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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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SUBJECT: Bladex/Atrazine (2:1) 80W Herbicide Caswell No. 63,188C  
EPA Reg. No. 201-403 UNG

*Atrazine / Review #17*

*9 pages / 5-18-78*

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*Releasable*

TO: Robert Taylor  
Product Manager (25)

Action Type: Evaluation of 6 animal studies, 5 acute and one subacute.

It should be called to the attention of all concerned that Shell Chemical Co. considers this entire submission (VOLUME II - HUMAN SAFETY) "private and confidential".

SUMMARY

Shell Chemical Co. submitted 6 animal toxicity studies, 5 acute and one subacute, in support of registration of a package mix of Bladex/Atrazine (2:1) 80W Herbicide for preemergence use on corn. This formulation, known also as an SD 50093 (80% W.P.), is a mixture of Bladex 80W Herbicide and Shell Atrazine 80W Herbicide, in a ratio of 2:1 (on the weight basis), respectively. The active ingredient of Bladex 80W is cyanazine, whereas the active ingredient of Shell Atrazine 80W is atrazine. According to the proposed label (copy attached to this evaluation), the chemical composition of Bladex/Atrazine (2:1) 80W is as follows: 2-[[4-chloro-6-(ethylamino)-s-triazin-2-yl]amino]-2-methylpropionitrile, 53.4%; 2-chloro-4-(ethylamino)-6-isopropylamino)-s-triazine, 25.3%; related compounds, 1.3%; and inert ingredients, 20%.

Both herbicides are already registered separately for preemergence use on corn (Bladex 80W, EPA Reg. No. 201-297; Shell Atrazine 80W, EPA Reg. No. 201-397). A tank mix combination of these two herbicides was also registered by EPA for the same purpose in 1972. Because of labor-saving advantages, Shell Chemical Co. now prefers the package mix of Bladex/Atrazine over the tank mix.

Bladex/Atrazine mixture is a powder, wettable with but insoluble in water, and was used as such, as a slurry or as a suspension, in the studies summarized in Table 1. All of these studies were conducted by the Industrial Bio-Test Laboratories (IBT) and, therefore, will require "validation". The report on the inhalation study (No. 8562-09472) from IBT to Shell Chemical Co. is dated 9/14/76. The two reports on the remaining studies (both numbered 8530-09471) are both dated 11/12/76. The test material used in all of these studies is identified as an SD 50093 (80% W.P.), batch No. M 2089-16. All of these studies but one, the oral toxicity study, meet the core-minimum data requirements. The oral toxicity study satisfies the core-guideline criteria.

Bladex/Atrazine (2:1) 80W is moderately toxic orally to rats and is moderately irritating to the unwashed rabbit eyes (Toxicity Category II). This formulation is also slightly toxic to the rabbit skin and the rat lungs (Toxicity categories III or IV). This material is not a sensitizer.

The RPAR criteria have not been exceeded by the toxicity data in this submission. Both Bladex and Atrazine do not pose nitrosamine problem.

Toxicology Branch has no objection to the registration of the package mix of Bladex/Atrazine (2:1) for preemergence use on corn, provided the proposed label is slightly modified as is detailed in the COMMENTS ON THE PROPOSED LABEL section below. These two modifications would result in a prominent display of the precautionary statements and in a clearer understanding of some statements.

#### COMMENTS ON THE PROPOSED LABEL

The front panel of the proposed label for package mix of Bladex/Atrazine (2:1) 80W contains the signal word WARNING, the chemical composition of this formulation, and the statement that additional precautions are found on the back panel of this label. Both the signal word and the precautionary statements are appropriate for an overall Toxicity Category II of this formulation. However, the front panel of the proposed label is unacceptable because the signal word and the precautionary statements are not displayed prominently and, therefore, are likely to be overlooked by an ordinary individual. As can be seen on the attached copy of this label, both the signal word and the precautionary comments appear between the sale and warranty statement and the address of the manufacturer. The signal word and the precautionary comments are typed in capital (or uppercase) letters, are underlined, and appear just below the sale and warranty statement. The sale and warranty statement is also written in capital letters and is also underlined (in part). The signal word and the precautionary statements are, therefore, neither readily noticeable nor are they readily distinguishable from other writing on the front panel of this label. Below are a few obvious suggestions which should remedy this situation.

1. Print the sale and warranty statement on the front panel in small (or lowercase) letters.
2. Underline the signal word and the precautionary statements in red or in some other readily visible color.
3. Print the signal word and the precautionary comments further away from other writing on the front panel of the proposed label.

In order to avoid ambiguity, a minor correction is also required in the PRECAUTIONS IN USING statement on the back panel of the proposed label. This is explained below.

"Wash thoroughly with soap and water. . .". one reads in line 4 of that statement. Yet, in line 5, one is told to "Avoid contact with water, feed or food". It would be more understandable if the expression "Avoid contact with water. . ." were replaced by one reading "Avoid contamination of water. . ."

TABLE I ACUTE AND SUBACUTE STUDIES

NO.	Study <sup>a</sup>	Animals	Dose Level	Expo. Hours	Observ. Days	LD50	Tox. Categ.	Type of Study
1	Acute Oral	80 Rats	118.5, 177.8, 266.7, 400, 600, 900, 1350, 2025 mg per kg.	-	14	348 <sup>b</sup> (266-456) mg per kg.	II	Core - Guideline
2	Acute Dermal	4 Rabbits	2000 mg per kg.	24	14	> 2000 mg per kg.	III	Core-minimum Data
	Eye Irrit.	3 Rabbits 3 Rabbits	100 mg 100 mg	30 sec. -	14 14	- -	IIC	Core-minimum Data
4	Skin Irrit.	6 Rabbits	500 mg	24	3	-	IV	Core-minimum Data
5	Acute Inhal.	10 Rats	2.25 mg per kg (Analytical)	4	14	> 2.25 mg per kg.	III	Core-minimum Data
6	Skin Sensitization Test	10 Guinea Pigs	0.5 ml of 10% suspension	9 5-hour exposures, 2 weeks of rest, then challenge dose.			-	Core-minimum Data

a. All of these studies were conducted by the Industrial Bio-Test Laboratories and, therefore, will require "validation".

b. Combined value; single values: males, 480 (348-662) mg per kg. females, 270 (201-363) mg per kg.

c. Based on unwashed eyes.

STUDIES

1. Acute Oral Toxicity (80 rats).

Procedure

Eight groups of rats of the Sprague-Dawley strain, 5 males (weighing 198-316g) and 5 females (weighing 170-272 g) per dose level, received SD 50093 (80% W.P.)\* at the following levels: 118.5, 177.8, 266.7, 400, 600, 900, 1350 and 2025 mg/kg of body weight. The test formulation was administered as a 5, 30 or 50% (w/v) aqueous suspension. The observation period was 14 days. Necropsy was done on all of the rats dying during the observation period and on those sacrificed at the end of the observation period. The LD<sub>50</sub> values were calculated by the procedure of Litchfield and Wilcoxon (1949). The test material was assigned a toxicity classification according to the procedure of Hodge (1965).

Results

There was no mortality at the lowest dose level; two animals died at each of the next two levels, six rats died at the 400 mg level; and 9 or 10 rats died at each of the four highest levels. All of the deaths occurred within 6-24 hours after dosing. With the exception of hypoactivity, there were no toxic reactions at the 118.5 mg level. The following symptoms were noted at other dose levels; hypoactivity, salivation, muscular weakness, labored breathing, rhinitis, lacrimation, prostration, diarrhea, hypothermia and diuresis. These symptoms occurred within 5 min.-22 hours after exposure and disappeared within 2 days. During the 14-day observation period, male rats gained 66-140g and female rats gained 38-56 g.

Necropsy on the nonsurviving rats revealed pale areas on the livers, pale kidneys and, in one case, enlarged purple testes. Necropsy on the surviving rats revealed very small, purple testis which contained fibrous tissue in one animal. There were no pathological changes in any of the other animals.

The LD<sub>50</sub> values and the 95% confidence limits were as follows (mg/kg of body weight): males, 480 (348-662); females, 270 (201-363); and combined, 348 (266-456).

Comments

Based on the LD<sub>50</sub> values, SD 500 93 falls into the Toxicity Category II. This study meets the core-guideline category requirements.

\*SD 50093 (80% W.P.) is the same as the mixture of Bladex 80W and Atrazine 80W in a ratio of 2:1, respectively.

2. Acute Dermal Toxicity (4 Rabbits).  
Procedure

An aqueous slurry of SD 50093 (80% W.P.) was applied to the hairless backs of rabbits (New Zealand strain) weighing 2.5-2.8 kg. Two of the rabbits, one male and one female, had their skin abraded. The dose level used was 2000 mg/kg of body weight. The exposure time was 24 hours and the observation time was 14 days.

Results

SD 50093 was slightly irritating to skin, as evidenced by mild edema and "barely perceptible" erythema at 24 hours. Slight desquamation was present at the application sites at 7 and 14 days. None of the rabbits died and all of them gained weight (0.12-0.22 kg in 14 days). Necropsy revealed no abnormalities, except for hemorrhaged lungs in one rabbit. The LD<sub>50</sub> value is, therefore, greater than 2000 mg/kg of body weight.

Comments

Although only 4 rabbits were used, this study can be accepted as a core-minimum data study. The reason for this acceptance is an apparent low dermal toxicity of this formulation.

Based on the LD<sub>50</sub> value, SD 50093 (80% W.P.) falls into the Toxicity Category III.

3. Eye Irritation (6 rabbits).  
Procedure

SD 50093 (80% W.P.), 100 mg, was placed into the conjunctival sac of the right eye of 6 rabbits (New Zealand strain). The eyes of 3 rabbits were then washed with 40 ml of water after 30 seconds of exposure, whereas the eyes of 3 other rabbits were left unwashed for 7 days. The eyes (cornea, iris, conjunctiva) were examined at one hour, and then at 1, 2, 3 and 7 days, following exposure. The appearance of the eyes was evaluated by the Draize procedure (1944).

Results

The test formulation was found moderately irritating to the unwashed rabbit eyes and minimally irritating to the washed eyes. In the case of washed eyes, the irritation scores at 1, 24, 48 and 72 hours were 12.3/110, 3.3/110, 0.7/110 and zero, respectively. In the case of unwashed eyes, the corresponding scores were 32.3/110, 27.4/110, 19.7/110 and 10/110. The score was zero after 7 days of exposure.

Comments

SD 50093 (80% W.P.) falls into the Toxicity category II or III, depending upon whether or not the rabbit eyes were washed after exposure. In the case of washed eyes, the test formulation falls into the Toxicity Category III. This classification is based on the absence of corneal opacity after exposure to SD 50093 and the disappearance of eye irritations at 72 hours after exposure. In the case of unwashed eyes, the test formulation falls into the Toxicity Category II. This classification is based on the reversibility of corneal opacity and other eye irritations before 7 days, following exposure.

This study meets the core-minimum data requirements.

4. Primary Skin Irritation (6 Rabbits).

Procedure

SD 50093 (80% W.P.), 500 mg, was applied to the hairless, premoistened backs of rabbits (New Zealand strain). One of the test sites on each rabbit was abraded. The exposure time was 24 hours. The skin was then examined for erythema and edema at 24 hours and 72 hours after exposure to SD 50093. It is not stated in the procedure whether the residual test material was removed by washing or by wiping the skin.

Results

SD 50093 was found slightly irritating to the rabbit skin (irritation score at 24 hours, 1.0/8.0). Treatment with this formulation produced some erythema, but not edema. The erythema disappeared within 72 hours following exposure.

Comments

SD 50093 (80% W.P.) falls into the Toxicity Category IV. This study satisfies the core-minimum data requirements.

5. Acute Inhalation (10 Rats).

Procedure

Five male and 5 female rats (Charles River strain) were continuously exposed to an air - SD 50093 mixture, in an 80-liter chamber. The analytical concentration of the test formulation in the chamber was 2.25 mg/liter of air. The size of the SD 50093 dust particles was as follows: 1-0 microns, 58.1%; 11-25 microns, 26.1%; and greater than 25 microns, 15.8%. Following the 4 hour exposure, the animals were observed for 14 days and then were necropsied.

### Results

Ptosis, salivation and lacrimation were noted among all test rats during the exposure time. During the 14-day observation period, male rats gained 48 g and female rats gained 23 g. Necropsy, performed on all of the animals, revealed no abnormalities. Since there were no deaths, the LC50 value is, therefore, greater than 2.25 mg/liter of air.

### Comments

Based on the LC50 value, SD 50093 (80% W.P.) falls into the Toxicity Category III. This study can be classified as the core-minimum data.

#### 6. Skin Sensitization Test (10 guinea pigs).

##### Procedure

This test was conducted according to the procedure of E.V. Buehler (Delayed contact hypersensitivity in the guinea pig," Arch. Dermat. 91, February issue, 1965).

Using 0.1, and 1.0 and 10% (W/v) aqueous suspensions of SD 50093 (80% W.P.), the irritation threshold was first established. This was done as follows. The test material, 0.5 ml per site, was applied to the hairless backs of guinea pigs. Two application sites per animal and 2 animals per dose level were used. The exposure time was 5 hours and the observation time was 48 hours. Since none of the applications produced skin irritations, the maximum nonirritating concentration of the test material (or the threshold) was, therefore, 0.5 ml of the 10% suspension.

The experimental group consisted of 10 guinea pigs. A Webril pan containing 0.5 ml of the 10% aqueous suspension of SD 50093 was applied on the shaved backs of each animal. Following a 5-hour exposure, the patches were removed and the skin was examined for the presence of irritation. This procedure was repeated until a series of 9 consecutive exposures were made. The application sites were graded for irritation 24 and 48 hours after the initial insult, and 24 hours after each intermediate insult.

The challenge dose (2 applications) was given 2 weeks after the last exposure. One 0.5 ml dose of SD 50093 was applied on the insult site and the other dose was applied on the virgin site. The skin was then evaluated for irritation at 24 and 48 hours after exposure.

### Results

There were no skin irritations after the 9 consecutive exposures and after the challenge dose. It was concluded, therefore, that SD 50093 (80% W.P.) was not a sensitizer.

Comments

This study meets the core-minimum data requirements.

K.L./gjl  
R/D init: GEWhitmore 5/12/78

*PR GEW 5/19/78*