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

MEMORANDUM

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TO: Henry Jacoby (21)
Registration Division (TS-767)

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

THRU: Orville E. Paynter, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Review of Ten-Week Inhalation Reproduction Study of D-D (1,2-Dichloropropane, 1,3-Dichlorpropene) in Rats;
Reg. No. 201-253 Acc. No.: 246670
CASWELL Nos.: 324 and 324A

Registrant: Shell Oil Company
Suite 200
1025 Connecticut Ave., N.W.
Washington, D.C. 20036

Recommendation:

This study is classified as supplementary data in the area of reproductive toxicity. No effects on reproduction are indicated at the highest dose tested, 443 mg/m^3. The NOEL of 145 mg/m^3 for nonreproductive effects observed at the high dose included decreased body weight and increased kidney and liver organ to body weight ratios in both males and females.

Review of Data:

Ten-Week Reproduction Study Via Inhalation, Rats. Conducted at the Shell Toxicology Laboratory, Tunstall, England and submitted by Shell Oil Company, January 15, 1982. Report No. TLGR. 80.023.

Specific pathogen free albino rats of the Wistar strain, 10-15 weeks old, were randomly assigned to control and treatment groups. Animals were housed in groups of 3 per cage, 18 cages per

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1.5 cubic meter chamber. Chamber design was such as to allow airflow to be dispersed throughout the chamber (via filters and fans) prior to exiting. Temperature and humidity were monitored daily. Test atmosphere was generated by volatilization of epichlorohydrin-free (< 0.1%) D-D in a wick-type saturator heated to 22.5°C into a controlled flow of nitrogen near the inlet duct of the chamber. Test atmosphere concentrations were monitored using two separate methods: total hydrocarbon analysis to allow continuous measurement and gas chromatography to allow qualitative and quantitive measurement on an hourly (or bihourly) basis.

Groups of 30 males and 24 females (at each dose level) were exposed to either 0, 64, 145 or 443 mg/m^3 D-D, 6 hours/day, 5 days/week, for 10 weeks. Airflow means ranged from 1.6 to 1.8 cubic meters per minute, temp. from 19-24°C and relative humidity from 29-61%. For assessment of reproductive toxicity, animals were randomly assigned to subgroups and the following parameters were examined for each subgroup:

Subgroup	Number of Animals		Experimental Parameters
	Males	Females	
I	10	9	Toxicology: body weight, hematology, clinical chemistry, urinalysis, vaginal cytology, organ weights, pathology.
II	20	-	Male repro. performance, body weight, organ weights, pathology.
III	--	15	Female repro. performance, body weight, organ weights, pathology.

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Male reproductive performance was assessed as follows: "Beginning with the Monday night of weeks 3, 5, 8 and 11, each male rat (of subgroup II) was taken every night for 7 days from the exposure chamber and housed with two unexposed virgin females...". Females were then examined for presence of sperm, pregnancy and for the presence of gross morphologic changes in sperm. Males were returned to the exposure chambers daily. Females were sacrificed on the 12th day after the final mating and examined for corpora lutea, implantation sites and resorptions.

Female reproductive performance was assessed as follows: "On the Sunday beginning week 11 each female (of subgroup III) was taken from the exposure chambers and housed for seven days with one unexposed male of proven fertility in a breeding cage in the animal room." Vaginal smears were taken daily and males were rotated after 7 days. Females were allowed to litter and pups were externally examined and retained for 4 days to determine survivability.

Vaginal smears were taken daily from the 9 females of subgroup I. After exposure, animals of all subgroups were sacrificed and necropsied. The following organ weights were determined for all surviving animals: liver, kidneys, spleen, brain, heart and testes. Microscopic examination was performed on the following tissues of all animals: kidneys, adrenals, testes, epididymides, vasa deferens, ductuli efferentes, seminal vesicles, coagulating ducts, blubo-urethral glands, prostates, ovaries, oviducts, uteri and cervix.

Hematology consisted of measurement of RBC and WBC counts, MCV, MCH, MCHC, Hct, prothrombin and kaolin-cephalin coagulation time, and differential leukocyte count. Clinical chemistry consisted of total protein, BUN, AP, Cl, total bilirubin, Ca, Creatinine, PO_4, uric acid, Na, K, alanine aminotransferase, aspartate aminotransferase and albumin. Urinalysis consisted of measurement of glucose, protein, ketones, bilirubin, pH and blood pigments.

Results

The mean actual concentrations of D-D were 64, 145 and 443 mg/m^3 and concentrations of test compound appeared to be consistent during the exposure periods.

Male and female body weights were significantly less for the high dose group compared to the controls for each subgroup. No effects on hematology, clinical chemistry, clinical signs or urinalyses were associated with treatment.

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A review of the relevant findings from subgroups I, II and III revealed the following:

No effects of treatment on the mating, fertility or reproductive indices of males or females were apparent. Esterous cycling was similar in control and treated animals as indicated by the vaginal cytology smears. Gestation length, implantation loss, pup weight and survival were not affected by treatment.

Liver and kidney weight/body weight ratios were significantly increased for high-dose males and females. Gross observations did not indicate any compound related macroscopic pathology with the possible exception of increased renal subcapsular granularity in medium and high exposure females. Microscopic observations did not indicate any compound related histopathology with the possible exception of increased amorphous protein casts in proximal convoluted tubules of the high exposure males. Sperm morphology was not affected by treatment.

Core Classification: Supplementary Data. This study assesses a variety of reproductive parameters through only one generation.

This study indicates a lack of effect on reproductive parameters for rats exposed at 64, 145 and 443 mg/m^3 (HDT). The NOEL for nonreproductive toxicity is suggested as 145 mg/m^3, based on possible liver and renal toxicity at 443 mg/m^3; however it is noted that this study was designed primarily to assess reproductive toxicity and was not adequate for the assessment of nonreproductive effects due primarily to limited histopathology.

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