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

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MAY - 4 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Dantobrom S and Dantobrom P (6836-116, 6836-118)
EPA ID #'s ~~38906-13~~; ~~38906-15~~
Acc. Nos 403313-01 - 403313-07

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To: Jeffrey Kempter/Ruth Douglas PM# 32
Disinfectants Branch (TS-767C)
Registration Division

From: Joycelyn E. Stewart, Ph.D. JS 4/26/88
Section VII, Toxicology Branch (TS-769C)
Hazard Evaluation Division

Thru: Albin B. Kocialski, Ph. D.
Supervisory Pharmacologist
Section VII, Toxicology Branch (TS-769C)
Hazard Evaluation Division

ABK
4/29/88

Registrant: Lonza Inc.
Fair Lawn, N.J. 07410

Lonza Inc.(formerly Glyco Inc) has submitted additional information on six toxicology studies submitted to support registration of Dantobrom P and Dantobrom S as disinfectants in swimming pools and spas. These data had been requested in Toxicology Branch's memorandum dated 5/14/1987. The additional information consists of: (1) composition and purity information on dimethylhydantoin (DMH) and ethylmethylhydantoin (EMH) used in the delayed hypersensitivity study, the rat teratology study, the teratology study in New Zealand White rabbits, and the 90 day gavage study in rats (2) company responses to Toxicology Branch's request for individual animal data for the 90 day rat study, and for historical control data for the rabbit teratology study, and (3) company response to the review of the distribution study in rabbits using ^{14}C-DMH and ^{14}C-EMH.

Recommendations

Ethylmethylhydantoin (EMH).

1. The guinea pig study for delayed hypersensitivity is upgraded to core-Minimum since the composition and purity of the test material has been submitted.

2. The rat teratology study is upgraded to core-Minimum since the composition and purity of the test material has been submitted.

3. The test material has been identified for the rabbit teratology study. However, other considerations stated in the discussion cause this study to be still classified core- Supplementary.

4. The test material has been identified for the 90 day gavage study in rats. However, other considerations stated in the discussion cause this study to be still classified core-Supplementary. The individual animal data on which the summary tables were based was not submitted.

Dimethylhydantoin (DMH)

1. The guinea pig study for delayed hypersensitivity is still considered core-Supplementary since the composition and purity of the test material was not provided.

2. The rat teratology study is still considered core-Supplementary since the composition and purity of the test material was not provided.

3. The rabbit teratology study is still considered core-Supplementary since the composition and purity of the test material was not provided.

4. The 90 day gavage study in rats is still considered core-Supplementary because the test material has not been identified as to purity or composition and the individual animal data has not been submitted.

The company's response to the review of the metabolism study has been sent to the contractor who reviewed the original submission. A separate report will be issued when the review has been completed.

Discussion

1. Test compound purity: Information relative to the test compound purity was requested in Toxicology Branch's memorandum dated 5/14/87 based on § 80-3 (2) of Subdivision F Guidelines which indicate that the composition of each lot of test substance shall be determined, including the name and quantities of known contaminants and impurities, as far as is technically feasible. The determination shall include quantities of unknown materials, if any, so that 100% of the test sample is accounted for.

The registrant's response references DMH Batch # 436649 and EMH Batch # 335759. These batches reference 1083.32 (QC Assay) and 1083.45 (Specification) for DMH and 1083.31 (QC Assay) and 1083.46 (Specification) for EMH. The purity of EMH is given under 1083.31 as 98.8% for QC Assay and 91% maximum under Specification. However, the purity of DMH is not addressed. Thus, the company has not completely responded to Toxicology Branch's request for the composition and purity of the test substance. In addition, the company should clarify whether 1083.32 and 1083.45 are identical batches of DMH; and whether 1083.31 and 1083.46 are the same EMH batch. Information in the 90 day rat study seem to indicate that two separate batches of DMH and EMH, designated by all of the above batch numbers, were used in that study.

2 a. Individual Animal Data: The registrant indicated that Toxicology Branch wants to review raw data archived at EPL's facility in Herndon, Virginia. Toxicology Branch does not need to review all the raw data which are stored in EPL's archives. Rather, Toxicology Branch requested the individual animal data upon which the summary tables submitted in the report of the 90 day rat study were based, in order that an independent analysis could be made of the data. The registrant is referred to Subdivision F § 82-1 (Test Report) of the Pesticide Assessment Guidelines regarding individual animal data. This section suggests that the following individual animal data should be submitted in a study report: time of death during the study or whether animals survived to study termination, time of observation of each abnormal sign and its subsequent course, food and water consumption data, body weight data, results of ophthalmological examination (if performed), clinical chemistry and hematological data, necropsy findings, description and histopathological findings. The registrant is also referred to Section 80-4 of the Guidelines which indicate that data should be presented in such a manner that they may be analysed independently. The registrant has not satisfied Toxicology Branch's request for the individual animal data, therefore, the 90 day rat study remains classified core- Supplementary.

2b. Rabbit-Teratology Study: With respect to the teratology study in New Zealand White rabbits Lonza Inc. (formerly Glyco Inc.) has indicated that historical control data on the incidence of fetal resorptions and pup weights of New Zealand White rabbits in their facility are unavailable, since this is the first teratology study performed at Findley Laboratories. The registrant has responded with an explanation of the conclusion drawn by the study director, who stated that under the conditions of the study, neither DMH nor EMH gave teratogenic responses in New Zealand White rabbits. The registrant's reply indicated that multiple resorptions and and lower pup weights were more prevalent in litters where the dams demonstrated more implantation sites.

By comparing individual litter performance of control and DMH and EMH treated animals, the registrant argued that at implantation sites of 9 or less, there were no significant differences between control and EMH/DMH animals with respect to viable fetuses, resorption rates and mean pup weights. weights. At implantation sites of 10 or more, the registrant stated that the multiple resorptions reported at implantation sites of 12, 13, 14, and 16 were found within 2 experimental groups.

However, in observing the registrant's Appendix 1, it is apparent that possible interpretation of the data depends upon the selection of implantation sites as the cut off point for litters with fetal resorptions and low pup weights. Table 1, abstracted from the registrant's Appendix 1 (attached) demonstrates that in does with up to 7 implantation sites, there were 1,4, 5, resorptions in in the control, EMH and DMH groups respectively which indicate an increased resorption incidence and lower pup weights in the EMH and DMH treated groups. In does with up to 9 implantation sites, the resorptions remained unchanged for treated does while they increased for controls because there were no EMH or DMH does with 8 implantation sites, and only one DMH doe with 9 implantation sites. Although the data using 9 implantation sites seem to indicate that there were no differences between controls and EMH/DMH treated rabbits with respect to resorptions, the pup weights for EMH treated animals are still below control. There were no control or EMH dams and only one each DMH treated with 12, 13, 14, or 16 implantation sites. If all dams with 12 or more implantation sites are excluded from the data set, comparisons of the relevant data may be made between control and EMH and DMH treated rabbits, and the total number of resorptions and the mean pup weights in the DMH treated rabbits are similar to the controls, while resorptions are still increased and pup weights are still decreased in the EMH treated rabbits.

Additionally, no maternal toxicity was demonstrated in either the EMH or DMH treated animals. Thus it appears that under conditions of this study, administration of DMH at 1000 mg/kg/day to pregnant New Zealand White rabbits from day 6 through day 18 of gestation resulted in no maternal toxicity, and no embryofetotoxocity. The NOEL for maternal toxicity and for embryofetotoxicity is greater than 1000 mg/kg/day as administered in the "limit test". However, the study remains classified core-Supplementary because the test compound has not been identified as to its composition or purity.

On the other hand, administration of EMH to pregnant New Zealand White rabbits at 1000 mg/kg/day from day 6 through day 18 of gestation resulted in increased fetal resorptions, decreased litter size, and decreased pup weights in the absence of maternal toxicity. The LEL for embryofetotoxicity is 1000 mg/kg. The NOEL for maternal toxicity is > 1000 mg/kg.

A battery of mutagenicity studies have been submitted for EMH. EMH was weakly positive in the chromosomal aberration study in CHO cells with metabolic activation, but negative in the other tests for mutagenicity. Positive results were obtained when 1,3, dichloro,5-methyl-5-ethylhydantoin was tested for chromosomal aberrations in metabolically activated CHO cells. Positive results were also observed at the high dose in the unactivated compound. The test compound has been satisfactorily identified as requested bt Toxicology Branch. However, based on the absence of a NOEL for embryofetotoxicity, the study is still classified core-Supplementary. A new teratology study will be required for EMH.

TABLE 1

Implantation Sites	Group	Resorptions	Pup Weights
7	Control	1	48.5
	EMH	4	43.4
	DMH	5	46.5
9	Control	5	47.2
	EMH	4	43.4
	DMH	6	45.0
11	Control	6	45.4
	EMH	13	41.5
	DMH	6	44.0

HISTORICAL CONTROL DATA

In response to EPA letter of 7/16/87, the following information is provided for question 1b:

The supplementary information regarding a historical data base for the facility cannot be provided since this was the first reproduction study undertaken at the test laboratory. Reproductive studies began at FRI with the employment of Dr. Hoar. The study contract was awarded based on Dr. Hoar's recognition as a qualified investigator in this area of study. However, it is doubtful whether reference to a historical data base, even if available, would make immediately evident the basis for Dr. Hoar's position. The basic problem resides with the tabular representation of the data and its failure to reflect the variables which Dr. Hoar assumes to be self-evident. These assumptions become more obvious by a comparison of individual litters for each experimental group.

Appendix I of the study gives a comparison of each litter for the four experimental groups as a function of implantation sites which closely approximate the viable litter sizes at termination of the study. Under these conditions, the assumptions made by Dr. Hoar are clearly evident.

It can further be demonstrated by Appendix I that the majority of animals in the vehicle control group experienced a higher incidence of lower implantation sites and as a consequence, smaller viable litters. By contrast, almost 50% of the animals in each experimental group experienced 10 or more implantation sites and commensurate larger litters, as well, where an increase in late resorbtion and smaller fetal weight would not be unanticipated.

In addition, by differentiating reproduction performance on the basis of 9 or less and 10 or more implantation sites, the correspondence of data between control and experimental animals is even more clearly evidenced. Appendix II compares the mean values for variables of concern. This comparison demonstrates that in implantation sites of 9 or less there are no significant differences in the number of viable fetuses, resorbtion rates and mean pup weights between groups. Multiple resorbtions in the DMH and EMH groups are no different than that to be found in controls and in no instant did resorbtions within the same litter exceed 2 in any group.

Although no significant differences of the same variable were noted between groups at implantation sites of 10 or more, multiple resorptions within the same litter were more prevalent, particularly at implantation sites of 12, 13, 14 and 16 within two

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experimental groups. Although control animals at a like performance level were not available for comparison, increased resorbtion would not be unanticipated under these conditions. The absence of controls at like levels would have a significant influence on biasing overall mean averages unless consideration is given to these dissimilarities. Of particular significance, is the absence of differences when viewed with the represented objectivity.

Therefore, it can be concluded that at equivalent reproduction performance levels, there are no significant differences for the reported values in controls and DMH/EMH treated animals. Under these conditions and in the absence of any significant differences in abnormalities in the same group, it is valid and resonable to conclude the DMH/EMH are not teratogenic.

By contrast, although like differentiation can be made for the AN group, these animals demonstrated notable abnormalities of congenital origin, indicative of satisfactory experimental conditions.

APPENDIX I

REPRODUCTION PERFORANCE BY INDIVIDUAL LITTERS

Implant Sites	VEHICLE I	R	V	MPW	EMH I	R	V	MPW	DMH I	R	V	MPW	AN I	R	V	MPW
≤ 9	3	1	2	50.0	3	0	3	49.4	–	–	–	–	–	–	–	–
	–	–	–	–	3	0	3	42.3	–	–	–	–	–	–	–	–
	5	0	5	50.0	5	1	4	41.3	5	0	5	54.0	5	0	5	44.8
	–	–	–	–	6	2	4	42.7	6	1	5	43.4	6	2	4	37.8
	–	–	–	–	6	1	5	48.7	6	1	5	47.4	6	2	4	37.2
	7	0	7	43.7	7	0	7	36.2	7	1	6	47.1	7	7	0	*
	7	0	7	50.5	–	–	–	–	7	0	7	41.0	–	–	–	–
	–	–	–	–	–	–	–	–	7	2	5	46.5	–	–	–	–
	8	1	7	48.3	–	–	–	–	–	–	–	–	8	2	6	37.1
	–	–	–	–	–	–	–	–	–	–	–	–	8	1	7	38.0
	9	1	8	43.2	–	–	–	–	9	1	8	35.9	9	0	9	40.8
	9	2	6	45.9	–	–	–	–	–	–	–	–	–	–	–	–
	9	0	9	46.3	–	–	–	–	–	–	–	–	–	–	–	–
≥ 10	10	1	9	39.8	10	1	9	43.2	10	0	10	39.8	10	1	9	40.1
	–	–	–	–	10	2	8	36.8	–	–	–	–	10	3	7	31.9
	11	0	11	36.9	11	2	9	37.2	–	–	–	–	11	4	7	43.5
	–	–	–	–	11	4	7	38.1	–	–	–	–	11	2	9	36.7
	–	–	–	–	–	–	–	–	12	3	9	35.2	–	–	–	–
	–	–	–	–	–	–	–	–	13	4	9	35.5	–	–	–	–
	–	–	–	–	–	–	–	–	–	–	–	–	14	1	13	37.4
	–	–	–	–	–	–	–	–	16	3	13	23.0	–	–	–	–

I = Implantations. R = Resorbtions. V = Viable Fetuses. MPW = Mean Pup Weights.

* Not included in resorbtion calculations (TABLE II). Attribute appears to be a male deficiency inasmuch as near 70% of females impregnated by this buck resulted in abortions, nonpregnancies and/or total resorbtions.

APPENDIX II

MEAN VALUES (S.D.)

IMPLANT SITES	GROUP	# VIABLE FETUSES (SD)	# RESORBTIONS (SD)	BODY WEIGHTS (SD)
≤ 9	V	6.37 (1.99)	0.63 (0.69)	47.2 (2.7)
	EMH	4.33 (1.37)	0.67 (0.74)	43.4 (4.5)
	DMH	5.86 (1.12)	0.85 (0.64)	45.0 (5.3)
	AN	5.83 (1.77)	1.16 (0.89)	39.2 (2.8)
≥ 10	V	10.00 (1.00)	0.50 (0.50)	38.4 (1.5)
	EMH	8.25 (0.83)	2.25 (1.90)	38.8 (2.5)
	DMH	10.25 (1.64)	2.50 (1.50)	36.8 (2.1)
	AN	9.00 (2.19)	2.20 (1.67)	37.9 (3.8)

S.D. = Standard Deviation. V = Vehicle.