UNITED STATES ENVIRONMENTAL PRC — D-7690 / Linuron SR 12-10-79

Releasable

DATE: December 10, 1979

SUBJECT: Review of Linuron Rat Teratology Study - Re: Lorox Weed Killer, EPA Reg.#352-270 CASWELL#528

FROM: Charles Frick C. Frick
Toxicology Branch (TS-769)

TO: Mr. Taylor & Toxicology Branch Files
Product Manager#25

THRU: Dr. Adrian Gross, Chief William S. Butler for A. Adrian Gross
Toxicology Branch (TS-769)

Data Source: DuPont, Wilmington, Delaware

Action: Review of Rat Teratology Study on the compound Linuron (3-(3,4-Dichlorophenyl)-1-methoxyl-1-methylurea - Haskell Laboratory Report No. 33-79.

Use: Herbicide

Conclusion: This reviewer cannot concur with the conclusion given in this study that the no effect dose is 625 PPM. Because of the resorptions seen at this dose level (625 PPM), a no effect of 125 PPM is indicated by this study.

Comments: This study was conducted to define the teratogenic potential of this compound in light of a study by K.S. Khera published in Toxicology and Applied Pharmacology, Volume 45, 1978. In this published study, Linuron was noted as being teratogenic at 200 mg/kg (Lorox 50% WP) by incidences of nonapposed sternebrae. Du Pont toxicologists considered nonapposed sternebrae to be fetal variations which suggest a fetotoxic response and not a teratogenic response as concluded by Khera. If this reviewer's understanding of nonapposed sternebrae is correct I would tend to agree with Du Pont's position. This study indicated some slight reproductive effects at 625 PPM and a no effect level at 125 PPM. This study is classified as Core-Guideline.

Protocol

Test material was stated to be about 97% pure and was coded INZ-326-118.

Test animals were Charles River - CD primigravida rats. The day on which sperm were found in the vaginal smear was counted as day 1 of gestation. Groups were dosed as follows:

Group	No. of Rats	Diet
I (control)	27	0
II	27	50 PPM
III	27	125 PPM
IV	27	625 PPM

Individual food consumption was measured and recorded throughout the test. Rats were observed daily for clinical signs of toxicity and changes in behavior. The animals were weighed to within one gram on the day of arrival and on days 6, 10, 16, 21 of gestation.

At the time of sacrifice, the abdominal wall of the female was opened and both ovaries and uterus were removed and inspected. The uterus was then opened and the fetuses removed and examined.

The following was recorded:

1) Number of corpora lutea in each ovary.
2) Number of implantation sites in each horn.
3) Number and location of all live and dead fetuses.
4) Number and location of resorptions.
5) Weight of each live fetus.
6) Crown-rump length of each live fetus.
7) Gross anomalities.

About half of the fetuses were examined for skeletal anomalities, the rest were examined for visceral anomalities.

Results

Body Weight - The 625 PPM dose group demonstrated significantly lower mean body weights during the test period.

Food Consumption - Dose groups at 125 PPM and 625 PPM consumed significantly less food than control group.

Clinical Signs and Mortality - Weight loss in the 625 PPP dose group and one animals in this group had chromodacryorrhea. It was stated no other signs of toxicity were observed. All the rats survived the test period.

Variants Anomalies and Malformations - The malformations found in seven fetuses from six different litters in all three test groups did not suggest organ or tissue specific teratogenicity or dose-response relationships. Agnathia in one fetus and anophthalmia together with great vessel irregularities in the 50 PPM group.

At 125 PPM, one fetus was a runt with multiple defects; umbilical hernia, anophthalmia and absence of one ovary. Another fetus had an uncomplicated umbilical hernia.

In the high dose group, one fetus was found with an umbilical hernia, one with great vessel irregulatities and another with hydrocephaly.

No malformations of the skeletal system were detected. All abnormalities were classified as either biological variations in the process of ossification or as anomalies of genetic origin present in this strain of rats (14th rudimentory ribs, wavy ribs, hydronephrosis)

The outcome of pregnancy measured by the number of implantation sites, resorptions, and live fetuses was not extraordinary with the exception of resorptions in the 625 PPM group; 59.1% compared to 36.0% in control. While this is not a dramatic finding it cannot, in this reviewer's opinion, be established as a valid No-Effect Level. The NEL in this study is 125 PPM.

TOX/HED:th:RD Initial WWOODROW:12-7-79