significantly decreased body weights and body weight gains) at 300 ppm. The NOEL for maternal and fetotoxicity is 225 ppm in this study.

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