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

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MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor (PM#25)
Registration Division (TS-767C)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

WLB

SUBJECT: PP#9F2232; Bladex/Soybeans; EPA Reg.#201-279 and 201-281. Historical Data for the Teratology Study In the New Zealand Strain of Rabbits. CASWELL#188C

Background

A teratology study in New Zealand rabbits with Bladex was performed by Shell Toxicology Laboratory (Tunstall), Sittingbourne Research Center, England (Project #221/81, experiment #AHB-2321, November 1982). The study was submitted by Shell on 2/1/83 under document #SBGR.82.357; and it was given Accession#071382.

The study was classified as Core-Minimum (see our review of 4/29/83), and historical data were requested for comparison.

Historical data for the New Zealand strain of rabbits are submitted in this action as Shell's response to our previous request for these data.

Recommendation and Discussions:

The registrant submitted two sets of historical data; these data are as follows:

1. Control data from the Shell UK Tunstall Laboratory.

These data included controls A. B and C. Control A is the vehicle control group of the Bladex teratology study in rabbits. This control is more similar to control B than C.

2. Historical data from other laboratories (11 laboratories referred to as C_1,C2...C_{11}). The incidences of fetal anomalies from all the above laboratories were presented individually and combined. The number of litters affected was not reported.

The study control and the other two controls B and C from Shell's laboratory reflected a much higher incidence of fetal malformations than the historical data from other laboratories, see tables #1 and # 2 below in the review section.

In the Bladex rabbit study, the following major anomalies only increased at the highest dose tested 4 mg/kg/day; domed head, dilated brain ventricle, anophthalmia/microphthalmia, acephaly, and thoracoschisis (see table #1 below in the review section; and table #1 and 2, page 9, in our 4/29/83 review, attached). However, some maternal toxicity was also demonstrated at this level, i.e. a significant weight loss was noted at termination, the mean maternal body weight at this dose level decreased by 10% from the time of dosing to termination as compared to an increase of 3% in the vehicle control (for additional maternal toxicity data, see also the attached review on pages 4,5 and 6):

Hence, our conclusion remains the same as in our 4/29/83 memo, that the above mentioned anomalies are apparently related to maternal toxicity and are not considered a classical teratogenic response. The NOEL for maternal and fetal toxicity in rabbits is 1 mg/kg/day, and the LEL is 2 mg/kg/day.

Finally, although a classical teratogenic response (i.e., a teratogenic effect below the level of significant maternal toxicity) was not noted, significant terata were present at a relatively low dose, 4 mg/kg/day (HDT); a level at which some maternal toxicity was evident. Furthermore, since the dose range between teratogenicity and a NOEL for maternal and fetal toxicity is so small (3 mg/kg/day), it is suggested that special precautions should still be exercised to preclude exposure to women of child bearing age.

It is also noted that this chemical is considered teratogenic in the F344 rat ; however, certain outstanding issues still remain unresolved concerning these rat data, and additional data have been requested (see our memo of 11/3/83). Once the necessary data are available, a margin of safety assessment will be performed by the Toxicology Branch.

Review:

Table #1 below reflects the major malformations which only increased at the high dose level in the Bladex study as compared to controls from the same laboratory and to historical data from other laboratories (only the fetal incidences of anomalies are listed below as a percentage of the total number of examined fetuses):

Table 1: Percent Incidence of Fetal Malformations

Study No. Malformations	High dose group in the Bladex study 4 mg/kg/day for day 6 to 18 of gestation	Control data from Shell Laboratory A	B	C	Historical data from other Laboratories
A.					
1) Dilated Brain ventricle	8.8	2.1	0	0	0.15
2) Domed cranium* (hydrocephaly)	4.08	0	0	0	0.15
B.					
1) Anophthalmia/ Microphthalmia	5.9	0	__	1.5	0.12
2) Acephaly	1.02[a]	0	__	___	____
3) Thoracoschisis	1.02[a]	0	__	0.7	____

a: Same fetus, this fetus is also included in the incidence of fetuses with anophthalmia/microphthalmia.

The above table clearly reflects an increase in the incidence rate of the above listed malformations at 4 mg/kg/day Bladex as compared to the study control (A) and to data from the same laboratory (control B and C) and from other laboratories. However, as mention in our 4/29/83 memo these anomalies were seen only at the high dose and appear to be associated with maternal toxicity.

*NOTE: A skeletal variation, enlarged fontanelle, was also reported in this study and it may be potentially associated with hydrocephaly, see table #2 below. This finding was also noted at all dosage levels in this rabbit study, i.e., 2%, 8%, 10.9% at the low, mid and high dose levels respectively as compared to 9.5% in the vehicle control. As noted in the table on the next page, the 9.5% value for the concurrent control data is inconsistant with other available historical data.

The following anomalies, Table 2 occurred at a higher incidence rate in Shell's laboratory than the historical data from other laboratories.

Table 2: Percent Incidence of Fetal Malformations

Malformations	High dose group in the Bladex study	Control data from Shell Laboratory			Historical data from other Laboratories
	4 mg/kg/day for day 6 to 18 of gestation	A	B	C	
1. Enlarged Fontanelle	10.9	9.5	.1.6	1.2	0.33
2. Gall Bladder -					
absent	-	1.5	-	-	0.06
bipatite	1.0	2.1	0.8	0.8	0.03
small	3.6	1.05	-	-	0.03
3. Proximal Portion of left common carotid and innominate arteries joined	9.1	7.8	10.3	20.4	-

The above anomalies were also noted to occur at the mid and low dosages in the Bladex study and do not appear to be compound related. However it is clear from the above table that the incidences of enlarged fontanelles and gall bladder anomalies are much higher in Shell's laboratory than in the historical data from other laboratories. The incidence of the artery anomaly listed in the table above under #3 appears to be high in Shell's laboratories but no comparison could be made with the historical data from other laboratories because this specific lesion was not listed in this data.

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A.M for L.C.