5-19-95

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

011557

MAY 19 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine.
Review of Toxicology Data.
DP Barcode: D212071. Submission #: S481738.

To: Kathryn Davis/Bonnie Adler PM# 52 Tox. Chem. No.: 481C
Reregistration Branch
Special Review and Reregistration Division (7508W)

From: Raymond K. Locke, Toxicologist Raymond K. Locke 5/1/95
Section II, Toxicology Branch I
Health Effects Division (7509C)

Thru: Joycelyn E. Stewart, Ph.D., Section Head 5/10/95
Section II, Toxicology Branch I
Health Effects Division (7509C)

KB 5/17/95

Registrants: A. B. M. Chemicals, Ltd.
Leeds, England

Angus Chemical Company
Northbrook, IL

Buckman Laboratories, Inc.
Memphis, TN

Action Requested: Review toxicology data submitted to support reregistration of hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine and indicate whether these data meet the requirements of the guidelines for these study types.

Discussion: The dermal sensitization study submitted for review (MRID No.: 155987) actually contains two studies: a dermal sensitization study in guinea pigs and a skin irritation test in rabbits. These two studies were reviewed separately.

Conclusion: Of the six studies reviewed, only the acute oral toxicity study in the rat (81-1; MRID No.: 416752-06) currently supports the reregistration of hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine. The remaining five studies are unacceptable, but upgradable with the submission of adequate data on the chemical identity, purity, and stability of the test substances used.

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The data presented demonstrate that, under the study conditions, the studies may be classified as follows:

MRID No.: 416752-06. Acute Oral Toxicity (Rat): LD_{50} = 1250 (840-1858) mg/kg b.w. for males and 763 (701-832) mg/kg b.w. for females. Toxicity Category III. Acceptable.

MRID No.: 155984. Acute Dermal Toxicity (Rabbit): LD_{50} > 2000 mg/kg b.w. for males and females. Toxicity Category III. Unacceptable, but upgradable.

MRID No.: 155985. Primary Eye Irritation (Rabbit): Severe eye irritant (corrosive). Toxicity Category I.
Unacceptable, but upgradable.

MRID No.: 155986. Primary Dermal Irritation (Rabbit): Non-irritating to the skin. Primary Cutaneous Irritation Index = 0.00. Toxicity Category IV.
Unacceptable, but upgradable.

MRID No.: 155987. Primary Dermal Irritation (Rabbit): Non-irritating to the skin. Primary Irritation Index = 0.06 (0.1% distilled water solution); 0.44 (1.0% distilled water solution). Toxicity Category IV.
Unacceptable, but upgradable.

MRID No.: 155987. Dermal Sensitization (Guinea Pig): Not a dermal sensitizing agent.
Unacceptable, but upgradable.

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Reviewed by: Raymond K. Locke, Toxicologist Raymond K. Locke 5/1/95 81-1
Section II, Tox. Branch I (7509C)
Secondary reviewer: Joycelyn E. Stewart, Ph.D. JES 5/9/95
Section Head, Section II, Tox. Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral - Rat TOX. CHEM. NO.: 481C

MRID NO.: 41675206

TEST MATERIAL: Busan 1060; clear yellow liquid
Lot No.: 9E-6107; (79.4% a.i.)

SYNONYMS: Hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine; Dihydro-5-(2-hydroxyethyl)-1,3,5-triazine-1,3(2H,4H)-dipropanol

STUDY NUMBER(S): 3138.47

SPONSOR: Buckman Laboratories, Inc.
1256 N. McLean Blvd.
Memphis, TN

TESTING FACILITY: Springborn Laboratories, Inc.
Mammalian Toxicology Division
553 North Broadway
Spencerville, OH

TITLE OF REPORT: Acute Oral Toxicity Study in Rats with Busan 1060

AUTHOR(S): Rusty E. Rush, B.A.

REPORT ISSUED: 9/29/89

EXECUTIVE SUMMARY: Distilled water solutions of Busan 1060 were administered as a single oral (gavage) dose to groups (5 animals/group) of male and female Sprague-Dawley rats. Male rats received doses of 0, 500, 1000, and 1500 mg/kg; female rats were dosed at 0, 500, 750, and 1000 mg/kg. Animals were observed daily for mortality and toxic and pharmacological signs and were weighed at study start, Day 8 and Day 15 (study termination), or at time of unscheduled death (if Day 2 or later). Animals that died on test and those sacrificed at study termination were subjected to gross necropsy. All survivors gained weight. Frequently observed clinical signs were: underactivity, breathing difficulties, prostration, soft stools, "cool-to-touch," decreased fecal production, fecal/urine stains, and dark material around the facial area. Gross pathology revealed no adverse findings in survivors at any dose level, with the single exception of one 500 mg/kg male that exhibited a dilated renal pelvis. Gross necropsy findings for animals found dead included: dark red adrenal glands, reddened mucosa of the digestive tract, dark red lymph nodes, and colored fluid/mucoid contents in the

digestive tract. The LD_{50} was calculated to be 1250 (840-1858) mg/kg for male rats and 763 (701-832) mg/kg for female rats.

Toxicity Category: III

Classification: Acceptable

MATERIALS: Busan 1060 (Lot No. 9E-6107; 79.4% a.i.), described as a clear yellow liquid, was the test chemical. The test chemical was administered orally (gavage) as a solution prepared in distilled water. Young adult male and female Sprague-Dawley rats were the test animals. Males weighed 182 to 219 grams and females weighed 173 to 203 grams at study start.

METHODS: Animals were randomly assigned to dosage groups and fasted overnight prior to dosing. Groups of five male and five female rats were administered distilled water solutions of Busan 1060 by gavage at doses of 0, 500, or 1000 mg/kg as a single dose. Additionally, a group of five female rats was dosed at 750 mg/kg and a group of five male rats was dosed at 1500 mg/kg. The single-sex dosage groups were employed because a dose range-finding study (discussed later) was thought to indicate sex-related differences in the lethality of Busan 1060. The volume of dosing solution administered was maintained at a constant of 10 ml/kg of body weight. These dose levels were based upon a preliminary dose range-finding study which was included as page 9 and Appendix II (pages 29 and 30) of this submission (MRID No.: 41675206).

In the dose range-finding study, groups (one male and one female) of Sprague-Dawley rats were fasted overnight and administered single oral doses (gavage) of distilled water solutions (constant dosing volume of 10 ml/kg) of Busan 1060 to yield dose levels of 0, 250, 500, 750, 1000, and 1500 mg/kg. Animals were observed for mortality for seven days. The results of this range-finding study (extracted from page 30 of this submission (MRID No.: 41675206) are presented on page 3 of this DER, and appear to be adequate for use in setting the dose levels for the definitive study.

In the definitive study (MRID No.: 41675206), animals were observed daily after dosing (Day 1) for mortality and toxic and pharmacological signs for a total of 15 days. Individual body weights were recorded prior to treatment on Day 1 and on Days 8 and 15 (study termination) of the study or at death. Gross necropsies were performed on all animals sacrificed at study termination, and on those found dead during the study.

STATISTICAL ANALYSIS: Mortality data were analyzed separately for male and female rats by probit analysis. LD_{50} values and 95% confidence intervals were calculated by the method of Litchfield

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and Wilcoxon (J. Pharmacol. Exp. Ther., 96:99-113, 1949). Body weight means and standard deviations were calculated.

QUALITY ASSURANCE: A signed and dated quality assurance statement is included in the submission.

RESULTS: All deaths occurred by Day 2 after dosing (Day 1), and the mortality data are shown in the following Table I:

Table I: Mortality Observed in the Acute Oral Toxicity Study of Busan 1060[a]

Dosage (mg/kg)	Mortality	
	Males	Females
500	0/5	0/5
750	ND[b]	2/5
1000	2/5	5/5
1500	3/5	ND

[a]Data extracted from page 9 of this submission (MRID No.: 41675206).
[b]Indicates that no data are available.

Frequently observed clinical signs in animals treated with Busan 1060 were: underactivity, breathing difficulties, prostration, soft stools, "cool-to-touch," decreased fecal production, fecal/urine stains, and dark material around the facial area. As shown in the following Table II, all survivors gained weight during the 15-day observation period.

Table II. Mean Body Weights of Surviving Animals Following Single Oral (Gavage) Doses of Busan 1060[a]

	Males		
Dose Level (mg/kg)	500	1000	1500
Day 1:	198[b]	199	211
	10.1[c]	9.3	7.5
	5[d]	5	5
Day 8:	273	259	246
	8.9	9.1	10.6
	5	3	2
Day 15:	322	303	294
	14.0	16.1	17.7
	5	3	2

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		Females	
Day 1:	187	190	183
	5.4	11.1	6.2
	5	5	5
Day 8:	223	233	0
	11.6	2.1	0.0
	5	3	0
Day 15:	244	250	0
	10.8	2.6	0.0
	5	3	0

[a]Data extracted from pages 16 and 17 of this submission (MRID No.: 41675206).
[b]Mean body weight of survivors.
[c]Standard deviation from the mean.
[d]Number of survivors for which mean was determined.

Gross pathology revealed no adverse findings in survivors at any dose level, with the single exception of one 500 mg/kg male that exhibited a dilated renal pelvis. Gross necropsy findings for animals found dead included: dark red adrenal glands, reddened mucosa of the digestive tract, dark red lymph nodes, and colored fluid/mucoid contents in the digestive tract. The LD_{50} was calculated to be 1250 (840-1858) mg/kg for male rats and 763 (701-832) mg/kg for female rats.

DISCUSSION: The data presented are consistent with the registrant's calculation of the LD_{50} values for male and female Sprague-Dawley rats. The study is classified acceptable. The data presented place Busan 1060 in Toxicity Category III for oral toxicity.

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Reviewed by: Raymond K. Locke, Toxicologist Raymond K. Locke 5/1/95 81-2
Section II, Tox. Branch I (7509C)
Secondary reviewer: Joycelyn E. Stewart, Ph.D. JS 5/9/95
Section Head, Section II, Tox. Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity - Rabbit

TOX. CHEM. NO.: 481C

MRID NO.: 155984

TEST MATERIAL: Bioban GK (no chemical identity, purity, or stability data given); yellow liquid with pungent odor

SYNONYMS: Hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine; Dihydro-5-(2-hydroxyethyl)-1,3,5-triazine-1,3(2H,4H)-dipropanol

STUDY NUMBER(S): 85-0866-21

SPONSOR: Angus Chemical Company
2211 Sanders Road
Northbrook, IL

TESTING FACILITY: Hill Top Research, Inc.
P. O. Box 42501
Cincinnati, OH

TITLE OF REPORT: Acute Dermal Toxicity Screen In Rabbits of Bioban GK

AUTHOR(S): Teri L. Hughes, et al.

REPORT ISSUED: 8/30/85

EXECUTIVE SUMMARY: Bioban GK (no chemical identity or purity data provided) was applied undiluted to the skin of five male and five female New Zealand White rabbits at a dosage level of 2 mg /kg of body weight. The exposure site (unabraded clipped flank skin) was occluded with rubber dental dam and exposure continued for 24 hours. Animals were weighed at study initiation (Day 0), Day 8, and at study termination (Day 15). At the end of the exposure period, the rubber dams were removed and animals were observed for mortality, moribundity, gross systemic toxicity, and dermal irritation once on the day of treatment and twice daily thereafter. No animals died on test. With the exception of one male, all animals appeared to be normal and gained weight during the entire study period. Gross necropsies were conducted on all animals at study termination; the one abnormal-appearing male exhibited mottled lungs, a complete depletion of body fat stores, a green-purple colored spleen, and a gall bladder distended with dark green fluid. Two other animals exhibited pale adrenal glands. None of these findings are considered to be related to treatment. Dermal application of Bioban GK caused dermal

irritation characterized by edema, erythema, necrosis, desquamation, and coriaceousness. The data presented demonstrate that the acute dermal LD_{50} of Bioban GK for both male and female New Zealand White rabbits is greater than 2000 mg/kg body weight.

Toxicity Category: III

Classification: Unacceptable, but upgradable if satisfactory data are submitted on the chemical identity, purity, and stability of the test substance.

MATERIALS: Bioban GK (no lot number, chemical identity, purity, or stability data submitted), described as a yellow liquid with a pungent odor, was the test chemical. The test chemical was administered neat (no vehicle). Young adult male and female New Zealand White rabbits were the test animals. Males weighed 2.07 to 2.67 kilograms, and females weighed 2.27 to 2.59 kilograms at study start.

METHODS: Animals were randomly assigned to dosage groups. They were housed individually and identified with ear tags and cage cards. Food (Purina Laboratory Chow) and water were available ad libitum. The fur on the trunks of five male and five female New Zealand White rabbits was clipped with electric clippers prior to dose administration. Bioban GK was applied to the inside surface of a sleeve of rubber dental dam, which was wrapped around the clipped trunk of the animals and secured with staples. A layer of gauze and tape was then applied to cover the dosed area. All animals received a dose of 2000 mg of Bioban GK/kg of body weight. Animals were restrained by a Newmann harness for 24 hours, and the binders were removed 24 hours after dose administration, and the exposed sites were gently wiped with a clean water-moistened towel to remove as much non-absorbed test material as possible, and a scoring of dermal irritation using a Draize scoring system was calculated for this time 24-hour period and once daily thereafter until study termination (Day 15). The animals were observed for mortality and toxic and pharmacological signs at 2-1/2 hours post-dosing on the day of dosing and twice daily thereafter for a total of 14 days. Individual body weights were recorded prior to treatment on Day 0 and on Days 8 and 15 (study termination) of the study. Body weight gain or loss was calculated for the entire 15-day period. All animals were sacrificed by "T-61 Euthanasia Solution" at study termination (Day 15), and gross necropsies were performed on all animals. No tissues were saved for later histopathological examination.

STATISTICAL ANALYSIS: Mean body weights (Days 0, 8, and 15) and body weight changes over the 15-day study period (and standard deviations) were calculated for the five male and five female New Zealand White rabbits on test [page 4 of this DER represents Table 1 from page 8 of this submission (MRID No.: 155984)].

QUALITY ASSURANCE: A signed and dated quality assurance statement is included in the submission.

RESULTS: All five female and five male rabbits survived to the end of the study (Day 15). At the end of the exposure period, the exposed areas of skin exhibited adhering test substance, suggesting poor absorption of Bioban GK. With the exception of one male, all animals appeared to be normal during the entire study period (Days 0-15). This one male exhibited fecal stains, emaciation, diarrhea, and (during Days 14-15) decreased production of feces. As these findings were observed in one animal only, they are not considered to be related to treatment with Bioban GK. Dermal application of Bioban GK caused dermal irritation characterized by edema, erythema, necrosis, desquamation, and coriaceousness. As shown in Table 1 on page 3 of this DER, with the exception of the one abnormal-appearing male (lost 830 grams during the study period), all animals gained weight during the study. Gross necropsy of the one abnormal-appearing male revealed mottled lungs, a complete depletion of body fat stores, a green-purple colored spleen, and a gall bladder distended with dark green fluid. Two other animals exhibited pale adrenal glands. None of these findings are considered to be related to treatment. The acute dermal LD_{50} of Bioban GK in both male and female New Zealand White rabbits was reported to be greater than 2000 mg/kg body weight.

DISCUSSION: The data presented are consistent with the registrant's report that the acute dermal LD_{50} of Bioban GK is greater than 2000 mg/kg body weight for both male and female New Zealand White rabbits. These data place Bioban GK in Toxicity Category III for acute dermal toxicity. However, this study must be classified as unacceptable, but upgradable with the submission of data on the chemical identity, purity, and stability of the test substance used.

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Reviewed by: Raymond K. Locke, Toxicologist Raymond K. Locke 5/1/95 81-5
Section II, Tox. Branch I (7509C)
Secondary reviewer: Joycelyn E. Stewart, Ph.D. JS 5/9/95
Section Head, Section II, Tox. Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation - Rabbit

TOX. CHEM. NO.: 481C

MRID NO.: 155987

TEST MATERIAL: Glokill 77 (Batch No.: K249; no data on chemical identity, purity, or stability); clear viscous liquid

SYNONYMS: Hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine; Dihydro-5-(2-hydroxyethyl)-1,3,5-triazine-1,3(2H,4H)-dipropanol

STUDY NUMBER(S): CL74:74:1024

SPONSOR: A.B.M. Chemicals Limited
Wortley Low Mills
Whitehall Road
Leeds LS12 4RF
England

TESTING FACILITY: Consultox Laboratories Ltd.
188 Brent Crescent
London, N.W. 10
England

TITLE OF REPORT: Glokill 77: Draize Skin Tests
(Report also contains a dermal sensitization test, which is reviewed separately)

AUTHOR(S): M. B. Thomas

REPORT ISSUED: July, 1974

EXECUTIVE SUMMARY: Glokill 77 (0.1 or 1.0% distilled water solution; 0.5 ml) was applied to clipped and depilated intact or abraded back skin of four New Zealand White rabbits for each dosing solution. The treatment sites were occluded with sterile gauze and exposure continued for 24 hours. The dose of Grokill 77 delivered as a 0.1% solution was 0.5 mg; that for the 1.0% solution was 5.0 mg. After 24 hours of exposure, the patches were removed and the skin reactions on both the abraded and unabraded skin scored by a Draize scoring system. Additional scores were recorded at 72 hours post-treatment. At a concentration of 0.1%, Glokill 77 was non-irritating to intact skin and, on abraded skin, produced only mild erythema in one

animal at 24 hours post-treatment, which was absent at 72 hours post-treatment. At a concentration of 1.0% on intact skin, Glokill 77 produced only mild erythema in one animal at 24 hours post-treatment, which was absent at 72 hours post-treatment; on abraded skin, mild erythema was evident at 24 hours post-treatment for all four animals, but this condition persisted only for one animal at 72 hours post-treatment. A Primary Irritation Index of 0.06 was calculated for the 0.1% solution of Glokill 77, with a corresponding value of 0.44 calculated for the 1.0% solution. These results place Glokill 77 in Toxicity Category IV for skin effects. However, this study must be classified as unacceptable, but upgradable with the submission of acceptable data on the chemical identity, purity, and stability of the test substance used.

Toxicity Category: IV

Classification: Unacceptable, but upgradable if satisfactory data are submitted on the chemical identity, purity, and stability of the test substance.

MATERIALS: Glokill 77 (Batch No.: K249; no data on chemical identity, purity, or stability), described as a clear viscous liquid, was the test chemical. The test chemical was utilized as 0.1% and 1.0% solutions in distilled water. Four Zealand White rabbits (no age, sex, body weight, or source data) were used to test each Grokill 77 dosing solution.

METHODS: This skin irritation test was conducted according to the procedure outlined in the "F.D.A. Handbook, Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics", F.D.A. (1959), page 47. The backs of the animals were shaved with electric clippers, and one-half of the clipped area was abraded with an abrading tool. For each of the two concentrations (0.1 and 1.0 %) of Grokill 77 distilled-water solutions used, 0.5 ml was applied to both intact and abraded back skin of four test animals. The treatment sites were occluded with a one-inch square of sterile gauze held in place with adhesive tape and further secured with "Stockinette" sleeves, which covered the entire trunk of the test animal. The dose of Grokill 77 delivered as a 0.1% solution was 0.5 mg; that for the 1.0% solution was 5.0 mg. After 24 hours of exposure, the patches were removed and the skin reactions on both the abraded and unabraded skin scored by a Draize scoring system. Additional scores were recorded at 72 hours post-treatment. The Primary Irritation Index for each Glokill solution was calculated by taking the arithmetic mean of all scores from both abraded and abraded sites for both the 24- and 72-hour observation periods.

STATISTICAL ANALYSIS: None

QUALITY ASSURANCE: No quality assurance statement is included in the submission for this 1974 report.

RESULTS: At a concentration of 0.1%, Glokill 77 was non-irritating to intact skin and, on abraded skin, produced only mild erythema in one animal at 24 hours post-treatment, which was absent at 72 hours post-treatment. At a concentration of 1.0% on intact skin, Glokill 77 produced only mild erythema in one animal at 24 hours post-treatment, which was absent at 72 hours post-treatment; on abraded skin, mild erythema was evident at 24 hours post-treatment for all four animals, but this condition persisted only for one animal at 72 hours post-treatment. The Draize scores recorded in this study are presented on pages 4 and 5 of this DER, which have been extracted from pages 6 and 7 of this submission (MRID No.: 155987). A Primary Irritation Index of 0.06 was calculated for the 0.1% solution of Glokill 77, with a corresponding value of 0.44 calculated for the 1.0% solution. These results place Glokill 77 in Toxicity Category IV for skin effects.

DISCUSSION: The data presented are consistent with the registrant's calculation of a Primary Irritation Index for a 0.1% distilled water solution of Glokill 77 as 0.06, and the corresponding value for a 1.0% solution as 0.44. However, this study must be classified as unacceptable, but upgradable with the submission of acceptable data on the chemical identity, purity, and stability of the test substance used.

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Reviewed by: Raymond K. Locke, Toxicologist Raymond K. Locke 5/1/95 81-6
Section II, Tox. Branch I (7509C)
Secondary reviewer: Joycelyn E. Stewart, Ph.D. JES 5/9/95
Section Head, Section II, Tox. Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization - Guinea Pig

TOX. CHEM. NO.: 481C

MRID NO.: 155987

TEST MATERIAL: Glokill 77 (Batch No.: K249; no data on chemical identity, purity, or stability); clear viscous liquid

SYNONYMS: Hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine; Dihydro-5-(2-hydroxyethyl)-1,3,5-triazine-1,3(2H,4H)-dipropanol

STUDY NUMBER(S): CL74:74:1024

SPONSOR: A.B.M. Chemicals Limited
Wortley Low Mills
Whitehall Road
Leeds LS12 4RF
England

TESTING FACILITY: Consultox Laboratories Ltd.
188 Brent Crescent
London, N.W. 10
England

TITLE OF REPORT: Glokill 77; Guinea Pig Sensitisation Test (This report also contains a Draize skin test, which is reviewed separately)

AUTHOR(S): M. B. Thomas

REPORT ISSUED: July, 1974

EXECUTIVE SUMMARY: The skin sensitization potential of Grokill 77 (no data on chemical identity, purity, or stability provided) was investigated in six young adult (300-400 g body weight) Hartley strain albino guinea pigs using a modified Draize procedure. Following nine induction intradermal injections (clipped and depilated back skin; 0.1 mg Grokill 77 delivered as 0.1 ml of a 0.1% distilled water solution) given every other day, followed by a two-week period of no treatment, a single challenge intradermal (same dose and procedure as for induction) gave no greater Draize scores for erythema and edema at 24 hours post-injection than scores for the same animal at 24 hours after induction injections. These data are consistent with the registrant's assertion that Grokill 77 is not a skin sensitizer.

However, this study must be classified as unacceptable, but upgradable with the submission of acceptable data on the chemical identity, purity, and stability of the test substance used.

Classification: Unacceptable, but upgradable with the submission of acceptable data on the chemical identity, purity, and stability of the test substance

MATERIALS: Glokill 77 (Batch No. K249; no data on chemical identity, purity, or stability provided), described as a clear viscous liquid, was the test chemical. The test chemical was administered by injection, using a 0.1% solution in distilled water. Six male Hartley strain albino guinea pigs (source not reported) were the test animals. Animals weighed 300 to 400 grams at study start.

METHODS: This dermal sensitization study was conducted using a modification of the Draize technique (Draize, Woodward and Calvary, 1944; National Academy of Sciences-National Research Council, 1964). No information is provided regarding animal housing, diet or water used, or method of identification of individual test animals. Hair was removed from the flanks and backs of the test animals by clipping with electric clippers following by treatment with depilatory cream (product not identified). A 0.1% solution of Glokill 77 was prepared in distilled water just prior to each induction or challenge injection procedure. For induction, each guinea pig was injected intradermally with 0.1 ml of this dosing solution on the clipped back area (resulting in 0.1 milligrams of Glokill 77 being injected). This procedure was repeated every other day, using a different injection site for each treatment, for a total of nine injections. At 24 hours post-injection, the injection sites were examined and scored by a Draize scoring system for erythema and edema. After the ninth induction injection, the animals were left untreated for a period of two weeks. A single challenge injection (same dose as for induction injections) was administered and, after 24 hours, the sites were scored for erythema and edema using the same Draize scoring system used during the induction phase. The Draize scores resulting from the challenge dose were compared with those obtained during the induction phase to determine whether sensitization to Glokill 77 had been produced.

STATISTICAL ANALYSIS: None

QUALITY ASSURANCE: No quality assurance statement is included in the submission for this 1974 report.

RESULTS: All animals survived to study termination. Slight erythema and/or edema were noted in all animals after each of the induction injections. No greater edema and/or erythema was noted in any animal following the challenge injection than had been

observed in the same animal following the induction injections. The Draize scores are presented on page 4 of this DER [extracted from page 8 of this submission (MRID No.: 155987)]. These data are consistent with the registrant's assertion that Grokill 77 is not a skin sensitizer.

DISCUSSION: The data presented are consistent with the registrant's assertion that Grokill 77 does not cause dermal sensitization reactions under the test conditions employed. However, this study (MRID No.: 155987) must be classified as unacceptable, but upgradable with the submission of acceptable data on the chemical identity, purity, and stability of the test substance used.

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____ Description of the product manufacturing process.

____ Description of quality control procedures.

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____ A draft product label.

____ The product confidential statement of formula.

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Reviewed by: Raymond K. Locke, Toxicologist Raymond K. Locke 5/1/95 81-5
Section II, Tox. Branch I (7509C)
Secondary reviewer: Joycelyn E. Stewart, Ph.D. JS 5/9/95
Section Head, Section II, Tox. Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation - Rabbit

TOX. CHEM. NO.: 481C

MRID NO.: 155986

TEST MATERIAL: Glokill 77 (Batch No.: TS704; no data on chemical identity, purity, or stability); clear colorless viscous liquid

SYNONYMS: Hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine; Dihydro-5-(2-hydroxyethyl)-1,3,5-triazine-1,3(2H,4H)-dipropanol

STUDY NUMBER(S): 317/8505

SPONSOR: A.B.M. Chemicals Limited
Wortley Low Mills
Whitehall Road
Leeds LS12 4RF
England

TESTING FACILITY: Safepharm Laboratories Limited
P. O. Box No. 45
Derby DE1 2BT
England

TITLE OF REPORT: Primary Dermal Irritation Test: Determination of the Degree of Primary Cutaneous Irritation Caused by Glokill 77 in the Rabbit

AUTHOR(S): R. L. Guest and T. A. Collier

REPORT ISSUED: 5/23/85

EXECUTIVE SUMMARY: Glokill 77 (undiluted; 0.5 ml) was applied to clipped back skin of six young adult (12-16 weeks of age; no sex data given) New Zealand White rabbits. The test sites were occluded with a patch of surgical gauze and elasticized corsets (Tubigrip), and exposure continued for 4 hours. Test sites were swabbed with cotton wool soaked in distilled water, and skin irritation was scored using a Draize method at 1, 24, 48, and 72 hours post-treatment. Glokill 77 produced minimal erythema in 3 rabbits and minimal edema in one rabbit at one hour post-dosing. However, these effects had disappeared at 24 hours post-dosing, and no other effects were observed throughout the 72-hour study period. The calculated Primary Cutaneous Irritation Index for

Glokill 77 was reported to be 0.0. These data place Glokill 77 in Toxicity Category IV for skin effects. However, this study must be classified as unacceptable, but upgradable with the submission of acceptable data on the chemical identity, purity, and stability of the test substance used.

Toxicity Category: IV

Classification: Unacceptable, but upgradable if satisfactory data are submitted on the chemical identity, purity, and stability of the test substance.

MATERIALS: Glokill 77 (Batch No.: TS704; no data on chemical identity, purity, or stability), described as a clear colorless viscous liquid, was the test chemical. The test chemical was administered neat (no vehicle). Young adult (12-16 weeks of age; no sex data given) New Zealand White rabbits (obtained from Nottingham University, School of Agriculture) were the test animals. Animals ranged in weight from 2.32 to 2.90 kilograms at study start.

METHODS: Approximately 24-hours prior to study initiation, the dorsal/flank areas of several animals were clipped with electric clippers. Only animals with healthy intact epidermis were selected for use in this study. They were housed individually and identified with indelible markings on the inner surface of the ear and cage cards. Food (Rabbit Diet, A. W. Tindall Limited) and water were available ad libitum. To a two-layer thick surgical gauze patch (2.5 cm^2) was applied 0.5 ml of undiluted Glokill 77. The patch was applied to a suitable clipped test site on the back of each animal and was held in place with adhesive strapping ("Sleek"; Smith and Nephew Limited). The trunk of each animal was then wrapped in an elasticized corset (Tubigrip), and the animals were returned to their individual cages for the 4-hour exposure period. After 4 hours, the corset was removed and any residual test substance gently swabbed with cotton wool soaked in distilled water. Scorings for primary dermal irritation using a Draize scoring system were conducted at 1, 24, 48, and 72 hours after the 4-hour exposure period.

STATISTICAL ANALYSIS: None

QUALITY ASSURANCE: A signed and dated quality assurance statement is included in the submission.

RESULTS: Glokill 77 produced minimal erythema in 3 rabbits and minimal edema in one rabbit at one hour post-dosing. However, these effects had disappeared at 24 hours post-dosing, and no other effects were observed throughout the 72-hour study period. The calculated Primary Cutaneous Irritation Index for Glokill 77

was reported to be 0.0. The individual Draize scores for all observation periods are presented on page 4 of this DER [extracted from page 10 of this submission (MRID No.: 155986)]. These data place Glokill 77 in Toxicity Category IV for skin effects.

DISCUSSION: The data presented are consistent with the registrant's calculation of the Primary Cutaneous Irritation Index for Glokill 77 as 0.0. However, this study must be classified as unacceptable, but upgradable with the submission of acceptable data on the chemical identity, purity, and stability of the test substance used.

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Reviewed by: Raymond K. Locke, Toxicologist Raymond K. Locke 5/9/95 81-4
Section II, Tox. Branch I (7509C)
Secondary reviewer: Joycelyn E. Stewart, Ph.D. 5/9/95
Section Head, Section II, Tox. Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation - Rabbit

TOX. CHEM. NO.: 481C

MRID NOs.: 41675206; 155984

TEST MATERIAL: Glokill 77 (no chemical identity, purity, or stability data given); clear liquid

SYNONYMS: Hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine; Dihydro-5-(2-hydroxyethyl)-1,3,5-triazine-1,3(2H,4H)-dipropanol

STUDY NUMBER(S): 371/8408

SPONSOR: ABM Chemicals Limited
Wortley Low Mills
Whitehall Road
Leeds LS12 4RF
England

TESTING FACILITY: Safepharm Laboratories Limited
P. O. Box No. 45
Derby DE1 2BT
England

TITLE OF REPORT: OECD Eye Irritation Test: Determination of the Degree of Ocular Irritation Caused by Glokill 77 in the Rabbit

AUTHOR(S): T. A. Collier and J. C. Axelrad

REPORT ISSUED: 9/3/84

EXECUTIVE SUMMARY: Glokill 77 (undiluted; 0.1 ml) was instilled into the right eyes of six young adult (12-16 weeks of age; no sex data given) New Zealand White rabbits and eye irritation was scored using a Draize method at 1, 24, 48, and 72 hours post-treatment. Glokill 77 was a severe eye irritant (corrosive) for all six animals on test. Effects at 72 hours included iritis, beefy-red coloration of the conjunctivae accompanied with considerable swelling, copious discharge from the eye, and areas of complete corneal opacity. These data place Glokill 77 in Toxicity Category I for eye irritation. However, this study must be classified as unacceptable, but upgradable with the submission of acceptable data on the chemical identity, purity, and stability of the test substance used.

Toxicity Category: I

Classification: Unacceptable, but upgradable if satisfactory data are submitted on the chemical identity, purity, and stability of the test substance.

MATERIALS: Glokill 77 (no lot number, chemical identity, purity, or stability data submitted), described as a clear liquid, was the test chemical. The test chemical was administered neat (no vehicle). Young adult (12-16 weeks of age; no sex information provided) New Zealand White rabbits (obtained from Nottingham University, School of Agriculture) were the test animals. Animals ranged in weight from 2.53 to 3.10 kg at study start.

METHODS: Animals were examined within 24 hours of study start with an ophthalmoscope and six animals having no ocular lesions were selected for the study. They were housed individually and identified with indelible markings on the inner surface of the ear and cage cards. Food (Rabbit Diet, A. W. Tindall Limited) and water were available ad libitum. For each animal, 0.1 ml of undiluted Glokill 77 was instilled into the right eye. The eyelids were then held together for about one second to prevent leakage of the test material from the eye. The left eye of each animal remained untreated and served as a control. Eye irritation was scored using a Draize method at 1, 24, 48, and 72 hours following treatment. Eyes were examined with a standard ophthalmoscope and, after the 24-hour irritation scoring was completed, corneal opacity was also investigated at this and remaining observation periods with UV light after instillation of 0.05 ml of fluorescein B.P. into the eye. Due to the severity of the ocular reactions, all test animals were sacrificed following the eye irritation readings made at 72 hours post-treatment.

STATISTICAL ANALYSIS: None

QUALITY ASSURANCE: A signed and dated quality assurance statement is included in the submission.

RESULTS: Glokill 77 was a severe eye irritant (corrosive) for all six animals on test. Effects at 72 hours included iritis; beefy-red coloration of the conjunctivae accompanied with considerable swelling, copious discharge from the eye, and areas of complete corneal opacity. Page 3 of this DER, extracted from page 11 of this submission (MRID Nos.: 41675206 and 155985), presents the Draize eye irritation scores, which resulted in a Group Total Score of 239.

DISCUSSION: These data place Glokill 77 in Toxicity Category I for eye irritation. However, this study must be classified as unacceptable, but upgradable with the submission of acceptable data on the chemical identity, purity, and stability of the test substance used.

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