

US EPA HPV Chemical Challenge Program

ROBUST SUMMARIES FOR TRIGLYCIDYL ISOCYANURATE

**CHEMICAL NAME: S-TRIAZINE-2,4,6(1H,3H,5H)-TRIONE, 1,3,5-TRIS(2,3-EPOXYPROPYL)-
(CAS No. 2451629)**

**CONSORTIUM NAME: *HUNTSMAN-NISSAN-TGIC*
CONSORTIUM NUMBER:**

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This document was reviewed by the officials at Huntsman Corporation (and its predecessor companies, Vanitico and Ciba Specialties) and Nissan Chemical Industries, Inc.

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Physical/Chemical Elements

1a

1 Melting Point

TEST SUBSTANCE

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 102

GLP(Y/N): Unknown

Year Study Performed: 1994

Remarks for Method:

RESULTS:

Precision: =

Melting Point Value: 95

Upper Value: 0

Unit: °C

Decomposition: Yes

Sublimation: No

Results Remark:

Purity: 97%

CONCLUSIONS:

Submitter's Comments: The endpoint has been obtained from the published literature (NICNAS, 1994).

DATA QUALITY

Reliability: Klimisch Code 1b

Data Reliability Remarks: Reliable without restriction; Comparable to guidelines/standards

REFERENCES

1) NICNAS (1994) Priority Existing Chemical No. 1- Triglycidyl Isocyanurate, full public report, National Industrial Chemicals Notification and Assessment Scheme. Canberra, Australian Government Publishing Service, April.

2) International Programme on Chemical Safety (IPCS). CICADS 1999.

3) The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 128. Triglycidyl Isocyanurate. Editor - in - Chief: Staffan Marklund, National Institute for Working Life, 2001, Stockholm, Sweden.

2a

2 Boiling Point

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 102

GLP (Y/N): Unknown

Year Study Performed: 1994

Remarks for Methods: Product has been shown to decompose at temperatures greater than 250 degrees C. An accurate boiling point cannot be determined.

RESULTS:

Precision: =

Boiling Point Value: 0

Upper Value: 0

Unit: $^{\circ}$ C

Pressure: 760.00

Pressure Unit: mm Hg

Decomposition: Yes

Results Remarks: Product has been shown to decompose at temperatures greater than 250 degrees C. An accurate boiling point cannot be determined.

CONCLUSIONS:

Submitter's Comments: None.

DATA QUALITY:

Reliability: Klimisch Code 1b

Data Reliability Remarks: Comparable to guideline/standards.

REFERENCES:

1) NICNAS (1994) Priority Existing Chemical No. 1- Triglycidyl Isocyanurate, full public report, National Industrial Chemicals Notification and Assessment Scheme. Canberra, Australian Government Publishing Service, April.

2) International Programme on Chemical Safety (IPCS). CICADS 1999.

3) The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 128. Triglycidyl Isocyanurate. Editor - in - Chief: Staffan Marklund, National Institute for Working Life, 2001, Stockholm, Sweden.

3a

3 Vapor Pressure

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Gas Saturation Procedure, 50 FR 39252 (Vol. 50, No. 188, printed September 27, 1985).

GLP (Y/N): No

Year Study Performed: 1997

Remarks for Method:

The vapor pressure is too low to measure accurately. The value given is the detection limit of the method used.

RESULTS:

Precision: =

Vapor Pressure Value: 7.2

Upper Value: 0.00

Unit: mPa

Temperature: 20

Decomposition: Yes

Results Remarks:

The vapor pressure is too low to measure accurately. The value given is the detection limit of the method used.

DATA QUALITY:

Reliability: Klimisch Code 1b

Data Reliability Remarks: Reliable without restriction; comparable to guideline/standards.

REFERENCES:

1) NICNAS (1994) Priority Existing Chemical No. 1- Triglycidyl Isocyanurate, full public report, National Industrial Chemicals Notification and Assessment Scheme. Canberra, Australian Government Publishing Service, April.

2) International Programme on Chemical Safety (IPCS). CICADS 1999.

4a

4 Partition Coefficient

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 107

GLP (Y/N): Unknown

Year Study Performed: 1994

Remarks for Method:

RESULTS:

Precision: =

Value of Log Pow: - 0.80

Upper Value: 0.00

Temperature: 95

Results Remark:

Water solubility is 9 g/L at 25 degrees Celsius.

CONCLUSIONS:

The endpoint has been obtained from the published literature. NICNAS (1994).

DATA QUALITY:

Reliability: Klimisch Code 1b

Data Reliability Remarks: Reliable without reservation. Comparable to guideline/standards.

REFERENCES:

1) NICNAS (1994) Priority Existing Chemical No. 1- Triglycidyl Isocyanurate, full public report, National Industrial Chemicals Notification and Assessment Scheme. Canberra, Australian Government Publishing Service, April.

2) International Programme on Chemical Safety (IPCS). CICADS 1999.

5a

5 Water Solubility

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 105
GLP (Y/N): Unknown
Year Study Performed: 1985
Remarks for Method:

Method of detection and analysis include infrared spectroscopy, mass spectroscopy, epoxy equivalent weight, gas chromatography and high-performance liquid chromatography.

RESULTS:

Precision: =
Water Solubility Value: 10
Upper Value: 0
Unit: g/L
Temperature: 25
Solubility Category: Soluble
pH Value: 7
pKa Value: 1

Results Remark:

The water solubility of the technical grade substance is 10 g/litre at 25⁰C.

CONCLUSIONS:

The endpoint has been obtained from the published literature. (MSDS. Nissan Chemical Industries, Ltd. 1985.)

DATA QUALITY:

Reliability: Klimisch Code 1b.
Data Reliability Remarks: Reliable without restriction; Comparable to guideline/standards.

REFERENCES:

- 1) Material Safety Data Sheet. Nissan Chemical Industries, Ltd. 1985
- 2) Budnowski M. Preparation and Properties of the diastereoisomeric 1,3,5-triglycidyl-s-triazinetriones. Angew Chem Internat Edit & (10) 827 - 828: 1968.

Environmental Fate and Pathway Elements

6a

6 Photodegradation

TEST SUBSTANCE

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

Since there is no relevant information on the Photodegradation of TGIC, we have used the data on triazine herbicide that contain the triazine moiety as present in TGIC. The studies that we reference are: The Photodegradation of Triazine-Based Pesticides ⁽¹⁾, and Photodegradation of Sodium Cyanurate and Selected Herbicides in Aqueous Solutions and Soil ^(2,4,5).

METHOD:

Method/Guideline Followed: Other (see below)
Light Source: LASER
Light Source Spectrum in nm: 193 (ArF) excimer laser, 248 (KrF) excimer laser, 266 Nd³⁺ YAG, 308 (XeCL) excimer Laser.
Relative Intensity: 20 ns and 15 ns for the 266 Nd³⁺ YAG
Absorption Spectrum of Substance: 293 \pm 2 K.
GLP(Y/N): unknown
Year Study Performed: unknown
Remarks for Method:

RESULTS:

Concentration Value: pH ca. 7 with 193, 248, 266 and 308 nm light.
Unit: nm
Photon energies: 6.40, 5.00, 4.67, and 4.03 eV).
Direct Photolysis Precision:=
Direct Photolysis: 0% after 20 ns.
Indirect Photolysis: Water (ground, river, lake, marine) samples (2-10mg/L), and soil samples (5-20 mg/kg).
Sensitizer: N/A
Sensitizer Concentration: N/A
Sensitizer Unit: N/A
Rate Constant: 26-73 days for water and 12-40 days for soil.
Breakdown Products: None
Results Remarks:

The photoionization of the triazine derivatives is around 9.9eV, of which 6.4 eV are provided by the exciting 193 nm photons and 3.5 eV come from the hydration of the photoionization products.

From an environmental point of view since the only photo-initiated processes were observed when exciting with 193 nm light, which is not contained in the solar spectral irradiance. This in practice means that the triazines do not undergo Photodegradation to sunlight.

CONCLUSIONS:

Submitter's Comments: No relevant information on Photodegradation of TGIC in water or soil is available. In aqueous solutions, TGIC is sparingly soluble (5g/100ml water at pH). Photolysis is likely to accelerate hydrolysis resulting in ring opening of three epoxide rings to give hydroxylated compounds (Tepol). Sunlight may accelerate polymerization of TGIC when it is present in the soil (undergoes UV-curing process, similar to the process in powder coatings). It is expected to be bound tightly to soil as a cross-linked polymer and the resultant product is unlikely to be leached into ground water or enters the surface water.

TGIC contains three epoxide (oxirane) moieties attached to the triazine moiety. Influence of light on TGIC in water is likely to facilitate rapid hydrolysis leading to ring opening of the epoxide moieties giving rise to trihydroxy compound. The triazine ring would be resistant to photolysis in the ultraviolet region (e.g., wavelengths at 248 nm, 266 nm, and 308 nm) based on the Photodegradation studies on triazine herbicides (atrazine and related compounds). Studies on cyanuric acid (as sodium salt) further showed that the triazine moiety is resistant to Photodegradation under the influence of sunlight.

REFERENCES

- 1) M. Cranle L., Mi.I. Fernandez, J.A. Santaballa and S. Steenken. Photodegradation of Triazine-based Herbicides. www.ch.ic.ac.uk/ectoc/echet98/pub/108/
- 2) H.C. Hu. "Photodegradation study of Aqueous Sodium Salt Solutions of 2,4,6-Trihydroxy-1,3,5-Triazine"; Unpublished Study Conducted by Center Analytical Services. Princeton Chemical Research & Development Center, Princeton, NJ 08540 for the Isocyanurate Industry Ad Hoc Committee (EPA Consortium 55643); Study No. International Programme on Chemical Safety (IPCS). CICADS 1999.
- 3) A. Rezig, T. Nguyen, D. Martin, L. Sung, X. Gu, J. Jasmin, and J. W. Martin. NIST. Relationship between Chemical Degradation and Thickness Loss of an Amine-cured Epoxy Coating Exposed to Different UV Conditions.
- 4) I.K. Konstantinou, A.K. Zarkadis, and T.A. Albanis. Photodegradation of Selected Herbicides in Various Natural Waters and Soils under Environmental Conditions. J. of Environmental Quality 30: 121-130 (2001).
- 5) E. Evgenidou, K. Fytianos. Photodegradation of Triazine Herbicides in Aqueous Solutions and Natural Waters. J. Agric. Food Chem. 2002 Oct.23;50(22): 6423-7.
- 6) C. Ganapathy. Dept. of Pesticide Regulation. Environmental Fate of Hexazinone. May1, 1996.

7a

7 Stability in Water

TEST SUBSTANCE

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 111

Test Type: Abiotic

GLP(Y/N): Unknown

Year Study Performed: 1987

Remarks for Method:

After extraction with HPLC eluent, the sample is analyzed by using HPLC using UV detection

RESULTS:

Nominal Concentration: NA

Measured Concentration: 9

Precision =

Hydrolysis Results: N/A

Upper Value: N/A

Unit: g/L

pH Value: 2, 7, 11

Temperature: 25°C

Breakdown Product: None

Results Remarks:

pH	Temperature °C	t ½ Hours
7	25	160
7	60	4.5
7	70	1.25
2	25	1
1	25	0.66

CONCLUSIONS:

Submitter's Comments: The endpoint has been obtained from the published literature (NICNAS, 1994).

DATA QUALITY

Reliability: Klimisch Code 1b

Data Reliability Remarks: Reliable without restriction; Comparable to guidelines/standards

REFERENCES

- 1) Ciba - Geigy AG: Stability in Water of PT810. 1987
- 2) NICNAS (1994) Priority Existing Chemical No. 1- Triglycidyl Isocyanurate, full public report, National Industrial Chemicals Notification and Assessment Scheme. Canberra, Australian Government Publishing Service, April.
- 3) International Programme on Chemical Safety (IPCS). CICADS 1999.
- 4) The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 128. Triglycidyl Isocyanurate. Editor - in - Chief: Staffan Marklund, National Institute for Working Life, 2001, Stockholm, Sweden.

8a

8 Transport and Distribution (Fugacity)

TEST SUBSTANCE

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Other

Test Type: N/A

GLP(Y/N): Unknown

Year Study Performed: 2001

Remarks for Method:

-Fugacity calculated using EPIWIN (Estimation Program Interface for Windows)

3.05; US EPA version for Windows.

Input parameters were as follows;

Molecular Weight: 297.27

Henry's LC: 3.37e-007 atm-m³/mole (Henry database)

Vapor pressure: 9.63e-011 mm Hg (Mpbpwin program)

Liquid VP: 8.08e-009 mm Hg (super-cooled)

Melting point: 220⁰C (Mpbpwin program)

Log Kow: 1.21 (Kowwin program)

Soil Koc: 6.65 (calc by model)

RESULTS:

Media: Air, water, soil and sediment

Distribution Concentration:

Air: 0.665%

Water: 47.8%

Soil: 51.5%

Sediment: 0.102%

Results Remark:

-Data calculated by EPIWIN

Vapor Pressure: 9.63e-011 mm Hg

Liquid VP: 8.08e-009 mm Hg (super-cooled)

Log Kow: 1.21 (Kowwin program)

Henry's LC: 3.37e-007 atm-m³/mole (Henry database)

Soil Koc: 6.65 (calc by model)

Level 3 distribution modeling: t $\frac{1}{2}$ air: 13.78 hours, water and soil: 900 hours,

Sediment: 3600 hours.

CONCLUSIONS:

N/A

DATA QUALITY

Reliability: Klimisch Code 1b

Data Reliability Remarks: Estimated Value based on accepted model.

REFERENCES

Fugacity Model (TGIC)

9a

9 Biodegradation

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 302 B (May 1981)

Test Type: Aerobic

GLP (Y/N): Yes

Year Study Performed: 1993

Contact Time: 28

Inoculum: Activated sludge bacteria from a municipal STP

Remarks for Method:

1) Bacteria collected from activated sewage sludge from treatment plant CH-4153 Reinach on 9/28/92. The Ph after collection was 7.0. The preparation was conducted in accordance with the Zahn-Wellens method. The concentration of the test system was adjusted to 1g/l (dry weight of inoculum). After a preadaption phase of 21 days with the test substance at a concentration of 100 +/- 5 mg/l the biomass was collected for the CO2 Evolution Test. The final concentration of the test substance was 25 mg/l (dry weight suspended solids).

2) Temperature was 22 +/- 2 degrees C.

3) Air flow was 25 ml/min purified from carbon dioxide.

4) Test concentrations were 11.3 or 21.1 mg test substance per liter.

5) Sampling was conducted on days 0, 2, 6, 9, 13, 16, 20, 23, 27, and 28

6) Appropriate blanks and reference materials were used.

7) Evolved CO2 was captured in a sodium hydroxide filled absorption chamber.

8) Calculations and statistical methods were conducted in accordance with the guideline.

9) This study utilizes a "blank" and a "referenced" substance.

10) Method was OECD-Guideline no 302B (12.May 1981). Suggested in ISO 9439:1990(E), Chapter 8.2

RESULTS:

Precision: =

Degradation Value: 10

Upper Value: 0

Time Frame: 28

Time Units: Days

Breakdown Products: Unknown

Results Remarks:

1) Biodegradation of test substance at a concentration of 11.3 mg/l was 10% after 5 days and 44% after 28 days. Using a test substance concentration of 21.1 mg/l, biodegradation was 1% after 28 days.

2) Objective: Determination of the inherent biodegradability by measurement of the carbon dioxide formation in percent of THO₂ (Theoretical Carbon Dioxide) calculated from the ThOC (Theoretical Organic Carbon) or TOC (total Organic carbon).

3) Deviations: For the CO₂ evolution test, the volume of the test solution was reduced from 3.0:1 to 1.5:1. The CO₂ formed by biodegradation was absorbed with NaOH and determined on a carbon analyzer. Due to the poor solubility of the test substance in water, no stock solution was prepared and an emulsifier was used to achieve a better distribution in the medium.

CONCLUSIONS:

Using 11.3 mg of test substance/liter, biodegradation was 44% in 28 days. Using 21.3mg test substance/liter, biodegradation was 1% in 28 days. The conclusion is the test substance is inherently biodegradable under the specified test conditions.

DATA QUALITY:

Reliability: Reliability Code 1. See statement & reference below.

Data Reliability Remarks:

OECD/GLP Study (May 12, 1981). See reference below.

GENERAL COMMENTS:

Due to the poor water solubility of the test substance, an emulsifier (polyoxyethylene-Sorbitan-Monooleate [Tween 80]) was used to achieve a better distribution in water.

REFERENCES:

1) Report on the Test for Inherent Biodegradability in a Combined Zahn-Wellens/Carbon Dioxide Evolution Test of Araldite PT 810. Test No. 928394; Test Substance TK 10622 (TGIC); Study Director-W. Baumann; Testing Facility, Ciba-Geigy, Basel, Switzerland; Study Completed 2/5/93; Sponsor, Ciba-Geigy Basel, Switzerland.

2) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

9b

9 Biodegradation

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 301a-f(b), (Paris 1981)

Test Type: aerobic

GLP (Y/N): Yes

Year Study Performed: 1988

Contact Time: 28

Inoculum: activated sludge, domestic, non-adapted

Remarks For Method:

- 1) Duration was 28 days.
- 2) Temperature was 22 +/- 2 degrees C.
- 3) Deviations: The volume of the test solution was reduced from 3.0 l to 1.5 l. The CO₂ formed by biodegradation was absorbed in NaOH and determined on a carbon analyzer.
- 4) Reference substance was 20 mg/l.
- 5) Test substance concentration was 10 and 20 mg test substance /l.
- 6) Blank was water, as specified in the guideline.
- 7) Calculations: The biodegradation was calculated on the basis of the theoretical carbon content of the test substance and the cumulative quantities of carbon dioxide determined on the days of measurements (0, 5, 9, 12, 15, 20, 23, 27, and 28). For the calculation the formula is provided in the guideline was used.

RESULTS:

Precision: =

Degradation Value: 9

Upper Value: 0

Time Frame: 28

Time Units: Days

Breakdown Products: Yes

Results Remarks:

The biodegradation for the Test Substance at concentrations of 10 and 20 mg/l was 9% and 48%, respectively.

The biodegradation for the Reference Substance at a concentration of 20 mg/l was 90.1% during the 28 day test.

CONCLUSIONS:

According to the definition of the OECD expert group on biodegradation and bioaccumulation given in the OECD-guideline for testing of chemicals (1981), TK 10622 is not readily biodegradable in this test.

DATA QUALITY:

Reliability Code 1

Data Reliability Remarks: OECD Protocol and Report - data quality are acceptable.

REFERENCES:

- 1) Report on the Test for Ready Biodegradability of TK 10622 (Araldite PT 810) in the Modified Sturm Test, 6/23/88.
- 2) CIBA-GEIGY Ltd., Basel, Switzerland; GU3-Ecotoxicology
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

9c

9 Biodegradation:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD 301B: Ready Biodegradability: CO2 Evolution (Modified Sturm Test)

Test Type: aerobic

GLP (Y/N): Yes

Year Study Performed: 1997

Contact Time: 43

Inoculum: activated sludge, domestic, adapted

Remarks for Methods:

- 1) Test material was TK 10 622 (ARALDIT PT 810).
- 2) The objective of this study was to determine the ready biodegradability of Araldite PT 810 (TK 10622) in a 28 day biodegradation test (prolonged to 43 days) by following the carbon dioxide evolution of the test article in the incubation flasks.
- 3) The biodegradation of the test article was followed by exposing it to activated sludge from the aeration tank of a domestic waste water treatment plant. As a reference compound (procedure control), Aniline was tested simultaneously under the same conditions.
- 4) The inoculum was activated sludge from a domestic waste water treatment plant located in ARA Ergolz II, Fuellinsdorf/ Switzerland.
- 5) Test duration was 44 days (43 day exposure period).
- 6) Test temperature was 22 degrees C.
- 7) CO2-free air: The air was led through a bottle containing about 500 ml 2 M NaOH to trap CO2. The CO2 free air was sparged through the scrubbing solutions at a rate corresponding to about 30-100 ml/min.
- 8) The pH was 7.5-7.6 (measured at the beginning of the test in all test flasks).

RESULTS:

Precision: >

Degradation Value: 0

Upper Value: 0

Time Frame: 43

Time Units: Days

Breakdown Products: No

Results Remarks:

1) In the abiotic control containing PT 810 (TK 10622) and sterile test medium, no abiotic degradation was noted over the 43 day exposure period.

2) In the toxicity control, containing both PT 810 (TK 10622) and the reference compound Aniline, no inhibitory effect on the microorganisms was observed.

3) The results presented were expressed as % biodegradation:

* Degradation rate after 7 days: -5.5% / -7.3%.

* Degradation rate after 14 days: -7.4% / -9.4%.

* Degradation rate after 28 days: -4.9% to -5.7%.

* Degradation rate at the end of the test (day 43): -5.3% to -3.5%.

CONCLUSIONS:

Under the present test conditions, PT 810 (TK 10622) showed no signs of biodegradation. It was found to be nonbiodegradable and nondegradable (in the absence of activated sludge) over the 43 day test period. Furthermore, PT 810 (TK10622) showed no inhibitory effect on the microorganisms.

DATA QUALITY:

Reliability: Reliability Code 1

Data Reliability Remarks: OECD Protocol and Report-data quality are acceptable.

REFERENCES:

1) Ready Biodegradability of PT 810 (TK 10622) in a CO₂ Evolution (Modified Sturm Test), 9/23/97.

2) Study conducted by RCC Umweltchemie AG, Itingen, Switzerland.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

Ecotoxicity Elements

10a

10 Acute Toxicity to Fish

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 203(Paris 1988)

Test Type: static

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Brachydanio rerio

Analytical Monitoring: Measurements made, but methods not described

Exposure Period: 96 hours

Statistical Method: Method not identified in report

Remarks for Methods:

- 1) Test animal was zebra fish (Brachydanio rerio).
- 2) Number of fishes: 10 fishes per concentration and control; 10 fishes per aquarium; test concentration in duplicate.
- 3) Duration of test was 96 hours.
- 4) Temperature was 23 +/- 1 degree C.
- 5) Exposure was OECD Guideline No. 203, 1984 (static procedure).
- 6) Deviations: Test performed as limit test with concentration of 100 mg/l nominal.
- 7) Fish size: 27-34 mm (average: 30 mm)
- 8) Mean Body Weight: 0.2 g (0.13 - 0.3 g)
- 9) Loading was 0.13 g/l.
- 10) Adaptation: 24 hours. No food 24 hours prior to exposure.
- 11) Acclimatization was 89 days.
- 12) Mean concentrations (mg/l) for the 100 mg/l nominal dose measured throughout the 96 hour duration of this study were 79 and 74 mg/l.
- 13) Controls: Blank=water; vehicle=1101 mg DMSO per liter water in the concentration used for the highest test concentration.

RESULTS:

Nominal Concentration: 100mg/L and a 100 mg/L duplicate
Measured Concentration: Mean concentrations (over 96 hrs) were 79 and 74 mg/L
Precision: >
Endpoint Type: LC50
Endpoint Value: 77
Concentration Type: Measured
Units used: mg/L
Endpoint Time: 96 hrs
Statistical Results: Statistical analyses were not performed and "P" values not calculated.

CONCLUSIONS:

No fish died at the limit concentration of 77 mg/L. No adverse effects were noted with any of the fish at the limit concentration of 77 mg/L. The determination of LC50 (96h): the concentration at which 50% of the fish population died was > 77 mg/L, the highest dose tested.

DATA QUALITY:

Reliability: Reliability Code 1
Data Reliability Remarks: OECD protocol and report - data quality are acceptable.

REFERENCES:

- 1) Report on the test for Acute Toxicity of TK 10622 (Araldite PT 810) to Zebra Fish (*Brachydanio rerio*), Project 884055, 6/13/84.
- 2) Ciba-Geigy Ltd, Basel, Switzerland, GU3- Ecotoxicology
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; *Regulatory Toxicology and Pharmacology* 25, 1-5 (1997).
- 4) Maximum Likelihood Method from Mc Cullagh, P. and Nelder J. A., 1983 in *Generalized Linear Models*, Chapman & Hall, London.

11a

11 Toxicity to Aquatic Plants

TEST SUBSTANCE

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD

OECD Guideline No. 201 (April 1984), Semi-static

GLP: Yes

Year: 1993

Species: Green Algae (*Scenedesmus subspicatus*)

Analytical Monitoring: High Performance Liquid Chromatography DL = 0.2 mg/l

Exposure Period: 72 hours

Statistical Methods: See Reference Section

Remarks for Method:

1) Test guideline described as 87/302/EEC page 89-94; Algal Inhibition Test. No deviations noted.

2) Test organisms; see above.

3) Source/supplier was Pflanzenphysiologisches Institute University, D-3400 Gottingen, Germany.

4) Preculture period was 72 hours and cells were tested in accordance with the above referenced guideline.

5) Control (blank) material was water.

6) Assays were performed in triplicate.

7) All other test conditions reported to have been conducted in accordance with the referenced guidelines.

Test Conditions:

1) Test temperature range was 24 degrees 1 degree centigrade.

2) Lighting was continuous illumination with cold white fluorescent light, 117 uEm² sec 15% (approx. 8000 lux).

3) Initial density was 9700 cells/ml using a ""TOA"" Cell Counter. Cell density was also measured after 24, 48 and 72 hours.

4) Method of calculating mean measured concentration was that used to describe the Maximum Likelihood Method from McCullagh, P. and Nelder J. A., 1983 in Generalized Linear Models, Chapman & Hall, London.

RESULTS

Nominal Concentrations: 0.41, 1.23, 3.7, 11, 33, 100

Measured Concentrations: 0.21, 0.72, 2.1, 6.3, 19.4, 63.4

Endpoint type: EbC50

Endpoint Value: 29

Units Used: mg/L

Concentration Type: Measured

Endpoint Time: 72

NOEL:

LOEL:

Statistical Results: EbC 50 (0 to 72 hr) = 29 mg/l; 95%confidence limit is 22.5 to 36.0 mg/l. NOEbC (0 to 72 hr) at the 5% level was 6.3mg/l.

Remark fields for Results:

Biological observations:

1) EbC 50 (0 to 72 hr) = 29 mg/l; 95%confidence limit is 22.5 to 36.0 mg/l. NOEbC (0 to 72 hr) at the 5% level was 6.3mg/l.

2) Concentration response with 95% confidence limits. See above.

3) Control response was satisfactory.

CONCLUSIONS:

The objective of the study was the determination of the EbC50 of green algae.

DATA QUALITY:

Reliability: Reliability Code 2. See reference below.

Remarks field for Data Reliability: Study followed GLP for OECD, EPA, and MITI and appears to be similar to OECD Guideline 209.

REFERENCES:

1) Report on the Growth Inhibition Test of Araldite PT 810 to Green Algae (*Scenedesmus subspicatus*). Study conducted by Dr. R. Grade for and by, Ciba-Geigy Ltd. Basel, Switzerland, 1993.

2) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; *Regulatory Toxicology and Pharmacology* 25, 1-5 (1997).

3) Maximum Likelihood Method from Mc Cullagh, P. and Nelder J. A., 1983 in *Generalized Linear Models*, Chapman & Hall, London.

GENERAL COMMENTS:

An analytical method and report dated 9/7/93 were reviewed.

12a

12 Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD

Method/Guideline Followed: OECD Guideline No. 209 (April, 1984)

Test Type: static

GLP (Y/N): Yes

Year (study performed): 1993

Species: Activated Sludge from a Sewage Treatment Facility (Plant # CH-4153)

Analytical Monitoring: Oxygen Consumption using ORION Ionalizer Mod. 901

Exposure Period: 3 hours

Statistical Method: None required

Remarks for Method:

- 1) Activated sludge was collected from the sewage treatment plant of CH - 4153 on 5/4/93.
- 2) The pH after collection was 7.2.
- 3) The preparation was carried out according to the OECD guideline.
- 4) Sludge was separated from the aqueous layer by settling rather than centrifugation.
- 5) The pH of the sludge before testing was 8.0.

Test conditions:

- Stock solutions were prepared using standard nutrient solution and dechlorinated water.
- Test temperature range was 20 degrees +/- 2 degrees centigrade.
- Two blank samples (no TGIC) and 3 reference samples (high, medium and low oxygen consumers) were prepared in order to verify the oxygen consumption rates of the TGIC dilutions.

- 1) Instead of a centrifuged sludge a settled sludge was used. Due to the poor solubility of the test substance at test concentrations, no stock solution was prepared. The test substance was given directly into the medium. Therefore, a constant factor between the test concentrations could not be achieved.
- 2) The objective of the study was the determination of the inhibitory concentration of a chemical substance on the respiration of aerobic waste water bacteria.

3) The results were calculated based on nominal concentrations: EC50 (3h) => 100 mg/l, EC20 (3h) =>100mg/l, EC80 (3h) =>100 mg/l.

4) Reference substance was 3,5-Dichlorophenol.

5) This study used "blanks" as negative controls and a "reference substance" as a positive control.

6) Reference substance concentrations were 32.1, 10.0, and 3.2 mg/l.

RESULTS

Nominal Concentration: 103.0, 41.5, 16.5, 7.0, 3.0, and 1.5 mg/l
Measured Concentration: 103.0, 41.5, 16.5, 7.0, 3.0, and 1.5 mg/l
Precision: >
Endpoint Type: EC20
Endpoint Value: 100
Units Used: mg/L
Concentration Type: Nominal
Endpoint Time: 3
Statistical Results: Not specified
Results Remarks:
Biological observations:

1) Both control groups and all 3 reference groups responded satisfactorily and produced appropriate results.

2) Results were calculated for the test substance based on nominal concentrations: EC50 (3H) =>100mg/l, EC20 (3H) =>100mg/l, EC80=>100mg/l.

CONCLUSIONS

TGIC at concentrations ranging from 1.5 to 103.0 mg/l did not inhibit the utilization of oxygen by activated sewage sludge.

DATA QUALITY

Reliability: Reliability Code 2. See reference below.

Data Reliability Remarks: This study followed OECD Guideline No. 209 and GLP for USEPA, OECD, and JMAFF.

GENERAL COMMENTS:

This report provides information regarding the potential impact of TGIC on activated sludge from a sewage treatment facility.

REFERENCES:

1) Report on the Test for an Inhibitory Concentration on Aerobic Bacteria of Araldite PT 810. Conducted by W. Baumann for and by Ciba-Geigy Ltd., Basel Switzerland. May 14, 1993.

2) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

12b

12 Acute Toxicity to Aquatic Invertebrates

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD

Method/Guideline Followed: OECD Method 202(Paris, 1984)

Test Type: semi-static

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Daphnia magna

Analytical Monitoring: Analytical measurements made - method not reported

Exposure Period: 24 hours

Statistical Method: Unknown

Remarks for Method:

- 1) Test duration was 24 hours.
- 2) Temperature was 20 +/- degrees.
- 3) Vehicle control concentration: 1101 mg/l DMSO.
- 4) Stock solution: 1.0 g TK 10622 were dissolved in and made up to 10 ml with DMSO. This solution was diluted to 100 mg/l with water.
- 5) Strain: Daphnia Magnus Straus 1820.
- 6) Pretreatment: 24 hours before the start of the test reproductive daphnia are separated from the young by sieving through a 800 micrometer sieve. This operations repeated immediately before the start and the young daphnia (0-24 h old) are retained for the test.
- 7) Test concentrations (nominal): 10, 18, 32, 58, 100 mg/l. Measured concentrations ranged from 90 to 98% of nominal concentrations.
- 8) Controls: Blank-water, vehicle-1101 mg DMSO per l water in the concentration used for the highest test concentration.
- 9) Number of daphnia: 20 daphnia/conc. And control. (4 replicates of 5 daphnia).
- 10) Temperature: 20 +/- 1 degrees.
- 11) Duration: 24 hours.
- 12) Lighting: 16 hours fluorescent light daily, approx. 2000 lux.

13) Measurements: (pH, O₂, temperature) at the beginning and at the end of the test.

RESULTS:

Nominal Concentration: 10, 18, 32, 58, and 100 mg/l
Measured Concentration: 9.8, 17.1, 30.5, 54.5, and 90.6 mg/l
Precision: >
Endpoint Type: EC50
Endpoint Value: 50
Units Used: mg/L
Concentration Type: Measured
Endpoint time: 24
Statistical Results: No "P" value required for this endpoint.
Results Remarks:

- 1) EC50 (24h): >100 mg/L (nominal), >90.6 mg/L (measured)
- 2) ECO (24h): 58 mg/l (nominal), 54.5 (measured)
- 3) EC100 (24h): >100 mg/L (nominal), >90.6 mg/L (measured)
- 4) Controls: Immobilization blank 0%
- 5) Immobilization vehicle 0%
- 6) Immobilization at 100 mg/L (nominal): 4/20 animals (20%), no other immobilization/effects noted in other treatment groups.

CONCLUSIONS:

The empirical EC50 (24h) was greater than 100 mg/l (90.6 mg/L, measured), while the ECO (24h) was 58 mg/L (54.5 mg/L, measured).

DATA QUALITY:

Reliability: Reliability Code 1
Data Quality Remarks: OECD protocol and report - data quality are acceptable.

REFERENCES:

- 1) Report on the Test for Acute Toxicity of TK 10622 to Daphnia Magna, 9/3/88.
- 2) Ciba-Geigy Ltd, Basel, Switzerland, GU3- Ecotoxicology
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

Health Elements

13.1a

13.1 Acute Oral Toxicity

TEST SUBSTANCE

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD

Method/Guideline Followed: Acute Oral LD50 - Method not specified in the report.
GLP (Y/N): No
Year Study Completed: 1970
Species: rat
Strain: CFE (specific pathogen free)
Sex; Both
Number of males per dose: 4
Number of females per dose: 4
Vehicle: DMSO - (Test article was 4% w/v in DMSO)
Route of administration: Oral
Remarks for Method:

- 1) Test method not described in this report. Only a summary describing the LD50 was presented.
- 2) Age of animals at the time of testing was 12 to 16 weeks.
- 3) Rats were fasted overnight before being weighed and treated using a syringe fitted with a ball-point needle.
- 4) Water was available throughout the experiment and food was available before and after dosing.

RESULTS:

Precision: =
Acute Lethal Value: 222
Unit: mg/kg-bw
Deaths per Dose: Not described in the report.
Results Remarks:

The results of this Acute Oral Toxicity Study for TGIC are similar to those described in the literature (LD50s ranging from 188 to 950 mg/kg). See references below.

CONCLUSIONS:

The acute oral toxicity of TGIC was determined to be 222 mg/kg.

DATA QUALITY:

Reliability: Reliability Code 2, see discussion below.

Data Quality Remarks:

Because these studies used acceptable chemical evaluation methods, are well documented, reported toxicological results before there were any requirements to do so, and (based on the data toxicology developed over the past 30 years) accurately reported the health hazards associated with TGIC, I would assign these data a Reliability Code of 2 based on the Klimisch model.

GENERAL COMMENTS:

This study was conducted by and for Shell Oil Company at their Tunstall laboratory in London England. Only the description of the test article and the results of the study are available at this time. This appears to be an "age appropriate" study which would likely provide data sufficient for calculating an LD50.

REFERENCES:

- 1) Araldite CY 182 & 183 (9347 Triglycidylisocyanurate) Oral LD 50 Rat; Dermal LD 50 Rat; Skin Irritation; Skin Sensitization; and Eye Irritation; "Diglycidyl Esters of Tetrahydrophthalic Acid and Hexahydrophthalic Acid and of Triglycidylisocyanurate". April, 1970. Study conducted by the Shell Chemical Company Tunstall Laboratory in London, England.
- 2) International Program on Chemical Safety; Concise International Assessment Document Number 8, Triglycidyl Isocyanurate, 1998.
- 3) American Conference of Governmental Industrial Hygienists, 1997 Monograph.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.1b

13.1 Acute Oral Toxicity

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 401 - Acute Oral Toxicity

GLP (Y/N): Yes

Year Study Performed: 1990

Species: Rat

Strain: Tif. RAIF (SPF)

Sex: Both

Number of males per dose: 5

Number of females per dose: 5

Vehicle: Carboxymethylcellulose in .1% aqueous polysorbate 80

Route of Administration: Oral intubation

Remarks for Method:

- 1) Test article was TK 10622 (TGIC), trade name ARALDIT PT 810.
- 2) The test was performed on 30 young adult albino rats of both sexes, TIF: RAIF (SPF) raised on the premises for use in the experiments.
- 3) Average body weight ranged from 169 to 210 grams.
- 4) Initial age was 6 to 8 weeks.
- 5) They were kept at an animal room under conventional laboratory conditions: room temperature of 22 +/- 2 degrees C, at a relative humidity of 55 +/- 10% and on a 12 hours light cycle day, approximately 15 air changes/h.
- 6) The animals were housed in Macrolon cages type 4, with standardized soft wood bedding (Societe Parisienne des Sciures, Pantin, France). They were acclimatized at least for 5 days before administration. They received ad libitum standard rat food - NAFAG 890 Tox, NAFAG, Gossau SG/Switzerland- and water.
- 7) Prior to dosing, the animals fasted overnight.
- 8) Dose levels by sex group were as follows: 20 mg/kg, females; 100 mg/kg, males and females; 500 mg/kg, females.
- 9) One single oral dose, by gastric intubation (gavage) was administered.

10) The vehicle used was .5% (w/v) carboxymethylcellulose in .1% (w/v) aqueous polysorbate 80. (Prepared by Pharmaceuticals Division, Ciba-Geigy Ltd., Basel)

11) Observation period was 14 days.

12) From the body weights, the group means and their standard deviations were calculated.

13) The LD50 values for females and for both sexes (including their 95% lower confidence limits) were computed by the logit model (J. Berkson, J. AM. Stat.Ass. 39 (1944), 357-365).

RESULTS:

Precision: <

Acute Lethal Value: 100

Unit: mg/kg-bw

Deaths per Dose: Deaths/ mg/kg: Males: 3/100, Females: 0/20, 0/100, 5/500

Results Remarks:

1) The rates of death for male rats were 3 out of 5 for 100 mg/kg group. The rates of death for female rats were 0 of 5, 0 of 5, and 5 of 5, for the 20, 100, and 500 mg/kg groups, respectively.

2) Piloerection, abnormal body positions, and dyspnea were seen, being common symptoms in acute tests.

3) Additionally, reduced locomotor activity was observed in animals of the 100 and 500 mg/kg dose group immediately before they died spontaneously. In the females given 500 mg/kg respiratory sounds were recorded.

4) On male dosed with 100 mg/kg experienced convulsions.

5) The surviving animals recovered within 4 to 9 days.

6) In one spontaneous dead male of the 100 mg/kg dose group edematous and hemorrhagic lungs, a spotted thymus and liquid filled thoracic cavity were seen. In two females dosed with 500 mg/kg, a dilated stomach was observed, in one of them the small intestine was also dilated.

CONCLUSIONS:

Upon an acute oral administration and a 14 day post-treatment observation period, the following LD40 (with 95% confidence limits calculated, where possible) was determined for TK 10622:

LD50 in male rats: lower than 100 mg/kg body weight.

LD50 in female rats: 171 (low limit 67) mg/kg body weight.

LD50 in rats of both sexes: 138 (low limit 67) mg/kg body weight.

DATA QUALITY:

Reliability: Reliability Code 1

Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below

REFERENCES:

- 1) Acute Oral Toxicity in the rat of TK 10622 (Araldit PT 810), Test no. 894516, February 12, 1990.
- 2) Study conducted by CIBA-Geigy Ltd, Basel/ Switzerland, Plastics Division.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) The LD50 values for females and for both sexes (including their 95% lower confidence limits were computed by the logit model) (J. Berkson, J. AM. Stat.Ass. 39 (1944), 357-365).

13.1c

13.1 Acute Oral Toxicity

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 401 - Acute Oral Toxicity

GLP (Y/N): Yes

Year Study Performed: 1982

Species: Rat

Strain: TIF: RAIF (SPF)

Sex: Both

Number of males per dose: 5

Number of females per dose: 5

Vehicle: Arachis Oil

Route of Administration: Oral by gastric intubation

Remarks for Method:

- 1) Test article was TK 10622 (TGIC).
- 2) The test was performed on 40 rats, TIF: RAIF (SPF), F3-crosses of RII 1/TIF x RII 2/Tif.
- 3) Initial body weight ranges was 153-185 g.
- 4) Initial age was 7-8 weeks.
- 5) They were kept at a room temperature of 22 +/- 3 degrees C, at a relative humidity of 55 +/- 15% and on a 12 hours light cycle day, approximately 15 air changes/h. They received ad libitum standard rat food - NAFAG, No. 890, Gossau SG (Switzerland) - and water.
- 6) Dose levels were 100, 250, 400, 1000 mg/kg.
- 7) The number of animals per dose level was 5 males and 5 females.
- 8) Vehicle was arachis oil.
- 9) Administration was oral by gastric intubation (gavage).
- 10) Observation period was 14 days or until all symptoms disappeared, whichever was longer.

RESULTS:

Precision: =

Acute Lethal Value: 305

Unit: mg/kg-bw

Deaths per Dose: M: 0/100, 2/250, 4/500, 5/1000, F: 0/100, 1/250, 5/500, 5/1000

Results Remarks:

Upon an acute oral administration and a 14 day post-treatment observation period, the following LD50 (with 95% confidence limits calculated, where possible) was determined for TK 10622 (TGIC):

LD50 in male rats: 302 (154-521) mg/kg-bw.

LD50 in female rats: 305 (172-515) mg/kg-bw.

LD50 in rats of both sexes: 305 (217-416) mg/kg-bw.

CONCLUSIONS:

The acute oral LD50 for TK 10622 (TGIC) was determined to be 305 mg/kg.

DATA QUALITY:

Reliability: Reliability Code 1

Data Reliability Remarks:

OECD/GLP Protocol and Report - See reference below.

REFERENCES:

1) Acute Oral LD50 Study in the Rat Administered TK 10622. Study conducted by Ciba-Geigy, Basel Switzerland. 1982.

2) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.1d

13.1 Acute Oral Toxicity

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 401 - Acute Oral Toxicity
GLP (Y/N): Yes
Year Study Performed: 1990
Species: Rat
Strain: Tif RAIF (SPF)
Sex: Both
Number of males per dose: 5
Number of females per dose: 5
Vehicle: Carboxymethylcellulose in .1% aqueous polysorbate 80
Route of Administration: Oral gavage/gastric intubation
Remarks for Method:

- 1) Test article was TK 10622 (TGIC), trade name ARALDIT PT 810.
- 2) The test was performed on 30 young albino rats of both sexes, TIF: RAIF (SPF) raised on the premises for use in the experiments.
- 3) Average body weight ranged from 169 to 221 grams.
- 4) Initial age was 6 to 8 weeks.
- 5) They were kept at an animal room under conventional laboratory conditions: room temperature of 22 +/- 2 degrees C, at a relative humidity of 55 +/- 10% and on a 14 hours light cycle day, approximately 15 air changes/h.
- 6) The animals were housed in Macrolon cages type 4, with standardized soft wood bedding (Societe Parisienne des Sciures, Pantin, France). They were acclimatized at least for 5 days before administration. They received ad libitum standard rat food - NAFAG 890 Tox, NAFAG, Gossau SG/Switzerland- and water.
- 7) Prior to dosing, the animals fasted overnight.
- 8) Dose levels by sex group were as follows: 20 mg/kg, females; 100 mg/kg, males and females; 200 mg/kg, males and females; 500 mg/kg, females;
- 9) The vehicle used was .5% carboxymethylcellulose in .1% (w/v) aqueous polysorbate 80.

10) Administration of the test article was via one single oral dose by gastric intubation (gavage).

RESULTS:

Precision: <
Acute Lethal Value: 100
Unit: mg/kg-bw
Death per Dose: See Results Remarks Below.
Results Remark:

- 1) The rates of death for male rats were 3 out of 5 for both the 100 and 200 mg/kg groups. The rates of death for female rats were 0 of 5, 0 of 5, 1 of 5, and 5 of 5, for the 20, 100, 200 and 400 mg/kg groups, respectively.
- 2) Piloerection, abnormal body positions, and dyspnea were seen, being common symptoms in acute tests.
- 3) Additionally, reduced locomotor activity was observed in animals of the 100, 200 and 500 mg/kg dose group immediately before they died spontaneously. In one male given 200 and the females given 500 mg/kg respiratory sounds were recorded. One male of the 100 and the 200 mg/kg dose group each experienced convulsions. Diarrhea was observed in one male dosed with 200 mg/kg.
- 4) The surviving animals recovered within 4 to 12 days. Dose-dependent lethality and clinical signs reflected a remarkably higher sensitivity in male rats.
- 5) Edematous and hemorrhagic lungs were found in one male given 100, a liquid-filled thoracic cavity in the same male and in one male given 200 mg/kg. The thymus in the former male was spotted, in two males given 200 mg/kg hemorrhagic and in one involuted. In the latter male the testes were found involuted and one kidney was enlarged. In two females dosed with 500 mg/kg a dilated stomach was observed, in one of them also the small intestine was dilated.

CONCLUSIONS:

Upon an acute oral administration and a 14 day post-treatment observation period, the following LD40 (with 95% confidence limits calculated, where possible) was determined for TK 10622:

LD50 in male rats: lower than 100 mg/kg body weight.
LD50 in female rats: 255 (low limit 112) mg/kg body weight.
LD50 in rats of both sexes: 188 (108-329) mg/kg body weight.

DATA QUALITY:

Reliability: Reliability Code 1
Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below.

REFERENCES:

- 1) Acute Oral Toxicity in the rat of TK 10622 (ARALDIT PT 810), May 7, 1990.
- 2) Study conducted by CIBA-Geigy Ltd, Basel/ Switzerland, GU Toxicology.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

4) The LD50 value for females (including its 95% lower confidence limit) was computed by the logit model (J. Berkson, J. Am. Stat. Ass. 39 (1944), 357-365).

5) The LD50 value and its 95% confidence limits for both sexes were calculated by the probit/ maximum likelihood method (Rosiello, A.P, Essigmann, J.M., and Wogan, G. N., Journal of Toxicology and Environmental 1977), 797-809).

13.1e

13.1 Acute Oral Toxicity

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Acute Oral LD50 - Method not specified in the report.

GLP (Y/N): No

Year Study Performed: 1975

Species: Rat

Strain: Tif. RAIF (SPF)

Sex: Both

Number of males per dose: 5

Number of females per dose: 5

Vehicle: Carboxymethylcellulose 2%

Route of Administration: Oral intubation

Remarks for Method:

- 1) Test article was TK 10622 (TGIC).
- 2) The test was performed on 60 rats, TIF: RAIF (SPF) raised on the premises for use in the experiments.
- 3) Average body weight ranged from 160 to 180 grams.
- 4) They were kept at a room temperature of 22 +/- 1 degrees C, at a relative humidity of 55 +/- 5% and on a 14 hours light cycle day. They received ad libitum standard rat food - NAFAG, Gossau SG- and water.
- 5) Prior to treatment, the animals were adapted to our laboratories for a minimum of 4 days.
- 6) Dose levels were 100, 215, 317, 464, 600, or 1290 mg/kg.
- 7) The number of animals per dose level was 5 males and 5 females.
- 8) TK 10622 was suspended with carboxymethyl-cellulose 2%.. Before treatment the suspension was homogeneously dispersed with an Ultra-Turrax and during treatment it was kept stable with a magnetic stirrer.
- 9) Animals fasted overnight were treated by oral intubation.

RESULTS:

Precision: =

Acute Lethal Dose: 431

Unit: mg/kg in feed

Deaths per Dose: Deaths: M 0/100; 1/215; 1/317; 3/464; 5/600; 5/1290; F
0/100; 0/215; 1/317; 1/464; 4/600; 5/1290

Results Remarks:

Within 2 hours after treatment the rats in all dosage groups showed sedation, dyspnea, exophthalmus, curved position and ruffled fur.

CONCLUSIONS:

The acute oral LD50 (including 95% confidence limits) of TK 10622 in rats of both sexes observed over a period of 14 days is 431 (358-519) mg/kg. The substance has therefore a medium acute toxicity to the rat by this route of administration.

DATA QUALITY:

Reliability: Reliability Code 2

Data Reliability Remarks:

Basic data provided; comparable to guideline/standards. See reference below.

RESULTS:

- 1) Acute Oral toxicity in the rat of tk10622, June 16, 1975.
- 2) Study conducted by CIBA-Geigy Ltd, Basel/ Switzerland, Toxicology/ Pathology.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) Goulden A., Methods of Statistical Analysis, John Wiley and Sons, 1960, 3rd printing , pages 404-408.

13.1f

13.1 Acute Oral Toxicity

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 401 - Acute Oral Toxicity

GLP (Y/N): Yes

Year Study Performed: 1982

Species: Rat

Strain: TIF. RAIF (SPF)

Sex: Both

Number of males per dose: 5

Number of females per dose: 5

Vehicle: Arachis Oil

Route of Administration: Oral

Remarks for Method:

- 1) Test article was TK 10622 (TGIC), trade name ARALDIT PT 810.
- 2) The test was performed on 40 young adult albino rats of both sexes, TIF: RAIF (SPF), F3-crosses of RII 1/TIF x RII 2/TIF.
- 3) Average body weight ranged from 153-185 grams.
- 4) Initial age was 7 to 8 weeks.
- 5) They were kept at an animal room under conventional laboratory conditions: room temperature of 22 +/- 3 degrees C, at a relative humidity of 55 +/- 15% and on a 12 hours light cycle day, approximately 15 air changes/h.
- 6) The animals were housed in Macrolon cages type 4, with standardized soft wood bedding (Societe Parisienne des Sciures, Pantin, France). They received ad libitum standard rat food - NAFAG 890 Tox, NAFAG, Gossau SG/Switzerland- and water.
- 7) 5 males and 5 females were in each dose group.
- 8) One single dose, per OS, was administered. Route of administration was oral, by gastric intubation (gavage).
- 9) The vehicle used was arachis oil.
- 10) Observation period was 14 days, or until all symptoms disappeared, whichever lasted longer.

11) The animals were allocated to the different dose groups by random selection. Prior to dosing the animals were fasted overnight.

12) Dose levels were 100, 250, 500, 1000 mg/kg.

RESULTS:

Precision: =

Acute Lethal Value: 305

Unit: mg/kg-bw

Deaths per Dose: Male: 0/100, 2/250, 4/500, 5/1000 mg/kg; Female: 0/100, 1/250, 5/500, 5/1000 mg/kg

Results Remarks:

1) Deaths for males were: 0/100, 2/250, 4/500, 5/1000 mg/kg. Deaths for females were 0/100, 1/250, 5/500, 5/1000 mg/kg.

2) From the body weights, the group means and their standard deviations were calculated.

3) Where feasible, the LD50 value (including its 95% lower confidence limit) was computed by the logit model (J. Berkson, J. Am. Stat. Ass. 39 (1944), 357-365).

CONCLUSIONS:

Upon an acute oral administration and a 14 day post-treatment observation period, the following LD50 (with 95% confidence limits calculated, where possible) was determined for TK 10622:

LD50 in male rats: 302 (154-521) mg/kg body weight.

LD50 in female rats: 305 (172-715) mg/kg body weight.

LD50 in rats of both sexes: 305 (217-416) mg/kg body weight.

According to the company standard TK 10622 (TGIC) has a medium acute toxicity when administered orally to the albino rat.

DATA QUALITY:

Reliability: Reliability Code 1

Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below

REFERENCES:

1) Acute Oral LD50 in the rat of TK 10622, August 18, 1982.

2) Study conducted by CIBA-Geigy Ltd, Basel/ Switzerland, GU2 Toxicology.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

4) Where possible, the LD50 value (including its 95% lower confidence limit) was computed by the logit model (J. Berkson, J. Am. Stat. Ass. 39 (1944), 357-365).

13.1g

13.1 Acute Oral Toxicity

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD 401 - Acute Oral Toxicity

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Rats

Strain: Sprague-Dawley

Sex: Both

Number of males per dose: 5

Number of females per dose: 5

Vehicle: Arachis Oil

Route of Administration: Oral by gavage

Remarks for Method:

- 1) Test material was Tepic-G.
- 2) 20 male and 20 female Sprague Dawley CFY strain rats were used in the study.
- 3) Weight of male rats was 126-172g, weight of female rats was 120-162 g and age was approximately 5-8 weeks.
- 4) Acclimatization period was 5 days.
- 5) Animals were housed in groups of up to five by sex solid floor polypropylene cages furnished with sawdust bedding. With the exception of an overnight fast immediately before dosing and for approximately two hours after dosing, free access to mains drinking water and food (Rat and Mouse Expanded Diet No. 1, Special Diet Services Limited, Witham, Essex, UK) was allowed.
- 6) Animal room maintained at 19-21 degrees C and relative humidity of 48-65%. The rate of air exchange was 15 changes per hour and lighting was controlled by a time switch to give 12 hours light and 12 hours darkness.
- 7) For the purpose of this study the test material was ground to a fine powder using mortar and pestle and freshly prepared as required as a solution/suspension at the appropriate concentration in arachis oil B.P.
- 8) Four groups of ten rats (five males and five females received the test article at the following doses:

5 males/ 5 females received 1000 mg/kg at 100 mg/ml concentration in a dose of 10 ml/kg.
5 males/ 5 females received 1710 mg/kg at 171 mg/ml concentration in a dose of 10 ml/kg.
5 males/ 5 females received 2924 mg/kg at 292.4 mg/ml concentration in a dose of 10 ml/kg.
5 males/ 5 females received 5000 mg/kg at 500 mg/ml concentration in a dose of 10 ml/kg.

9) All animals were dosed only once at the appropriate dose level by gavage using a metal cannula attached to a graduated syringe. The volume administered to each animal was calculated according to its fasted bodyweight at the time of dosing. Animals were observed 1 and 4 hours after dosing and subsequently once daily for 14 days.

10) The mortality data did not permit calculation of an LD50 value and an additional group of animals were treated as follows:

5 males/ 5 females received 585 mg/kg at 58.5 mg/ml concentration in a dose of 10 ml/kg.

RESULTS:

Precision: >
Acute Lethal Value: 585
Unit: mg/kg-bw
Deaths per Dose: See Results Remarks
Results Remarks:

The mortality data are summarized as follows:

At a dose level of 585 mg/kg, deaths were 1/5 Males, 0/5 females, 1/10 total, or 10%.
At a dose level of 1000 mg/kg, deaths were 5/5 Males, 4/5 females, 9/10 total, or 90%.
At a dose level of 1710 mg/kg, deaths were 5/5 Males, 4/5 females, 9/10 total, or 90%.
At a dose level of 2924 mg/kg, deaths were 5/5 Males, 5/5 females, 10/10 total, or 100%.
At a dose level of 5000 mg/kg, deaths were 5/5 Males, 4/5 females, 9/10 total, or 90%.

CONCLUSIONS:

The acute oral median lethal dose (LD50) and 95% confidence limits of the test material, TEPIC-G, in the Sprague-Dawley CFY strain rat was calculated by the method of Thompson to be:

All animals: 715 (492-1040) mg/kg bodyweight
Males Only: 447 (123-1624) mg/kg bodyweight
Females Only: 948 (700-1284) mg/kg bodyweight

DATA QUALITY:

Reliability: Reliability Code 1
Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below

REFERENCES:

- 1) Tepic-G: Acute Oral Toxicity/ Test in the Rat Project Number 14/10, 10/28/88.
- 2) Study conducted by Safeparm Laboratories Limited, Derby, UK.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) Thompson W.R., Bact. Reviews, 11,115-145 (1947).

13.1h

13.1 Acute Oral Toxicity

TEST SUBSTANCE

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Acute Oral LD50 - Method not specified in the report.

GLP (Y/N): Yes

Species: Rat

Strain: CFE (specific pathogen free)

Sex: Both

Number of males per dose: 2

Number of females per dose: 2

Vehicle: n-methylpyrrolidone

Route of Administration: Dermal

Remarks for Methods:

- 1) Test method not described in this report. Only a summary describing the LD50 was presented.
- 2) Age of animals at the time of testing was 12 to 16 weeks.
- 3) Rats were fasted overnight before being weighed and treated using a syringe fitted with a ball-point needle.
- 4) Water was available throughout the experiment and food was available before and after dosing.

RESULTS:

Precision: =

Acute Lethal Value: 185

Unit: mg/kg-bw

Deaths per Dose: Not described in this report.

Results Remarks:

The results of this Acute Oral Toxicity Study for TGIC are similar to those described in the literature (LD50s ranging from 188 to 950 mg/kg). See references below.

CONCLUSIONS:

The acute oral toxicity of TGIC was determined to be 222 mg/kg.

DATA QUALITY:

Reliability: Reliability Code 2, see discussion below
Data Reliability Remarks:

Because these studies used acceptable chemical evaluation methods, are well documented, reported toxicological results before there were any requirements to do so, and (based on the data toxicology developed over the past 30 years) accurately reported the health hazards associated with TGIC, I would assign these data a Reliability Code of 2 based on the Klimisch model.

GENERAL COMMENTS

This study was conducted by and for Shell Oil Company at their Tunstall laboratory in London England. Only the description of the test article and the results of the study are available at this time. This appears to be an "age appropriate" study which would likely provide data sufficient for calculating an LD50.

REFERENCES:

- 1) Araldite CY 182 & 183 (9347 Triglycidylisocyanurate) Oral LD 50 Rat; Dermal LD 50 Rat; Skin Irritation; Skin Sensitization; and Eye Irritation; "Diglycidyl Esters of Tetrahydrophthalic Acid and Hexahydrophthalic Acid and of Triglycidylisocyanurate". April, 1970. Study conducted by the Shell Chemical Company Tunstall Laboratory in London, England.
- 2) International Program on Chemical Safety; Concise International Assessment Document Number 8, Triglycidyl Isocyanurate, 1998.
- 3) American Conference of Governmental Industrial Hygienists, 1997 Monograph.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.2a

13.2 Acute Inhalation Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: EPA OPP Method 81-3 which later became EPA OPPTS Method 870.1300

GLP (Y/N): Yes

Year Study Performed: 1991

Species: Mouse

Strain: CD-1

Sex: M

Number of males per dose: 5

Number of females per dose: 0

Vehicle: Air at 29.5 l/min.

Route of Administration: Inhalation

Remarks for Method:

- 1) Age of mice at exposure ranged from 53 to 64 days.
- 2) Animals were exposed to a single 4-hour inhalation exposure at concentrations of 3.88, 2.39 or 1.05 mg of TGIC dust per liter of air.
- 3) Post dosing observation period was 14 days.
- 4) This report was conducted using EPA OPP Method 81-3 which, in 1998, became EPA OPPTS Method 870.1300.

RESULTS:

Precision: >

Acute Lethal Value: 1

Unit: mg/L(air)

Deaths per dose: 5 of 5 deaths in the 3.88 mg/l group; and 3 of 5 deaths in the 2.39 mg/l group; no deaths low dose

Results Remark:

- 1) For the 3.88 mg/l group, deaths occurred on post-exposure days 2, 3 (2 deaths), 4 and 5.
- 2) For the 2.39 mg/l group, deaths occurred on post-exposure days 3, 5, and 11.
- 3) No deaths occurred in the 1.05 mg/l group.

4) In the 3.88 mg/l group, four of five mice did not exhibit any gross lesions. The fifth exhibited: Yellow encrustation around the face and penis, size decrease of spleen 1/4 normal, intestines appeared gaseous with post mortem changes, mottled red discoloration of lungs, light red discoloration of brain, and multiple areas of tan discoloration of the liver.

5) In the 2.39 mg/l group, all mice exhibited reduced body weight gain during the post-exposure period. The gross pathology of this group at necropsy was similar to, but less severe than, the descriptions cited for the 3.88 mg/l group.

6) The primary gross pathological finding at necropsy for the 1.05 mg/l group was periocular swelling. The acute 4-hour LC50 value (with 95% confidence limits) for male mice was 2.0 (1.4 to 3.0) mg/l.

DATA QUALITY:

Reliability: Reliability Code 1. Data Reliability Remarks:

Comparable to EPA Guideline. See reference 4 below.

GENERAL COMMENTS:

The periocular swelling observed for some animals may have resulted from either the irritant potential or the toxicity of the test article.

RESULTS:

1) PL90-810: Acute Dust Inhalation Toxicity Test in Mice. Study Completed: April 8, 1991. Study Performed by: Bushy Run Research Center; Export, PA

2) International Program on Chemical Safety; Concise International Assessment Document Number 8, Triglycidyl Isocyanurate, 1998.

3) American Conference of Governmental Industrial Hygienists, 1997 Monograph.

4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.2b

13.2 Acute Inhalation Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Protocol appears to be based on OECD Method 403
GLP (Y/N): Yes
Year Study Performed: 1991
Species: Rat
Strain: Wistar
Sex: M
Number of males per dose: 8
Number of females per dose: 0
Vehicle: Air
Route of Administration: Inhalation
Remarks for Method:

- 1) Protocol appears to be similar to, and based on OECD Method 403.
- 2) Age of animals used was 9 weeks at delivery.
- 3) Originally the test article was to be administered at 3 dosage levels to groups of 8 male rats and another group of 8 rats was to receive lactose powder as a control. However, because the LC50 was > 4.16 mg/l (the maximum dose) and the high dose of the test article did not produce the required 50% reduction in respiratory rate, the middle and low doses were not administered.
- 4) Post dosing observation period was 8 days.
- 5) The "whole-body" exposure duration was 4 hours.

RESULTS:

Precision: >=
Acute Lethal Value: 4
Unit: mg/L(air)
Deaths per Dose: None at the highest dose of 4.16 mg/l.
Results Remark:

- 1) There were no clinical signs of toxicity and no effect on body weights.
- 2) See General Comments below.

CONCLUSIONS:

The acute 4-hour LC50 value for male rats was greater than 4.16 mg/l. There were no clinical signs of toxicity and no effect on body weights. There was however a slightly decreased respiratory rate associated with exposure to the test article.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks:

Necessary data provided; comparable to OECD 403. See reference below.

GENERAL COMMENTS:

There appears to be a significant difference in the toxic response of rats (this study) and mice (previous study). This difference may be associated with species-specific toxicological response, age at dosing, the potential for preening with whole-body exposure, or be the result of using nose-only verses whole-body exposure.

The same laboratory using the same protocol evaluated Test Article TK 10 622/II. The identity of the test article was unknown to the laboratory. However, the results of the two analyses were slightly different in many small ways, but nearly identical in their overall result. This type of QA testing was often used to check laboratories procedures. For test articles TK 10 622/I and TK 10 622/II the laboratory performed well and the results were replicated very well within the limits reproducibility.

REFERENCES:

- 1) 4-Hour, Acute Inhalation Toxicity Study and Sensory Irritating Properties of TK 10 622/I [TGIC] in Rats.
- 2) International Program on Chemical Safety; Concise International Assessment Document Number 8, Triglycidyl Isocyanurate, 1998.
- 3) American Conference of Governmental Industrial Hygienists, 1997 Monograph.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.2c

13.2 Acute Inhalation Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Method not cited in the report

GLP (Y/N): Yes

Year Study Performed: 1991

Species: Mouse

Strain: CD-1

Sex: M

Number of males per dose: 12

Number of females per dose: 0

Vehicle: Air

Route of Administration: Inhalation

Remarks for Method:

Each group consisted of 12 mice. Ten were to be used to evaluate the 5-day inhalation toxicity (with a 14 day recovery period) and 2 were to be used as a screen to evaluate the potential to cause chromosomal aberrations.

RESULTS:

Precision: \leq

Acute Lethal Value: 100

Unit: mg/m³(air)

Deaths per Dose: 100 mg/m³ = 5 treatment-related deaths; at 350 & 750 mg/m³ there were 10 and 9 deaths, respectively.

Results Remark:

1) For the 100 mg/m³ group: 2 deaths occurred on Day 5; 2 more occurred on Day 8; and 1 occurred on Day 9.

2) For the 350 mg/m³ group: 2 deaths occurred on Day 3; 2 more occurred on Day 4; four deaths occurred on Day 5; and 1 occurred on each of Days 6, 7, 9, and 11.

3) Gas accumulation was present in all exposed animals, suggesting ingestion of the test article and oral toxicity.

4) As in earlier studies, the mid and high dose groups showed mottled lungs and reduced spleen size.

CONCLUSIONS:

Neither an LC50 nor a No Observed Effects Level (NOEL) could be established based on the results of this study.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks:

Basic data provided; this study appears to be comparable to OECD or EPA protocols. See reference below.

GENERAL COMMENTS:

As noted previously, there appears to be a significant difference in the toxic response of rats and mice. This difference may be associated with species-specific toxicological response, age at dosing, the potential for preening with whole-body exposures, or be the result of using nose-only verses whole-body exposure.

REFERENCES:

- 1) PL90 - 810: Five Day Dust inhalation Study in Mice. Bushy Run Research Center, Exton, PA. August 7, 1991. Project Report No. 54-502.
- 2) International Program on Chemical Safety; Concise International Assessment Document Number 8, Triglycidyl Isocyanurate, 1998.
- 3) American Conference of Governmental Industrial Hygienists, 1997 Monograph.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.2d

13.2 Acute Inhalation Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Study conducted according to the Method of Sachsse et al. (1973, 1976). See reference below.

GLP (Y/N): No

Year Study Performed: 1979

Species: Rat

Strain: Tif.RAIF (SPF)

Sex: Both

Number of males per dose: 20

Number of females per dose: 20

Vehicle: Air

Route of Administration: Inhalation

Remarks for Method:

1) Animals: The test was performed with 20 male and 20 female young adult rats of the Tif: RAIF (SPF) strain, raised on the premises. An additional group of 20 (10 males/ 10 females) rats served as a control. Before and after the inhalation the animals were kept at a room temperature of 22 +/- 2 degrees C, at a relative humidity of 55 +/- 10% and on a 10 hours light cycle day. They received ad libitum rat food - NAFAG, Gossau SG - and water. Prior to treatment they were adapted to our laboratories for a minimum of 4 days. Bodyweights were recorded immediately prior to exposure (control weights) and at 7 and 14) The males and females were segregated and kept in Macrolon cages, type 4, (10 animals to a cage).

2) Testing procedures: For inhalation the rats were kept in separate PVC tubes positioned radially around the exposure chamber such that snout and nostrils of the animals only were exposed to the aerosol.

3) Dosage: 10M + 10 F/ group. 3 groups: 1 group at 410 mg/m³., 1 group at 656 mg/m³ and a control at 0 mg/m³.

4) Exposure Duration: 4 hour inhalation.

5) Preparation of aerosol: The air flow rate was 20 l/min.

6) The concentration and the particle size distribution of the aerosol in the vicinity of the animals were monitored at regular intervals throughout the aerosol exposure.

7) Calculation: LC50 including 95% confidence limits was calculated by the logit model.

RESULTS:

Precision: =

Acute Lethal Value: 650

Unit: mg/kg-bw

Deaths per Dose: 5 of 10 females and zero of ten males died during the 14 day post observation period.

Results Remark:

- 1) Five of ten females and zero of ten males died during the 14 day post observation period.
- 2) Particle size distribution analysis of the chamber airborne particles showed that 60 to 80 % were smaller than 7 mm in diameter.
- 3) Signs & Symptoms: The surviving animals exposed to the test material recovered within 4 to 8 days. They were submitted for necropsy if they died during the study, survivors were necropsied at the end of the observation period.
- 4) Slight irritation effects of the mucous membranes of the nose were seen in the rats of the higher concentration during 3 days after exposures.
- 5) The autopsies for animals which died on test showed partially hemorrhages in the lungs

CONCLUSIONS:

The LC50 of a 4 hour aerosol exposure for female rats is approximately 650 mg/cubic meter air, for male rats it is greater than 650 mg/cubic meter air, when evaluated throughout the 14 day post-treatment observation period.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

- 1) K. Sachsse, L. Ullmann, G. Voss and R. Hess: Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Proceedings of the Europe. Soc. For the Study of Drug Toxicity. Vol. XV, pp. 239-251, Zurich, June, 1973.
- 2) K. Sachsse, L. Ullmann, G. Voss and K. Zubinden: Toxikologische Pruefungen von Aerosolen im Tierexperiment: Aus "Chemische Rundschau" 29 (1976), Nr. 38, Seite 1-4.
- 3) Acute Aerosol Inhalation Toxicity in the Rat of TK 10622/3. Study conducted by Ciba-Geigy, Basel, Switzerland. 1979.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.2e

13.2 Acute Inhalation Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: This study was conducted according to the Method of Sachsse et al. (1973, 1976)

GLP (Y/N): No

Year Study Performed: 1979

Species: Rat

Strain: TIF: RAIF (SPF)

Sex: Both

Number of males per dose: 10

Number of females per dose: 10

Vehicle: Acetone

Route of Administration: Inhalation

Remarks for Method:

1) Animals: There were 3 groups each with 10M + 10F. Group 1 was a negative (air) control; Group 2 received 309 mg of test article per cubic meter of air; and Group 3 was exposed to acetone at a rate of approximately 30 ml/hr. Before and after the inhalation the animals were kept at a room temperature of 22 +/- 2 degrees C, at a relative humidity of 55 +/- 10% and on a 10 hours light cycle day. They received ad libitum rat food - NAFAG, Gossau SG - and water. Prior to treatment they were adapted to our laboratories for a minimum of 4 days. Bodyweights were recorded immediately prior to exposure (control weights) and at 7 and 14) The males and females were segregated and kept in Macrolon cages, type 4, (10 animals to a cage).

2) Testing procedures: For inhalation the rats were kept in separate PVC tubes positioned radially around the exposure chamber such that snout and nostrils of the animals only were exposed to the aerosol.

3) During the exposure period the following parameters were controlled once at half time of the study inside the inhalation cylinder: temperature, relative humidity and oxygen content. After a 4 hour inhalation the rats were returned to their cages. Physical condition and incidence of death were monitored throughout an observation period of 14 days.

4) Exposure Duration: 4 hour inhalation

5) Calculation: LC50 including 95% confidence limits was calculated by the logit model.

RESULTS:

Precision: >

Acute Lethal Value: 309

Unit: mg/m³(air)

Deaths per Dose: No deaths during inhalation exposure or 14 day observation period.

Results Remarks:

1) No deaths occurred during inhalation exposure or 14 day observation period. No significant effects were noted on the rate of body weight gain.

2) Particle size distribution analysis of the chamber airborne particles showed that > 80 % were smaller than 7 micrometers in diameter.

CONCLUSIONS:

The LC50 of a 4 hour aerosol exposure for rats of both sexes is greater than 300 mg/cubic meter air, when evaluated for a 14 day post-treatment observation period.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks:

Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

1) Acute Aerosol inhalation toxicity in the rat of TK 10622. Study conducted by Ciba-Geigy, Basel Switzerland. 1979.

2) K. Sachsse, L. Ullmann, G. Voss and R. Hess: Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Proceedings of the Europ. Soc. For the Study of Drug Toxicity. Vol XV, pp. 239-251, Zurich, June, 1973.

3) K. Sachsse, L. Ullmann, G. Voss and K. Zubinden: Toxikologische Pruefungen von Aerosolen im Tierexperiment: Aus ""Chemische Rundschau"" 29 (1976), Nr. 38, Seite 1-4.

4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.3a

13.3 Acute Dermal Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Acute Dermal Toxicity - Method not specified in this report.

GLP (Y/N): No

Year Study Performed: 1975

Species: Rat

Strain: Tif.RAI

Sex: Both

Number of males per dose: 3

Number of females per dose: 3

Vehicle: Carboxymethylcellulose 2%

Route of Administration: Dermal

Remarks for Method:

- 1) There were no control animals used.
- 2) The compound was tested on 24 Tif. Rai rats (12 males, 12 females) that were 7 to 8 weeks old and weighed 180 to 200 g.
- 3) Treatment: Approximately 6 hours before treatment the rats' backs were shaved with an electric razor. The suspension was evenly dispersed on the skin with a Record syringe and covered with aluminum foil which was held around the trunk with ISO-ELAST plaster. After 24 hours, the plaster and the aluminum foil were peeled off carefully and the skin was cleaned with warm water to remove all traces of the suspension.
During the treatment and for the 14 day observation period, the rates were housed signally in Macrolon cages (type 2) in a room kept at a constant temperature of 22+/- 1 degree C and a relative humidity of approximately 50%. They were given water and food (NAFAG, Gossau SG, rat food) ad libitum.

RESULTS:

Precision: >

Acute Lethal Value: 3100

Unit: mg/kg-bw

Deaths per Dose: None

Results Remarks:

1) Within 24 hours after treatment, the rats in all dosage groups showed sedation, dyspnea, curved position and ruffled fur. Additionally in the two highest dosage groups a slight irritation of the skin was observed.

2) The animals had recovered within 7 to 12 days. They were killed and autopsied after an observation period of 14 days. No substance related gross organ changes were seen or noted at autopsy.

3) Results:

DOSE (mg/kg)	MALE	FEMALE
=====	=====	=====
215	3	3
1000	3	3
2150	3	3
3170	3	3

CONCLUSIONS:

- 1) The acute dermal LD50 of TK 10622 in rats of both sexes observed over a period of 14 days is greater than 3100 mg/kg.
- 2) The compound therefore has a slight acute toxicity to the rat by this route of administration.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below

REFERENCES:

1) Acute Dermal LD50 of TK 10622 in the Rat. Study conducted by Ciba-Geigy, Basel, Switzerland. 1975.

2) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.3b

13 Acute Dermal Study

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD 402 - Acute Dermal Toxicity

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Rats

Strain: Sprague-Dawley

Sex: Both

Number of males per dose: 5

Number of females per dose: 5

Vehicle: Arachis Oil

Route of Administration: Dermal

Remarks for Method:

- 1) Test material was Tepic-G.
- 2) 5 male and 5 female Sprague Dawley CFY strain rats were used in the study.
- 3) Weight of male rats was 200-207g, weight of female rats was 211-247g and age was approximately 10-14 weeks.
- 4) Acclimatization period was 5 days.
- 5) Animals were housed in solid floor polypropylene cages furnished with sawdust bedding with free access to mains drinking water and food (Rat and Mouse Expanded Diet No. 1, Special Diet Services Limited, Witham, Essex, UK) was allowed.
- 6) Animal room maintained at 19-22 degrees C and relative humidity of 50-66%. The rate of air exchange was 15 changes per hour and lighting was controlled by a time switch to give 12 hours light and 12 hours darkness.
- 7) A single group of 5 male and 5 female rats were treated with 2000 mg/kg of Tepic-G.
The appropriate amount of the test material, as received, was pre-weighed into a glass vial, and applied uniformly to an area of shorn skin approximating to 10% of the total body surface area which had previously been moistened with arachis oil B.P. A piece of surgical gauze measuring 7 cm x 4 cm was placed over the treatment area and semi-occluded with a double layer of elastic adhesive bandage (ELASTOPLAST) wrapped around the trunk of the rat.

RESULTS:

Precision: >

Acute Lethal Value: 2000

Unit: mg/kg-bw

Death per Dose: None

Results Remark:

No deaths, evidence of systemic toxicity or skin irritation occurred during treatment or the 14 day post treatment observation period; therefore, the acute dermal median lethal dose (LD50) of the test material was considered to be greater than 2000 mg/kg bodyweight.

CONCLUSIONS:

The acute dermal median lethal dose (LD50) of the test material, TEPIC-G, to the rat was found to be greater than 2000 mg/kg bodyweight.

DATA QUALITY:

Reliability: Reliability Code 1

Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below

REFERENCES:

- 1) Tepic-G: Acute Dermal Toxicity/ (Limit Test) in the Rat Project Number 14/11, 11/8/88.
- 2) Study conducted by Safeparm Laboratories Limited, Derby, UK.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.3c

13.3 Acute Dermal Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: US EPA 163.81-5 "Primary Dermal Irritation Study"
See reference below.

GLP (Y/N): No

Year Study Performed: 1979

Species: Rabbit

Strain: New Zealand white

Sex: Both

Number of males per dose: 3

Number of females per dose: 3

Vehicle: Propylene glycol + saline (70:30 parts)

Route of Administration: Dermal

Remarks for Method:

- 1) The test article was administered at a dose of .5 g/animal. It was prepared as a 50% solution of test article and 40% vehicle. The vehicle was a 70%/30% mixture of propylene glycol and saline.
- 2) The procedure used is described in the proposed guidelines of the United States Environmental Agency (EPA) paragraph 163.81-5 "Primary dermal irritation study", Federal Register, Vol. 43, no. 163, August 22, 1978.
- 3) The test was performed on 3 male and 3 female adult rabbits of the new Zealand white breed weighing 2 to 3 kgs. They were housed individually in metal cages, numbered by ear tags, were kept at a room temperature of 22 +/- 2 degrees C, at a relative humidity of 55 +/- 10% and on a 10 hours light cycle day. They received ad libitum standard rabbit food - NAFAG, No. 814, Gossau SG - and water. Prior to treatment they were adapted to our laboratories for a minimum of 4 days.
- 4) Before treatment, the entire back and the flank of the rabbits were shaved with an electric clipper and immediately before treatment the shaven skin on one side was slightly scarified with the help of a "Schroepgschnaepper", Aesculap, Switzerland. Gause patches of 2.5 x 2.5 cm laden with .5 g of the test material were applied to the prepared abraded and intact skin.
- 5) The patches were covered with an impermeable material and were fastened to the body of the rabbit with adhesive tape. The dressings were removed after a 24 hour application.

The skin reaction was appraised upon removal and during an observation period of 3 days on the basis of an evaluation scheme.

RESULTS:

Precision: >
Acute Lethal Value: 200
Unit: mg/kg-bw
Deaths per Dose: None
Results Remarks:

TK 10622 was found to cause a minimal irritation when applied to intact and abraded rabbit skin.

CONCLUSIONS:

- 1) Under the conditions of the present experiment TK 10622/3 was found to cause a minimal irritation when applied to intact and abraded rabbit skin.
- 2) The calculated primary irritation index was 0.25.

DATA QUALITY:

Reliability: Reliability Code 2.
Data Reliability Remarks:

Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

- 1) Skin Irritation in the Rabbit After Single Application of TK 10622. Study conducted by Ciba-Geigy, Basel Switzerland. 1979.
- 2) US EPA 163.81-5 Primary Dermal Irritation Study, Federal Register Vol.43, No. 163, August 22,1978.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.3d

13.3 Acute Dermal Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 402 - Acute Dermal Toxicity

GLP (Y/N): Yes

Year Study Performed: 1990

Species: Rat

Strain: TIF. RAIF (SPF)

Sex: Both

Number of males per dose: 5

Number of females per dose: 5

Vehicle: Carboxymethylcellulose in .1% aqueous polysorbate80

Route of Administration: Dermal

Remarks for Method:

- 1) Test article was TK 10622 (TGIC), trade name ARALDIT PT 810.
- 2) The test was performed on 15 young adult albino rats of both sexes, TIF: RAIF (SPF) raised on the premises for use in the experiments.
- 3) Average body weight ranged from 209 to 259 grams.
- 4) Initial age was 7 to 8 weeks.
- 5) They were kept at an animal room under conventional laboratory conditions: room temperature of 22 +/- 2 degrees C, at a relative humidity of 55 +/- 10% and on a 12 hours light cycle day, approximately 15 air changes/h.
- 6) The animals were housed in Macrolon cages type 4, with standardized soft wood bedding (Societe Parisienne des Sciures, Pantin, France). They were acclimatized at least for 5 days before administration. They received ad libitum standard rat food - NAFAG 890 Tox, NAFAG, Gossau SG/Switzerland- and water.
- 7) Group size: There were 5 males in the 200 mg/kg group and 5 males plus 5 females in the 20000 mg/kg group.
- 8) Approximately 24 hours before treatment, an area on the back of the rat of at least 10% of the body surface was shaved with an electric clipper.
- 9) The required amount of the test substance was evenly dispersed on the skin. It was covered with a gauze-lined semioclusive dressing fastened around the trunk with an adhesive elastic bandage. After an exposure period of 24 hours,

the dressing was removed and the skin was cleaned with lukewarm water. Thereafter the skin reaction was appraised repeatedly.

10) Frequency of application was one single dose.

11) The dose levels were 200 (males) and 2000 mg/kg body weight (males and females).

12) The vehicle used was .5% (w/v) carboxymethylcellulose in .1% (w/v) aqueous polysorbate 80. (Prepared by Pharmaceuticals Division, Ciba-Geigy Ltd., Basel).

13) Observation period was 14 days.

RESULTS:

Precision: >

Acute Lethal Dose: 2000

Unit: mg/kg-bw

Deaths per Dose: No deaths occurred in this study.

Results Remarks:

1) Piloerection, abnormal body position and dyspnea were observed, being common symptoms in acute tests.

2) The surviving animals recovered within 5 to 6 days.

3) At autopsy, no deviations from normal morphology were noted.

CONCLUSIONS:

Upon an acute dermal administration and a 14 day post-treatment observation period, the following LD50 (with 95% confidence limits calculated, where possible) was determined for TK 10622:

LD50 in male rats: greater than 2000 mg/kg body weight.

LD50 in female rats: greater than 2000 mg/kg body weight.

LD50 in rats of both sexes: greater than 2000 mg/kg body weight.

DATA QUALITY:

Reliability: Reliability Code 1

Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below

REFERENCES:

1) Acute Dermal Toxicity in the rat of TK 10622 (Araldit PT 810), Test no. 894517, March 21, 1990.

2) Study conducted by CIBA-Geigy Ltd, Basel/ Switzerland, Experimental Toxicology.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.4a

13.4 Dermal Irritation Study

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Skin Irritation Study - Administered to Covered and Uncovered Skin.

GLP (Y/N): No

Year Study Performed: 1970

Species: Rabbit and Guinea Pigs

Strain: Rabbit = New Zealand White; Guinea Pig

Sex: Both

Number of males per dose: 5

Number of females per dose: 5

Vehicle: Neat TGIC, or a 4% w/v solution of TGIC in DMSO

Route of Administration: Dermal

Remarks for Method:

COVERED APPLICATIONS:

- 1) The dorsal hair was removed using an electric clipper.
- 2) Approximately 1 gram of neat TGIC or 1 ml of a 4% w/v solution of TGIC in DMSO was applied to each of two 2X2 cm patches.
- 3) The patches were placed on 4 male and 4 female rabbits, covered with a thin sheet of polyethylene, bandaged with open weave gauze and the rabbits were immobilized for 6 hours.
- 4) Steps 2 and 3 above were repeated on test days 2 and 3 resulting in a total of 3 applications of the test article.
- 5) Assessments of irritation were made 7 days after the initial application of the test article.

UNCOVERED APPLICATIONS:

- 6) One male and 1 female rabbit, and 5 male and 5 female Guinea Pigs were used in this evaluation. Methods were similar to those described above with the exception that 0.5 ml of TGIC was applied to the midline shaved backs of the Guinea Pigs. No covering or bandaging was used in this portion of the study.

RESULTS:

Precision : >

Acute Lethal Value: 200

Unit: mg/kg-bw

Deaths per Dose: None

Results Remark:

TGIC is a skin irritant. With a carrier substance (vehicle) such as n-methylpyrrolidone it is moderately toxic percutaneously. Both sexes reacted similarly to exposure to TGIC.

CONCLUSIONS:

This study indicates that TGIC is a moderate skin irritant.

DATA QUALITY:

Reliability: Reliability Code 2; See reference below.

Data Reliability Remarks:

Because these studies used acceptable chemical evaluation methods, are well documented, reported toxicological results before there were any requirements to do so, and (based on the data toxicology developed over the past 30 years) accurately reported the health hazards associated with TGIC, I would assign these data a Reliability Code of 2 based on the Klimisch model.

GENERAL COMMENTS:

The physical state (dry powder or in solution with DMSO etc.,) will effect the irritant properties of TGIC.

REFERENCES:

- 1) Araldite CY 182 & 183 (9347 Triglycidylisocyanurate) Oral LD 50 Rat; Dermal LD 50 Rat; Skin Irritation; Skin Sensitization; and Eye Irritation; "Diglycidyl Esters of Tetrahydrophthalic Acid and Hexahydrophthalic Acid and of Triglycidylisocyanurate". April, 1970. Study conducted by the Shell Chemical Company Tunstall Laboratory in London, England.
- 2) International Program on Chemical Safety; Concise International Assessment Document Number 8, Triglycidyl Isocyanurate, 1998.
- 3) American Conference of Governmental Industrial Hygienists, 1997 Monograph.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 5) Hodge, H. and J. H. Sterner, American Industrial Hygiene Association Quarterly, Vol. 10 pp 93-96. 1949.

13.4b

13.4 Dermal Irritation Study

TEST SUBSTANCE

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: US EPA 163.81-5 "Primary Dermal Irritation Study"

GLP (Y/N): Unknown

Year Study Performed: 1979

Species: Rabbit

Strain: New Zealand white

Sex: Both

Number of males per dose: 3

Number of females per dose: 3

Vehicle: Propylene glycol + saline (70:30 parts)

Route of Administration: Dermal

Remarks for Method:

1) The test article was administered at a dose of .5 g/animal. It was prepared as a 50% solution of test article and 40% vehicle. The vehicle was a 70%/30% mixture of propylene glycol and saline.

2) The procedure used is described in the proposed guidelines of the United States Environmental Agency (EPA) paragraph 163.81-5 "Primary dermal irritation study", Federal Register, Vol. 43, no. 163, August 22, 1978.

3) The test was performed on 3 male and 3 female adult rabbits of the new Zealand white breed weighing 2 to 3 kgs. They were housed individually in metal cages, numbered by ear tags, were kept at a room temperature of 22 +/- 2 degrees C, at a relative humidity of 55 +/- 10% and on a 10 hours light cycle day. They received ad libitum standard rabbit food - NAFAG, No. 814, Gossau SG - and water. Prior to treatment they were adapted to our laboratories for a minimum of 4 days.

4) Before treatment, the entire back and the flank of the rabbits were shaved with an electric clipper and immediately before treatment the shaven skin on one side was slightly scarified with the help of a "Schroepgschnaepper", Aesculap, Switzerland. Gauze patches of 2.5 x 2.5 cm laden with .5 g of the test material were applied to the prepared abraded and intact skin.

The patches were covered with an impermeable material and were fastened to the body of the rabbit with adhesive tape. The dressings were removed after a 24 hour application.

The skin reaction was appraised upon removal and during an observation period of 7 days on the basis of an evaluation scheme.

RESULTS:

Precision: >
Acute Lethal Value: 200
Unit: mg/kg-bw
Deaths per Dose: None
Results Remark:

TK 10622 was found to cause a minimal irritation when applied to intact and abraded rabbit skin of the rabbit.

CONCLUSIONS:

- 1) Under the conditions of the present experiment, TK10622 / 3 was found to cause minimal irritation when applied to the intact or abraded rabbit skin.
- 2) The calculated primary irritation index was 0.92.

DATA QUALITY:

Reliability: Reliability Code 2.
Data Reliability Remarks:

Basic data provided; comparable to guideline/standards. See reference below.

REFERENCE:

- 1) Skin Irritation in the Rabbit After a Single Application of TK 10622/3. Study conducted by Ciba-Geigy, Basel Switzerland. 1979.
- 2) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 3) US EPA 163.81-5 "Primary Dermal Irritation Study, Federal Register Vol.43, No. 163, August 22, 1978.

13.4c

13.4 Dermal Irritation Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD 404 - Acute Dermal Irritation/ Corrosion

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Rabbit

Strain: New Zealand White

Sex: Both

Number of males per dose: 5

Number of females per dose: 5

Vehicle: Arachis Oil

Route of Administration: Dermal

Remarks for Method:

- 1) Test material was Tepic-G.
- 2) Three new Zealand White rabbits were supplied by David Percival Ltd., Moston, Sandback, Cheshire, U.K.
- 3) Weight of rabbits was 2.05 - 2.49 kg, and age was approximately 12-16 weeks.
- 4) Acclimatization period was 5 days, after which each animals was given a number unique within the study which was written with a black indelible marker pen on the inner surface of the ear and on the cage label.
- 5) Animals were housed in suspended metal cages with free access to mains drinking water and food (Rabbit Diet, Preston Farmers Limited, New Leake, Boston, Lincolnshire, UK) was allowed.
- 6) Animal room maintained at 15-18 degrees C and relative humidity of 53-60%. The rate of air exchange was 15 changes per hour and lighting was controlled by a time switch to give 12 hours light and 12 hours darkness.
- 7) For purpose of this study the test material was moistened with distilled water immediately before application.
- 8) Approximately 24 hours prior to the commencement of the test, each of a group of 3 rabbits was clipped free of fur from the dorsal/ flank area using veterinary clippers. Only animals with a healthy intact epidermis by gross observation were selected for the study.

9) On the day of the test a suitable test site was selected on the back of each rabbit. A quantity of 0.5 g of the test material moistened with 0.5 ml of distilled water was introduced under a 2.5 cm x 2.5 cm gauze patch and placed in position on the shorn skin. The patch was secured in position with a strip of surgical adhesive tape (BLENDERM: approximate size 2.5 cm x 4.0 cm). To prevent animals from interfering with the patches, the trunk of each rabbit was wrapped in an elasticated corset (TUBIGRIP) and the animals were returned to their cages for the duration of the exposure period.

10) Four hours after application the corset and patches were removed from each animal and any residual test material removed by gently swabbing with cotton wool soaked in distilled water.

RESULTS:

Precision: =
Acute Lethal Value: 220
Unit: mg/kg-bw
Deaths per Dose: None
Results Remark:

- 1) Very slight erythema was noted at all treated skin sites one hour after removal of the patches.
- 2) Very slight erythema persisted at two treated skin sites at the 24 hour observation and at one treated skin site at the 48 hour observation.
- 3) All treated skin sites appeared normal at the 72 hour observation.
- 4) The test material produced a primary irritation index of .3 and was classified as a MILD IRRITANT to rabbit skin. No corrosive effects were noted.

CONCLUSIONS:

The test material, TEPIC-G, was found to be a mild irritant to rabbit skin.

DATA QUALITY:

Reliability: Reliability Code 1
Data Reliability Remarks:
OECD/GLP Protocol and Report - See reference below

REFERENCES:

- 1) Tepic-G: Acute Dermal Irritation/ Test in the Rabbit Project Number 14/12, 11/25/88
- 2) Study conducted by Safepharm Laboratories Limited, Derby, UK
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.4d

13.4 Dermal Irritation Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Dermal Irritation - Draft OECD Guideline 404

GLP (Y/N): No

Year Study Performed: 1982

Species: Rabbit

Strain: New Zealand white

Sex: Both

Number of males per dose: 3

Number of females per dose: 3

Vehicle: None

Route of Administration: Dermal

Remarks for Method:

- 1) Test article was TK 10622 (TGIC).
- 2) The procedure used is described in the proposed guidelines of the United States Environmental Agency (EPA) paragraph 163.81-5 "Primary dermal irritation study", Federal Register, Vol. 43, no. 163, August 22, 1978.
- 3) The test was performed on 3 male and 3 female adult rabbits of the New Zealand white breed weighing 2 to 3 kgs.
- 4) They were housed individually in metal cages, numbered by ear tags, were kept at a room temperature of 22 +/- 3 degrees C, at a relative humidity of 55 +/- 15% and on a 12 hours light cycle day, approximately 15 air changes/h. They received ad libitum standard rabbit food - NAFAG, No. 814 Tox, NAFAG AG, Gossau SG (Switzerland) - and water.
- 5) Before treatment, the entire back and the flank of the rabbits were shaved with an electric clipper and immediately before treatment the shaven skin on one side was slightly scarified with the help of a "Schroepgschnaepfer", Aesculap, Switzerland. Gauze patches of 2.5 x 2.5 cm soaked with 0.5 ml of the test material were applied to the prepared abraded and intact skin.
- 6) The patches were covered with an impermeable material and were fastened to the body of the rabbit with adhesive tape. The dressings were removed after a 24 hour application.

7) The skin reaction was appraised upon removal and during an observation period of 7 days on the basis of an evaluation scheme.

RESULTS:

Precision: >

Acute Lethal Value: 140

Unit: mg/kg-bw

Deaths per Dose: Animal #160 died on day 3; autopsy showed signs of partial pneumonia.

Results Remark:

1) TK 10622 was found to cause a slight irritation when applied to intact and abraded rabbit skin.

2) Animal #160 died on day 3 of the test period. At autopsy, the lungs showed signs of partial pneumonia.

CONCLUSIONS:

Under the conditions of the present experiment TK 10622 was found to cause slight irritation when applied to the intact and abraded rabbit skin. The calculated primary irritation index was 1.3.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks:

Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

1) TK 10622 Acute Skin Irritation Study in the Rabbit, Administered TK10622, GU Project No. 820697, August 13, 1982.

2) Study conducted by CIBA-Geigy Ltd, Basel/ Switzerland, GU Toxicology.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.4e

13.4 Dermal Irritation Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 404 - Acute Dermal Irritations

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Rabbit

Strain: New Zealand White

Sex: M

Number of males per dose: 3

Number of females per dose: 0

Vehicle: Distilled water

Route of Administration: Dermal

Remarks for Method:

- 1) Test material was Tepic-G.
- 2) Three new Zealand White rabbits were supplied by David Percival Ltd., Moston, Sandback, Cheshire, U.K.
- 3) Weight of rabbits was 2.62-2.84, and age was approximately 12-16 weeks.
- 4) Acclimatization period was 5 days, after which each animals was given a number unique within the study which was written with a black indelible marker pen on the inner surface of the ear and on the cage label.
- 5) Animals were housed in suspended metal cages with free access to mains drinking water and food (Rabbit Diet, Preston Farmers Limited, New Leake, Boston, Lincolnshire, UK) was allowed.
- 6) Animal room maintained at 15-18 degrees C and relative humidity of 55-65%. The rate of air exchange was 15 changes per hour and lighting was controlled by a time switch to give 12 hours light and 12 hours darkness.
- 7) For purpose of this study the test material was moistened with distilled water immediately before application.
- 8) Approximately 24 hours prior to the commencement of the test, each of a group of 3 rabbits was clipped free of fur from the dorsal/ flank area using veterinary clippers. Only animals with a healthy intact epidermis by gross observation were selected for the study.

9) On the day of the test a suitable test site was selected on the back of each rabbit. A quantity of .5 g of the test material moistened with .5 ml of distilled water was introduced under a 2.5 cm x 2.5 cm gauze patch and placed in position on the shorn skin. The patch was secured in position with a strip of surgical adhesive tape (BLENDERM: approximate size 2.5 cm x 4.0 cm). To prevent animals from interfering with the patches, the trunk of each rabbit was wrapped in an elasticated corset (TUBIGRIP) and the animals were returned to their cages for the duration of the exposure period.

10) 24 hours after application the corset and patches were removed from each animal and any residual test material removed by gently swabbing with cotton wool soaked in distilled water.

RESULTS:

Precision: =

Acute Lethal Value: 40

Unit: mg/kg-bw

Deaths per Dose: None

Results Remark:

- 1) Very slight erythema was noted at all treated skin sites one hour after removal of the patches.
- 2) Very slight erythema persisted at two treated skin sites at the 24 hour observation and at one treated skin site at the 48 hour observation.
- 3) All treated skin sites appeared normal at the 72 hour observation.
- 4) The test material produced a primary irritation index of .3 and was classified as a MILD IRRITANT to rabbit skin. No corrosive effects were noted.

CONCLUSIONS:

The test material, TEPIC-G, was found to be a mild irritant to rabbit skin.

DATA QUALITY:

Reliability: Reliability Code 1

Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below

REFERENCES:

- 1) Acute Dermal Irritation test in the rabbit (24 hour exposure) Project number 14/13, 12/17/88.
- 2) Study conducted by Safepharm Laboratories Limited, Derby, UK.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.5a

13.5 Eye Irritation:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Eye Irritation Study

GLP (Y/N): No

Year Study Performed: 1970

Species: Rabbit

Strain: CFE (specific-pathogen-free)

Sex; Both

Number of Males: 0

Number of Females: 0

Vehicle: None

Route of Administration: Eye

Remarks for Method:

- 1) Age of animals used was 12 to 16 weeks.
- 2) The single dose used in this study was 100 mg of TGIC placed in one eye.
- 3) The test protocol used was that described in the US Federal Register (1964) and the assessment of irritancy was based on the recommendations of the US Department of Health, Education and Welfare.

RESULTS:

Precision: >

Acute Lethal Value: 40

Unit: mg/animal

Deaths per Dose: None

Results Remark:

Administration of 100 mg of solid TGIC was shown to be a severe eye irritant and, according to the authors of this report, appeared to cause temporary blindness in the rabbits. There was no reported difference in the irritation potential between male and female rabbits.

CONCLUSIONS:

Solid Araldite PT 810 (TGIC) is a severe eye irritant.

DATA QUALITY:

Reliability: Reliability Code 2; See reference below.

Data Reliability Remarks:

Because these studies used acceptable chemical evaluation methods, are well documented, reported toxicological results before there were any requirements to do so, and (based on the data toxicology developed over the past 30 years) accurately reported the health hazards associated with TGIC, I would assign these data a Reliability Code of 2 based on the Klimisch model.

GENERAL COMMENTS:

Irrigation of the eye with water was helpful in reducing the duration and severity of the reaction.

REFERENCES:

- 1) Araldite CY 182 & 183 (9347 Triglycidylisocyanurate) Oral LD 50 Rat; Dermal LD 50 Rat; Skin Irritation; Skin Sensitization; and Eye Irritation; "Diglycidyl Esters of Tetrahydrophthalic Acid and Hexahydrophthalic Acid and of Triglycidylisocyanurate". April, 1970. Study conducted by the Shell Chemical Company Tunstall Laboratory in London, England.
- 2) International Program on Chemical Safety; Concise International Assessment Document Number 8, Triglycidyl Isocyanurate, 1998.
- 3) American Conference of Governmental Industrial Hygienists, 1997 Monograph.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 5) Hodge, H. and J. H. Sterner, American Industrial Hygiene Association Quarterly, Vol. 10 pp 93-96. 1949.

13.5b

13.5 Eye Irritation Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Eye Irritation - Federal Register 1973, Volume 38, No. 187, 1500.42

GLP (Y/N): Yes

Year Study Performed: 1987

Species: Rabbit

Strain: New Zealand White

Sex: M

Number of males per dose: 1

Number of females per dose: 0

Vehicle: None

Route of Administration: Dermal

Remarks for Method:

1. Test material was TEPIC-G Lot No. 611203.
2. One new Zealand white rabbit used.
3. Weight was 2.73 kg and age was approximately 12-16 weeks.
4. Acclimatization period was 5 days.
5. Animal was individually housed and had free access mains drinking water and food.
6. Animal room maintained at 18-20 degrees C and relative humidity of 58%. The rate of air exchange was 15 changes per hour and lighting was controlled by a time switch to give 12 hours light and 12 hours darkness.
7. On the day of the test the animal was held firmly but gently until quiet. A volume of 0.1 ml of the test material (as measured by gently compacting the required volume into an adapted syringe) which was found to weigh 93 mg, was placed into the right eye of the rabbit.

RESULTS:

Precision: >

Acute Lethal Value: 34

Unit: mg/kg-bw

Vehicle: None

Results Remarks:

1) Severe ocular reactions and obvious signs of pain were seen in the single treated animal approximately four hours after treatment. Conjunctival reactions, identified by beefy redness, with hemorrhage of the capillaries of the conjunctival and nictitating membranes, severe chemosis and an extensive discharge were noted. The severity of the chemosis precluded examination of the cornea and iris at this stage. For humane reasons the animal was killed and the cornea and iris were examined immediately after death. Diffuse corneal opacity and iridial inflammation were noted.

2) It is considered reasonable to assume that the test material is a positive irritant according to the Federal Register (based on one rabbit only).

CONCLUSIONS:

The test material, TEPIC-G Lot No. 611203, was considered to be a positive irritant to the rabbit eye (based on one rabbit only).

DATA QUALITY:

Reliability: Reliability Code 1- See Reference 1 below
Data Reliability Remarks:

Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

- 1) Tepic-G Lot no. 611203: Federal Register Eye Irritation/ Test in the Rabbit, Project Number 14/6, 4-13-87.
- 2) Study conducted by Safeparm Laboratories Limited, Derby, UK.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.5c

13.5 Eye Irritation:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: US EPA 163.81-4 "Primary Eye Irritation Study". See reference below.

GLP (Y/N): No

Year Study Performed: 1979

Species: Rabbit

Strain: New Zealand white

Sex: Both

Number of males per dose: 3

Number of females per dose: 3

Vehicle: None

Route of Administration: Eye

Remarks for Method:

1) The test article was administered at a dose of 0.5 g/animal. It was prepared as a 50% solution of test article and 40% vehicle. The vehicle was a 70%/30% mixture of propylene glycol and saline.

2) The procedure used is described in the proposed guidelines of the United States Environmental Agency (EPA) paragraph 163.81-4 ""Primary eye irritation study"", Federal Register, Vol. 43, no. 163, August 22, 1978.

3) The test was performed on 3 male and 3 female adult rabbits of the new Zealand white breed weighing 2 to 3 kgs. They were housed individually in metal cages, numbered by ear tags, were kept at a room temperature of 22 +/- 2 degrees C, at a relative humidity of 55 +/- 10% and on a 10 hours light cycle day. They received ad libitum standard rabbit food - NAFAG, No. 814, Gossau SG - and water. Prior to treatment they were adapted to our laboratories for a minimum of 4 days. Only rabbits with normal ophthalmic findings were used for these tests.

4) In an additional group designed to evaluate the impact of rinsing the eye 30 seconds after administration of the test article, 0.1 g of the test article was inserted into the conjunctival sac of the left eye of the rabbits and the lids were gently closed for a few seconds. The right eye was not treated and served as an untreated control. In 3 of the 6 rabbits approximately 30 seconds after treatment the treated eye was flushed with 10 ml of physiological saline. The eye irritation was appraised with a slit-lamp on day 1, 2, 3, 4 and 7 and was scored each individual rabbit.

RESULTS:

Precision: >
Acute Lethal Value: 200
Unit: mg/kg-bw
Deaths per Dose: None
Results Remark:

- 1) TK 10622 was found to cause marked eye irritation when applied to the rabbit eye mucosa.
- 2) Rinsing the eye following installation of the test article was of little, but measurable effect.

CONCLUSIONS:

Under the conditions of this experiment the test material was found to cause a marked irritation when applied to the rabbit eye mucosa. Rinsing the eyes following instillation was of little but assessable effect.

DATA QUALITY:

Reliability: Reliability Code 2.
Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

- 1) USEPS 163.81-4 "Primary Eye Irritation Study", Federal Register, Vol. 43, No. 163, August, 22, 1978.
- 2) Eye Irritation in the Rabbit After Single Application of TK 10622/3. Study conducted by Ciba-Geigy, Basel Switzerland. 1979.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.5d

13.5 Eye Irritation

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: US EPA 163.81-4 "Primary Eye Irritation Study" See Reference below.

GLP (Y/N): Unknown

Year Study Performed: 1982

Species: Rabbit

Strain: New Zealand white

Sex: Both

Number of males per dose: 3

Number of females per dose: 3

Vehicle: None

Route of Administration: Eye

Remarks for Method:

1) Test article was TK 10622 (TGIC).

2) The procedure used is described in the proposed guidelines of the United States Environmental Agency (EPA) paragraph 163.81-4 ""Primary eye irritation study"", Federal Register, Vol. 43, no. 163, August 22, 1978.

3) The test was performed on 3 male and 3 female adult rabbits of the new Zealand white breed weighing 2 to 3 kgs. They were housed individually in metal cages, numbered by ear tags, were kept at a room temperature of 22 +/- 2 degrees C, at a relative humidity of 55 +/- 15% and on a 12 hours light cycle day, approximately 14 air changes/h. They received ad libitum standard rabbit food - NAFAG, No. 814, Gossau SG - and water. Prior to treatment they were adapted to our laboratories for a minimum of 4 days. Only rabbits with normal ophthalmic findings were used for these tests.

4) The test material in an amount of 0.1 ml was inserted into the conjunctival sac of the left eye of the rabbits and the lids were gently closed for 15 seconds. The right eye was not treated and served as an untreated control. In 3 of the 6 rabbits approximately 30 seconds after treatment the treated eye was flushed with 10 ml of physiological saline.

RESULTS:

Precision: =

Acute Lethal Value: 40

Unit: mg/kg-bw

Deaths per Dose: 1 male died on day 2.
Results Remarks:

Animal number 160 died on day 2 of the test period. Autopsy showed signs of enteritis in the small intestine.

CONCLUSIONS:

- 1) Under the conditions of the present experiment TK 10622 was found to cause extreme irritation when applied to the rabbit eye mucosa.
- 2) The calculated primary irritation index was: 88.6% in unrinsed eyes, 46.9% in rinsed eyes.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

- 1) USEPS 163.81-4 "Primary Eye Irritation Study" , Federal Register, Vol. 43, No. 163, August, 22, 1978.
- 2) Acute Eye Irritation in the Rabbit After Single Application of TK 10622/3. Study conducted by Ciba-Geigy, Basel Switzerland. 1982.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

13.6a

13.6 Dermal Sensitization Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 406 - Skin Sensitization

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Guinea pig

Strain: Pirbright White Strain (Tif:DHP)

Sex: Both

Number of males per dose: 10

Number of females per dose: 10

Vehicle: None

Route of Administration: Dermal

Remarks for Method:

- 1) Test article was TK 10622 (TGIC), trade name ARALDIT PT 810.
- 2) The test was performed on 10 male and 10 female guinea pigs, strain: Pirbright White Strain (Tif: DHP).
- 3) Average body weight ranged from 323 to 404 g.
- 4) Initial age was approximately 10 weeks.
- 5) They were kept at an animal room under conventional laboratory conditions: room temperature of 22 +/- 3 degrees C, at a relative humidity of 30 to 70% and on a 12 hours light cycle day.
- 6) The animals were housed in Macrolon cages type 3, assigned to different groups by means of random numbers generated by a random number generator, identified by individual ear tags. They received ad libitum standard guinea pig pellets - NAFAG 846 Gossau SG- and water.
- 7) All batches of the diet are assayed for nutrition ingredients and contamination level by the manufacturer. Analytical results are available at the animal supply office.
The drinking water is examined periodically by the IWB (Industrielle Werke Basel), results are available to CIBA-GEIGY Ltd.
- 8) A modified procedure from the maximization test of Magnusson and Kligman was performed. The method was selected on account of its suitability for final

formulations or for compounds which are not injectable on account of their insolubility in standard vehicles.

RESULTS:

Precision: =
Acute Lethal Value: 40
Unit: mg/kg-bw
Deaths per Dose: None
Results Remark:

1) Because only mild erythema was observed, a second challenge application has been performed after a further rest period of 10 days.

2) During the second challenge, the results of the first challenge have been truly confirmed. TK 10622 is, therefore, classified as a mild sensitizer in albino guinea pigs according to the grading of Magnusson and Kligman.

CONCLUSIONS:

According to the maximization grading TK 10622 showed a mild grade of skin-sensitizing (contact allergenic) potential in albino guinea pigs.

Under the experimental conditions employed, 20 to 25% of the animals of the test group showed skin reactions to the standard challenge application.

DATA QUALITY:

Reliability: Reliability Code 1
Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below

REFERENCES:

1) Skin sensitization test in the guinea pig; modified maximization test using Araldite PT 810; project 884210; June 7, 1988.

2) Study conducted by CIBA-Geigy Ltd, Basel/ Switzerland, Toxicology.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

4) A modified procedure from the maximization test of Magnusson & Kligman (J. invest. Dermatol. 52, 2680267, 1969; Contact Dermatitis 6, 46-50, 1980) was performed.

5) A modified procedure was used: Maximization test of Magnusson and Kligman (J. Invest. Dermatol. 52, 268-276, 1969; Contact Dermatitis 6, 46-50, 1980), and recommended in the OECD guidelines 1981 and in the EEC directive 79/831.

13.6b

13.6 Dermal Sensitization Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD 406 - Skin Sensitization - Magnusson & Kligman Maximization Test
GLP (Y/N): Yes
Year Study Performed: 1987
Species: Guinea pig
Strain: Albino Dunkin-Hartley
Sex: F
Number of males per dose: 0
Number of females per dose: 20
Vehicle: Arachis Oil
Route of Administration: Dermal
Remarks for Method:

- 1) Test material was Araldite PT 810/ Lot No. 620011.
- 2) A group of 40 female, albino Dunkin-Hartley guinea pigs were used for the main study, twenty test and twenty control.
- 3) Weight was 292-391 g and age was approximately 6-10 weeks.
- 4) Acclimatization period was 5 days.
- 5) Animal was individually housed in groups of up to four in solid floor polypropylene cages furnished with softwood shavings and had free access mains drinking water and food (Guinea Pig FD1 Diet, Special Diet Services Limited).
- 6) Animal room maintained at 18-23 degrees C and relative humidity of 45-55%. The rate of air exchange was 15 changes per hour and lighting was controlled by a time switch to give 12 hours light and 12 hours darkness.
- 7) A group of forty guinea pigs was used for the main study, twenty test and twenty control.
- 8) Induction of the test animals: The hair was removed from an area approximately 40 mm x 60 mm on the shoulder region of each animal with veterinary clippers and a row of three injections (.1 ml each) was made on each side of the mid-line. The injections were
 - Freund's Complete Adjuvant plus arachis oil BL in the ratio 1:1
 - A .05% (w/v) dilution of test material in arachis oil BP

•A .05% (w/v) dilution of test material in a 1:1 preparation of Freund's Complete Adjuvant plus arachis oil BP.

9) One week later, the same area on the shoulder region used previously for intradermal injections was clipped again and treated with a topical application of the test material formulation (50% w/w in petroleum jelly BP.) The test material formulation (.2-.3 ml) was applied on filter paper (WHATMAN No. 4: approximate size 40 mm x 20 mm) which was held in place with two strips of waterproof adhesive strapping (SLEEK) in the form of a cross and covered with an overlapping length of aluminum foil. The patch and foil were further secured by a strip of elastic adhesive bandage (ELASTOPLAST: approximate size 250 mm x 35 mm) wound in a double layer around the torso of each animal. This occlusive dressing was kept in place for 48 hours.

10) Two weeks after the topical inductions, an area, approximately 50-70 mm x 50 mm on both flanks of each animal, was clipped free of hair with veterinary clippers. A quantity of 0.1 -0 .2 ml of the test material formulation (50% w/w/ in petroleum jelly BP) was applied to the shorn right flank of each animal on a 20 mm x 20 mm square of filter paper which was held in place by two strips of waterproof adhesive strapping.

RESULTS:

Precision: >
Acute Lethal Value: 0
Unit: mg/kg-bw
Deaths per Dose: None
Results Remark:

The incidence of sensitization responses in test animals was 18/20. Therefore, Araldite PT 810 is considered to be an extreme sensitizer.

CONCLUSIONS:

The test material, Araldite PT 810 Lot No. 620011, was found to be an extreme sensitizer.

DATA QUALITY:

Reliability: Reliability Code 1
Data Reliability Remarks:
OECD/GLP Protocol and Report -See reference below

REFERENCES:

- 1) Araldite PT 810/ Lot No. 620011: Magnusson & Kligman Maximazation / Study in the Guinea Pig, Project Number 14/9, 4/18/87.
- 2) Study conducted by Safepharm Laboratories Limited, Derby, UK.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) Magnusson B. & Kligman A.M., J. Invest. Dermatol. (1969) 52: 268-276.

13.6c

13.6 Dermal Sensitization Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD 406 - Skin Sensitization

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Guinea pig

Strain: Albino Dunkin-Hartley

Sex: F

Number of males per dose: 0

Number of females per dose: 20

Vehicle: Arachis Oil

Route of Administration: Dermal

Remarks for Method:

- 1) Test material was Tepic-G,
- 2) 37 female, albino Dunkin-Hartley guinea pigs were used.
- 3) Weight was 330-409 g and age was approximately 8-10 weeks.
- 4) Acclimatization period was 5 days.
- 5) Animal was individually housed in groups of up to four in solid floor polypropylene cages furnished with softwood shavings and had free access mains drinking water and food (Guinea Pig FD1 Diet, Special Diet Services Limited).
- 6) Animal room maintained at 16-21 degrees C and relative humidity of 55-73%. On occasions the temperature of the animal room fell below the limit specified in the protocol (18 degrees C). The rate of air exchange was 15 changes per hour and lighting was controlled by a time switch to give 12 hours light and 12 hours darkness.
- 7) A group of thirty guinea pigs was used for the main study, twenty test and ten control.
- 8) Two main procedures were involved in the maximization test: a) an induction of a response and b) a challenge of that response.
- 9) Induction of the test animals: The hair was removed from an area approximately 40 mm x 60 mm on the shoulder region of each animal with

veterinary clippers and a row of three injections (.1 ml each) was made on each side of the mid-line. The injections were

- Freund's Complete Adjuvant plus arachis oil BL in the ration 1:1
- A .05% (w/v) dilution of test material in arachis oil BP
- A .05% (w/v) dilution of test material in a 1:1 preparation of Freund's Complete Adjuvant plus arachis oil BP.

10) One week later, the same area on the shoulder region used previously for intradermal injections was clipped again and treated with a topical application of the test material formulation (50% w/w in petroleum jelly BP.) The test material formulation (0.2 - 0.3 ml) was applied on filter paper (WHATMAN No. 4: approximate size 40 mm x 20 mm) which was held in place by a strip of surgical adhesive tape (BLENDERM: approximate size 60 mm x 25 mm) and covered with an overlapping length of aluminum foil. The patch and foil were further secured by a strip of elastic adhesive bandage (ELASTOPLAST: approximate size 250 mm x 35 mm) wound in a double layer around the torso of each animal. This occlusive dressing was kept in place for 48 hours.

11) Two weeks after the topical inductions, an area, approximately 50-70 mm x 50 mm on both flanks of each animal, was clipped free of hair with veterinary clippers. A quantity of 0.1 - 0.2 ml of the test material formulation (50% w/w/ in petroleum jelly BP) was applied to the shorn right flank of each animal on a 20 mm x 20 mm square of filter paper (WHATMAN No. 4) which was held in place by two strips of waterproof adhesive strapping.

RESULTS:

Precision: >

Acute Lethal Value: 0

Unit: mg/kg-bw

Deaths per Dose: None

Results Remarks:

The incidence of sensitization responses in test animals was 12/20. Therefore, Tepic-G is considered to be an moderate sensitizer.

CONCLUSIONS:

The test material, Tepic-G, was found to be a moderate sensitizer.

DATA QUALITY:

Reliability: Reliability Code 1

Data Reliability Remarks:

OECD/GLP Protocol and Report - See reference below

REFERENCES:

1. Tepic-G: Magnusson & Kligman Maximazation / Study in the Guinea Pig, Project Number 14/14, 12/25/88.
2. Study conducted by Safepharm Laboratories Limited, Derby, UK.
3. Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
4. Magnusson B. & Kligman A.M., J. Invest. Dermatol. (1969) 52: 268-276.

13.6d

13.6 Dermal Sensitization Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD 406: Skin Sensitization

GLP (Y/N): Yes

Year Study Performed: 1997

Species: Guinea pig

Strain: Albino

Sex: M

Number of males per dose: 20

Number of females per dose: 0

Vehicle: Corn Oil

Route of Administration: Dermal

Remarks for Method:

1. Test material was TK 10 622 (ARALDIT PT 810)
2. In order to assess the cutaneous allergenic potential of TK 10622, the Maximization Test in accordance with OECD Guideline No 406 and the Directive 96/54/EEC. B.6 was carried out in 30 (20 test and 10 control) male albino guinea pigs.
3. Age at beginning pretest/ acclimatization period was 5-7 weeks.
4. Body weight at beginning of acclimatization period was 382-502g.
5. Acclimatization period was one week for the control, test and pretest group under test conditions after health examination.
6. 30 males were studied in the main study, 3 males were studied in the pretest.
7. Animal room maintained at 22 +/-3 degrees C and relative humidity of 40-70% (values above 70% during cleaning process possible). The rate of air exchange was 10-15 changes per hour and there were 12 hours light and 12 hours darkness. Music was played during the light period.
8. Diet was standard NAFAG Ecosan 945 25W4 ad libitum. Water was also available ad libitum.

9. The testing laboratory "RCC, Research & Consulting Company Ltd." Is accredited according to EN 45001 under accreditation number STS 085 by the Swiss Accreditation Service.

10. Four intradermal injections of 0.1 ml of the test article ((in a 1:1 (v/v) Freund's Adjuvant/Physiological Saline)) at concentrations of 0.0, 1.0, 3.0, and 5.0% were initially administered to the neck area of guinea pigs.

11. One week later, 0.1 ml of the test article in corn oil, was applied to the shaved backs of the guinea pigs at concentrations of 10, 15, 25, or 30%.

RESULTS:

Precision: >
Acute Lethal Value: 0
Unit: mg/kg-bw
Deaths per Dose: None
Results Remark:

Control Group: Slight erythematous reactions were observed in four out of nine animals when treated with corn oil only. The animals were pretreated with 10% SLS in paraffinum perliquidum.

Test Group: Slight erythematous reactions were observed in ten out of twenty animals at the 24 and 48 hours reading when treated with the test article at 30% in corn oil. The animals were pretreated with 10% SLS in paraffinum perliquidum.

CONCLUSIONS:

In this study 20% and 5% of the animals of the test group were observed with positive skin reactions at the 24 and 48 hour reading, respectively after the challenge with a non irritant test article concentration of 25% in corn oil. No skin reactions were observed in the control group. One week later, 5% of the animals (i.e. only one out of 20 animals, which previously reacted during the first challenge) of the test group were observed with positive skin reactions at the 24 and 48 hour reading after the rechallenge with the same test article concentration of 25% in corn oil.

Since the skin reactions fade between the 24 and 48 hour reading of the first challenge and are not reproducible during the second challenge, the skin reactions were considered to be a response of a state of hyperactivity.

Therefore, the test article, TK 10622 applied at a concentration of 25% in corn oil is considered not to be a sensitizer when used under the described test conditions.

DATA QUALITY:

Reliability: Reliability Code 1
Data Reliability Remarks:
OECD/GLP Protocol and Report - See reference below

GENERAL COMMENTS:

In this study Araldite PT810 (TGIC) was shown not to be a skin sensitizer. Other reports following OECD and USEPA guidelines also indicate that TGIC is a mild sensitizer.

REFERENCES:

1. Contact Hypersensitivity to TK 10622 in albino guinea pigs Maximization Test, 9/18/97.
2. Study conducted by RCC Umweltchemie AG, Itingen, Switzerland.
3. Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
4. Magnusson B.; Kligman A.M., 1969. The Identification of Contact Allergens by Animal Assay, The Guinea Pig Maximization Test. J. Invest. Dermatol. 52: 268-276.

13.6e

13.6 Dermal Sensitization Study:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Skin Sensitization Study
GLP (Y/N): No
Year Study Completed: 1970
Species: Guinea pig
Strain: Pirbright-Hartley
Sex; Both
Number of males: 4
Number of females: 4
Vehicle: DMSO
Route of Administration: Subcutaneous injection 0.1 ml of 0.1% w/v solution
Remarks for Method:

Tests were conducted by injecting 0.1 ml of 0.1% w/v solution of TGIC in DMSO subcutaneously into the backs of the Guinea pigs. The test article was administered every Monday, Wednesday and Friday for three consecutive weeks. Eleven days following the last injection, the animals received a "challenge dose" of the same solution. Animals were examined at 1 hr, 24 hrs and 48 hrs post-challenge for signs of a sensitization reaction.

RESULTS:

Precision: >
Acute Lethal Value: 0
Unit: mg/l(injection)
Deaths per Dose: None
Results Remark:

Following 3 weeks of subcutaneous injections and administration of a "challenge dose", TGIC was shown to be a weak sensitizer in male and female guinea pigs.

CONCLUSIONS:

TGIC was shown to be a weak sensitizer in guinea pigs.

DATA QUALITY:

Reliability: Reliability Code 2; See reference below.
Data Reliability Remarks: Because these studies used acceptable chemical evaluation methods, are well documented, reported toxicological results before

there were any requirements to do so, and (based on the data toxicology developed over the past 30 years) accurately reported the health hazards associated with TGIC, I would assign these data a Reliability Code of 2 based on the Klimisch model.

GENERAL COMMENTS:

The protocol used in this study is similar to, or perhaps a little more aggressive than the Guinea Pig Maximization Test currently used to assess dermal sensitization. Therefore, the results of this assay should be conservative predictors of dermal sensitization.

REFERENCES:

- 1) Araldite CY 182 & 183 (9347 Triglycidylisocyanurate) Oral LD 50 Rat; Dermal LD 50 Rat; Skin Irritation; Skin Sensitization; and Eye Irritation; "Diglycidyl Esters of Tetrahydrophthalic Acid and Hexahydrophthalic Acid and of Triglycidylisocyanurate". April, 1970. Study conducted by the Shell Chemical Company Tunstall Laboratory in London, England.
- 2) International Program on Chemical Safety; Concise International Assessment Document Number 8, Triglycidyl Isocyanurate, 1998.
- 3) American Conference of Governmental Industrial Hygienists, 1997 Monograph.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 5) Hodge, H. and J. H. Sterner, American Industrial Hygiene Association Quarterly, Vol. 10 pp 93-96. 1949.

14a

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Other- Test Method was EPA 81-3 (Inhalation) which became EPA OPPTS Guideline 870.1300

Test Type: Mammalian germ cell cytogenetic assay - (Chromosome Aberration)

GLP (Y/N): Yes

Year Study Performed: 1992

Species: Mouse

Strain: CD-1

Sex: M

Number of males per dose: 10

Number of females per dose: 0

Route of Administration: Inhalation-Whole Body

Doses: 0; 1.79; 10.3; and 49.6 mg/m³; + positive control

Exposure period: 6 hours /day for 5 consecutive days

Statistical Method: Levene's Equality of Variance; ANOVA; and t-tests

Remarks for Method:

- 1) Age of mice at delivery was 42 days; age at exposure was approximately 60 days.
- 2) 10 animals per dose (3 treatment groups and 1 negative [air] control) plus a positive control using cyclophosphamide
- 3) Vehicle was air.
- 4) Test duration was 6 hours/day, 5 days/ week.
- 5) Chromosomal Aberration Test was performed. The only clinical observation performed was body weight and body weight gain.
- 6) One hundred metaphase spermatogonial cells (50 cells/ testis) were evaluated for chromosome number, chromosome- or chromatid-type aberrations and further classified for deletions or exchanges.

RESULTS:

Effects of Mitosis:

The test article was toxic to spermatogonial metaphase cells of mice exposed at 10 and 50 mg/m³. The Mitotic Index decreased as the concentration of the test article increased.

Genotoxic Effect: Negative

Statistical result: The mitotic index was significantly reduced ($0.01 > p > 0.001$) for the 10 mg/m³ group. The mitotic index was significantly reduced ($p < 0.001$) for the 50 mg/m³ group.

Results Remark:

- 1) There was no mortality at any dose.
- 2) Due to the toxicity of the test article at 10 and 50 mg/m³, the statistical evaluation of aberration frequencies was confined to the air exposed control group, the 1.79 mg/m³ exposure group and the cyclophosphamide positive control group.

CONCLUSIONS:

The test article " did not produce statistically significant increases in the incidence of chromosomal aberrations among virgin male CRL:CD1 (ICR) BR mice treated at the 2.5 mg/m³ target concentration 6 hours per day for 5 consecutive days."

DATA QUALITY:

Reliability: Reliability Code 2. See reference below.

Data Reliability Remarks: Study provides necessary data and was conducted in accordance with EPA guidelines in place as of 1992.

REFERENCES:

- 1) PL90-810: Chromosomal Aberration Assay in Mouse Spermatogonial Cells; Study conducted by Bushy Run Research Center, Exton, PA and completed on March 5, 1992.
- 2) International Program on Chemical Safety; Concise International Assessment Document Number 8, Triglycidyl Isocyanurate, 1998.
- 3) American Conference of Governmental Industrial Hygienists, 1997 Monograph.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

14b

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 483 (with one slight modification) See Method Remarks Below

Test Type: In Vivo Chromosome Aberration and Cytogenetics Assay.

GLP (Y/N): Yes

Year Study Performed: 1992

Species: Mouse

Strain: CD-1

Sex: M

Number of males per dose: 10

Number of females per dose: 0

Route of Administration: Inhalation with oral control

Doses: See Method Remarks

Exposure Period: 6 hours/day for 5 consecutive days.

Statistical Method: See below

Remarks for Method:

This study utilized a combination of test articles, dosages and routes of exposure to evaluate the chromosome damaging potential of TGIC and powder coating formulations containing 10% TGIC. The experimental design followed OECD Method 483 except that a single harvest of spermatogonial cells was performed 6 hours after the final exposure to the test material. The experimental design is best described by the following information:

Group 1 was a negative control group which was exposed to pure air via nose only inhalation;

Group 2 received pure TGIC via inhalation at a dose of 7.8 mg/m³;

Group 3 was exposed to a Powder Coating formulation which contained 10% TGIC. Exposure was via inhalation at a dose of 95.3 mg/m³;

Group 4 was exposed to a Powder Coating formulation which contained 10% TGIC. Exposure was via inhalation at a dose of 255.3 mg/m³;

Group 5 was exposed to pure TGIC at a dose of 115 mg/kg. The exposure route was via oral gavage;

Group 6 was an oral positive control group in which animals were exposed to cyclophosphamide via gavage; and

Group 7 was a positive control group for the cytogenetics assay. Animals in this group were exposed to Mitomycin -C intraperitoneally at a dosage of 3 mg/kg.

Pure TGIC at a dose of 7.8 mg/m³ via inhalation; Pure TGIC at 115 mg/kg/day via oral gavage; 10% TGIC powder at 100 and 255 mg/m³ via inhalation.

Mice were approximately 6 to 7 weeks old at the beginning of the study, with body weights ranging from 21.8 to 33.2g.

There were 10 animals per treatment group in groups 1 through 5, and 5 animals per group in groups 6 and 7.

The vehicle for exposure groups 1 through 4 was purified air.

Clinical observations included changes in general appearance, respiratory patterns, and behavior.

Group mean and absolute testes weights were recorded.

Testes were examined both macroscopically and microscopically and the number of cells exhibiting chromosomal aberrations was evaluated.

RESULTS:

Effects on Mitosis: Not specified

Genotoxic Effect: Negative

Statistical Result: The cytotoxic ratios for Groups 5 and 7 were significant at $p < 0.01$ and $p < 0.001$, respectively. Total aberrations for Groups 3, 5, and 7 were significant at $p < 0.05$, 0.01 and 0.001, respectively.

Results Remarks:

No deaths occurred during the study and no adverse effects on body weight were detected. There were no treatment-related effects to the study animals noted during the study.

Cytotoxic Ratio:

None of the TGIC inhalation dose groups had a cytotoxic ratio that showed a statistically significant difference from the vehicle control group. The TGIC oral dose group had a cytotoxic ratio which was significantly lower than that of the vehicle control group ($p < 0.001$) indicating marked toxicity to the spermatogonial cells.

There was no significant reduction in the cytotoxic ratio in the cyclophosphamide dose group, whereas in the mitomycin-C dose group there was a highly significant reduction.

Chromosome Aberrations:

When the frequency of cells with aberrations, either including or excluding gaps, for any of the TGIC dose groups were compared with the vehicle control group, none were statistically significant. The frequency of cells with aberrations excluding gaps in the TGIC Technical oral dose group was not quite significant with a p value of 0.077. However, when the total frequency of aberrations were compared, then the TGIC 10% Powder dose group at 100 mg/m³ was significant at $p < 0.05$ when gaps were included. This may be considered to be a

statistical false positive error due to the number of statistical comparisons made and the absence of any dose-response relationship. In the in the TGIC oral dose group, a high level of significance was observed ($p < 0.01$) when gaps were included or excluded. This dose group was typified by a large proportion of the cells with aberrations having more than one aberration per cell. None of the vehicle control cells were observed to contain more than one aberration per cell.

The oral positive control group (cyclophosphamide) did not give any increase in the frequency of aberrant cells. The dose level used (50 mg/kg) would normally give marked toxic and clastogenic effects in bone marrow tissue, therefore, it must be concluded that the cell cycle kinetics of spermatogonial cells are such that the effects of this chemical cannot be detected at a 24 hour sacrifice. The intraperitoneal positive control chemical (mitomycin C) gave a very strong clastogenic and toxic response in the spermatogonial cells indicating that the system was able to detect chromosome damage.

CONCLUSIONS:

TGIC, either in the technical form or as a 10% powder, did not induce significant toxicity or clastogenicity in the spermatogonial cells of mice exposed via the inhalation route.

TGIC Technical given by the oral route induced marked toxic effect in the spermatogonial cells of mice and also gave an equivocal response in terms of chromosome aberrations.

DATA QUALITY:

Reliability: Reliability Code 1;
Data Reliability Remarks: See Klimisch reference below

GENERAL COMMENTS:

This particular study does not fit neatly into any of the categories of test type provided in the HPV Tracker software. Therefore, after discussions with EPA, it was decided that the data may fit either in this In Vivo Toxicity category, or in the Reproductive Toxicity category.

This study provides data to suggest the oral high dose (115 mg/kg/day) systemic toxicity of TGIC, and data to conclude that relatively high workplace inhalation concentrations of TGIC (7.8 mg/m³) do not induce clastogenicity or chromosome aberrations.

REFERENCES:

- 1) TGIC Technical and TGIC 10% Powder: Chromosome Analysis in Mouse Spermatogonial Cells, Comparative Inhalation Study. Study conducted for Nissan Chemical Industries, Ltd. Tokyo, Japan by Safepharm Laboratories Limited, Derby, UK; May, 1992.
- 2) Number of cells with aberrations and total number of aberrations were calculated using Fishers Exact Test.
- 3) Cytotoxic ratios were compared using a Chi² Test and if necessary a one-way analysis of variance.

4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

14c

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 483

Test Type: Evaluate the chromosome damaging potential

GLP (Y/N): Yes

Year Study Performed: 1990

Species: Mice

Strain: B6D2F1 mice (a hybrid of C57B1/6 x DBA/2 origin)

Sex: M

Number of males per dose: 5

Number of females per dose: 0

Route of Administration: Intraperitoneal

Doses: 28.75, 57.5, 115 mg/kg

Exposure Period: One dose/day for 5 consecutive days

Statistical Method: Lovell et. Al. 1989

Remarks for Method:

- 1) 30 Adult male B6D2F1 mice (a hybrid of C57B1/6 x DBA/2 origin).
- 2) Weight range on day 1 of treatment was 27-31 g.
- 3) Age on day 2 of treatment was 82 days.
- 4) Acclimatization period was 18 days.
- 5) Temperature range during assay was 18-24 degrees C.
- 6) Humidity range during assay was 46-66%.
- 7) Vehicle was 0.5% (w/v) carboxymethyl cellulose (CMC).
- 8) Doses given were 29.75, 57.5, or 115 mg/kg.
- 9) Mitomycin C was freshly dissolved in saline at 0.012 mg/ml to serve as the positive control and administered intraperitoneally at 0.3 mg/kg (on day 4).
- 10) The negative control was 0.5% CMC.
- 11) Animals were dosed as follows:
5 animals orally at 28.75 mg/kg

5 animals orally at 57.5 mg/kg
10* animals orally at 115 mg/kg
5 animals ip at MMC, 0.3 mg/kg

*Includes an additional 5 mice to be included in the cytogenetic analysis if required to replace animals that died at this dose level or animals that suffered excessive cytotoxicity.

12) Where possible, 50 metaphases from each testis were analyzed for chromosome aberrations. Cells with 38 (ie., 2n-2) or more chromosomes were considered acceptable for scoring. Cytotoxicity was assessed by determining the cytotoxic ratio in samples of at least 100 cells per animal.

RESULTS:

Effects on Mitosis: NA

Genotoxic Effect: Positive

Statistical Result: For the low dose $p < 0.01$. For the middle dose results NS. For the high dose, $p < 0.001$. In all other cases statistical significance was defined as $p < 0.05$.

Results Remarks:

Structural aberrations: Group totals of aberrant cells excluding gaps in treated animals were higher than those in controls at all dose levels although increases were only statistically significant at the low and high doses. Mean frequencies of aberrant cells in several animals exceeded historical negative control ranges (based on published data) at all dose levels. It is noteworthy that although fewer aberrations, in total, were observed at the intermediate dose level than at the other 2 dose levels, several chromatid exchanges were observed, more in fact than at the low dose level. These are extremely rare events in untreated animals and thought to reflect the induction of aberrations. The lack of a clear dose relationship for these data is therefore likely to be fortuitous.

Numerical Aberrations: No endoreduplicated cells were observed. Mean frequencies of hyperdiploid cells were slightly higher in control animals than in treated groups.

CONCLUSIONS:

It is concluded that the TK 10622 was able to induce structural chromosome aberrations in the spermatogonial cells of the B6D2F1 mice.

DATA QUALITY:

Reliability: Reliability Code 1. See reference below.

Data Reliability Remarks: This is an OECD GLP protocol and report provides the data needed to properly evaluate this endpoint.

REFERENCES:

- 1) Study to Evaluate the Chromosome Damaging Potential of TK 10622 PT 810 (TGIC, 97%) by Its Effects on the Spermatogonial Cells of Treated Mice, October, 1990.
- 2) Study conducted by Hazleton Microtest, University Road, Heslington, York YO1 5DU, United Kingdom.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

14d

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guidelines Followed: Unknown

Test Type: Mammalian germ cell cytogenetic assay

GLP (Y/N): Yes

Year Study Performed: 1986

Species: Mouse

Strain: TIF: MAGF (SPF), NMRI-derived

Sex: M

Number of males per dose: 15

Number of females per dose: 0

Route of Administration: Oral by stomach tube

Doses: 42.7 and 128 mg/kg

Exposure Period: 5 consecutive daily doses

Statistical Method: None cited

Remarks for Method:

1) Animal species was male mice, TIF: MAGF (SPF), NMRI-derived.

2) Test material was TK 10 622 (ARLDIT PT 810).

3) Route of administration was oral by stomach tube.

4) Dosage was 42.7 and 128 mg/kg.

5) No of animals per group:

- In the tolerability test group 4 males;
- In the mutagenicity test group: 15 males;
- In the treatment group: 15,
- In the negative control group: 12.

6) Vehicle and negative control groups received arachis oil.

7) TK 10622 (ARALDIT PT 810) was administered by stomach tube once daily on each of five consecutive days. The mice were sacrificed on the fifth day after the first dose, three hours after receiving an intraperitoneal injection of 10 mg/kg colcemid, and drop preparations were made of the testicular parenchyma.

The investigations were performed to detect any mutagenic effects of the substance on the germinal epithelium and in particular on the spermatogonia. It

has been proven that mutagenic activity can be demonstrated by chromosomal examination of spermatogonia.

8) Tissue Preparation: Twelve animals of the control group and ten animals each of the treated groups were used for tissue preparation according to the following method: The testes were processed and drop-preparations made by the air drying technique according to a modification of the method described by Schleiermacher (1966). The only departures from method were in the centrifugation process, the first centrifugation being performed at 200 x g for 10 minutes and subsequent centrifugations at 150 x g for 5 minutes.

9) Scoring of the slides: 100 metaphase figures from seven animals in the control group, from eight animals in the low dose group and from three animals in the high dose group treated with TK 10 622 (ARALDIT PT 810) were examined for the following aberrations: a) specific aberrations: breaks, exchange, deletions, fragments and minutes, b) unspecific aberrations: gaps and chromosome decay, c) numerical aberrations (metaphases with >2n chromosomes).

RESULTS:

Effects on Mitosis: NA
Genotoxic Effect: Positive
Statistical Result: Not cited
Results Remarks:

One hundred metaphase plates each from seven mice in the control group and from eight mice of the low-dose group treated with TK 10 622 (ARALDIT PT 810) were examined. Due to a cytotoxic effect on the spermatogonial cells caused by the high dose of 128 mg/kg, only three of the ten animals processed in this group furnished sufficient amount of well spread spermatogonial cells for scoring. The chromosome displays from the animals in the control group showed one metaphases out of altogether 700 metaphases with a specific aberration in the form of a minute. In the 42.7 mg/kg group four metaphases with a specific chromosomal aberration each were found, one in the form of a chromatid exchange, one in the form of a chromatid fragment and two in the form of a minute each. In addition to the regular number of single metaphases scored for this dose, a group of cohering metaphases displayed an is-chromatid break and a chromatid exchange. In the three animals available for scoring at the high dose group, seven out of 300 metaphases with specific chromosomal aberrations were detected, one metaphase showed an iso-chromatid fragment had a double minute, two a chromatid break each, one a chromatid fragment, one a minute, one and iso-chromatid fragment and one metaphase an iso-chromatid break. At the dose of 128 mg/kg one numerical aberration (2n+1) was registered.

CONCLUSIONS:

The results obtained indicate that under the given experimental conditions, TK 10 622 (ARALDIT PT 810) exerted a mutagenic action on mouse spermatogonia.

DATA QUALITY:

Reliability: Reliability Code 2. See reference below.
Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

- 1) Chromosome studies on male Germinal Epithelium of mouse, spermatogonia, 7/29/86.
- 2) Study conducted by CIBA-GEIGY LTD., Basel Switzerland.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) Adler, I.-D.: Comparative cytogenetic study after treatment of mouse spermatogonia with mitomycin C. Mutation Research 23, 369-379 (1974).
- 5) Benirschke, K. and Brownhill, L.E.: Heterosexual cells in testes of chimeric marmoset monkeys. Cytogenetics 2, 331-341 (1963).
- 6) Evans, E.P., Breckon, G. and Ford, C.E.: An air-drying method for meiotic preparations from mammalian testes. Cytogenetics 3, 289-294 (1964).
- 7) Mueller, D. Grehn, F. and De Parade, G: Feulgen cytophotometric absorption measurements in prophase stages of meiosis in the male Chinese hamster. Beitr. Path. 148, 388-401 (1973).
- 8) Schleiermacher, E.L: Ueber den Einfluss von Trenimon und Endoxan auf die Meiose der maenlichen Maus. I. Methodik der Humangenetik 3, 127-133 (1966).

14e

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Mutagenicity in Mouse Spermatogonial Cells -OECD Method 483

Test Type: Cytogenetic assay

GLP (Y/N): Yes

Year Study Performed: 1989

Species: Mouse

Strain: CR

Sex: M

Number of males per dose: 10

Number of females per dose: 0

Route of Administration: Oral gavage

Doses: 30, 125, and 350 mg/kg

Exposure Period: 5 consecutive days

Statistical Method: The Krushkal-Wallis Test

Remarks for Method:

- 1) Adult male mice, strain ICR were used.
- 2) A commercial diet (Purina certified laboratory chow #5002) and water was available ad libitum. Animals were quarantined for at least five days before being placed on study.
- 3) Animals were randomly assigned to study groups and were individually weighed prior to the initiation of the study. All animals were dosed based upon the individual body weights. Animals were uniquely identified by ear tag. Dose or treatment groups were identified by cage card.
- 4) The dose levels administered in the assay were 30, 125, or 350 mg/kg body weight and were administered by oral gavage.
- 5) The animals used in the assay were dosed for five consecutive days. Triethylenemelamine (TEM) at 1.3 mg/kg was used as the positive control and was administered by a single intraperitoneal injection at a volume of about 10 ml/kg. The vehicle control consisted of peanut oil and was administered concurrently with the test article by oral gavage at a volume of 10 ml/kg. The weight range of the males used in this assay was 25.8 to 40.7 grams.
- 6) Sixty total animals were used in this assay in the following fashion:

Treatment	Primary Group Males	Secondary Group Males
30 mg/kg	10	
125 mg/g	10	
350 mg/kg	10	10
Vehicle Control	10	
Positive Control	10	

- 7) Age of animals was 8 « weeks at the initiation of dosing (day 1).
- 8) Analyses were performed on a per animal basis for the following variables:
- Number of structural aberrations (per cell, per animal)
 - Number of cells with at least one structural aberration
 - Number of cells with 2 or more structural aberrations
- 9) The Kruskal-Wallis test was performed at the alpha (p value) of 0.05 to determine whether any of the mean values (between the vehicle control and dose levels) were significantly different from each other.

RESULTS:

Effects on Mitosis: NA

Genotoxic Effect: Positive

Statistical Result: The positive control, 125 and 350 mg/kg treatments significantly increased the number of cells with aberrant chromosomes. (P < 0.05)

Results Remark:

No toxic effects were noted in any of the animals observed each day at the time of the dosing and periodically throughout the duration of the assay. Prior to colchicine administration one vehicle control (#0816) was noted to have a mass in the left side of the groin. At the time of the bone marrow harvest this mass was determined to be approximately 1 x .075 cm in size and was filled with green pus. All other animals appeared healthy although all had slightly scruffy coats. No significant reductions in body weight were observed in any of the males in any of the dose groups although a significant reduction on body weight was induced in those males treated with the positive control. The individual animal aberrations data from this trial are found in Tables 3 and the summarized aberrations data is listed in Table 5 of the report. Due to poor metaphase quality and apparent cellular toxicity at the 350 mg/kg dose level, an attempt was made to analyze metaphase cells from all harvested animals in the primary and secondary groups. The results for only those animals from which more than 50 metaphase cells could be analyzed are presented in the individual animal data tables.

CONCLUSIONS:

The test article was suspended in peanut oil and dosed by oral gavage at 30, 125, and 350 mg/kg. The animals were dosed daily with the test article for five consecutive days and were killed 6 hours after the final dosing for extraction of the testes. The test article, PL88-810, induced significant frequencies of chromosomally aberrant cells at the 125 mg/kg and 350 mg/kg dose levels and is considered positive for inducing chromosomal aberrations in murine spermatogonial cells under the conditions of this assay.

Those animals in the 30 mg/kg dose group had chromosomal aberration frequencies in the range of the vehicle controls.

DATA QUALITY:

Reliability: Reliability Code 2. See reference below.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

- 1) Mutagenicity Test on PL88-810 (Araldite PT 810) in the Mouse Spermatogonial Cell Cytogenetic Assay, May 25, 1989.
- 2) Study conducted by CIBA-GEIGY Corporation, Ardsley, NY, 10502.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) Sokal, R. R., and Rohlf, F. J., In ""Biometry"", Freeman, New York, 1981. (The Krushkal-Wallis Test).

14f

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Dominant Lethal Assay Guidelines supplied by USEPA (FR.1985 and 1989) from OECD Guideline 478 (1984)
Test Type: Dominant Lethal Assay
GLP (Y/N): Yes
Year Study Performed: 1989
Species: Mouse
Strain: ICR
Sex: Both
Number of males per dose: 20
Number of females per dose: 40
Route of Administration: Oral gavage
Doses: 137.5, 275, and 550 mg/kg
Exposure Period: 3 weeks
Statistical Method: Analysis of Variance (ANOVA)
Remarks for Method:

The objective of this study was to determine the level of fetal death in untreated females following mating to males (Epstein et al., 1972 and Green et al, 1987) acutely treated with PL88-810. The postmeiotic stages of male germ cell development were evaluated (three mating periods).

- 1) Adult male and female mice, strain ICR were used.
- 2) A commercial diet (Purina Certified Laboratory Chow #5002) and water were available ad libitum. Animals were quarantined for at least four days before being placed on study.
- 3) After dosing, all males were individually housed. All females were group housed before and after the mating period.
- 4) The dose levels administered in the assay were 137.5, 275, and 550 mg/kg body weight and were administered by oral gavage.
- 5) 20 animals were in each group.
- 6) Triethylenemelamine (TEM, Polysciences, Inc, Lot #80386) at 0.3 mg/kg was used as the positive control ad was administered by a single intraperitoneal injection at a volume of about 10 ml/kg. The vehicle control consisted of peanut oil and was administered concurrently with the test article by oral

gavage at a volume of 10 ml/kg. The weight range of the male animals at the time of dosing was 22.3 - 39 grams.

7) Approximately eighteen to nineteen hours after dosing, the males were sequentially mated to two females per male. Each group was mated for a period of up to 5 days. The males were rested for 2 days and on the following Monday two new females were introduced to each male. This mating sequence was followed for three consecutive weeks after the acute dosing of the males.

8) A total of 684 animals were used in this assay in the following fashion:

Treatment	Week 1		Week 2		Week 3	
	M	F	M	F	M	F
137.5 mg/kg	20	40	20	40	20	40
275 mg/ kg	20	40	20	40	20	40
550 mg/ kg	20	40	17*	34	17*	34
Vehicle Control	20	40	19*	38	19*	38
Positive Control	20	40	20	40	20	40

* Males died during week 1 of mating

9) Age of animals was ~8 1/2 weeks at the initiation of dosing. The age of females at the time of mating was ~8 ½ weeks.

10) The Krushkal-Wallis Test was performed at the alpha (p value) 0.05 to determine whether any of the mean values between the vehicle control and dose levels were significantly different from each other.

RESULTS:

Effects on Mitosis: NA

Genotoxic Effect: Negative

Statistical Result: There were no statistically significant dominant lethal effects at $p < 0.05$

Results Remark:

No toxic effects were noted in any of the male animals immediately after dosing. On the third day of mating during the first week four males (vehicle control # 0986; 137.5 mg/kg # 0929; and 550 mg/kg #'s 0879 and 0881) were observed to have scruffy coats and had arched backs. One additional high dose male (# 0939) was noted to have an arched back, a scruffy coat and diarrhea on the morning of the following day. This animal was found dead during the afternoon observations. On the fifth day of mating during the first week, one vehicle control male (# 0968) and two more high dose males (#s 0879 and 0881) were found dead. Several animals in the high and low dose groups were observed to have scruffy coats during the rest interval between the first and second weeks of mating. These symptoms had subsided by the beginning of the second week of mating and all male animals appeared normal and healthy for the duration of the assay. No adverse health signs were noted in any of the females during the conduct of the assay. No significant reductions in body weight were observed in any of the males in any of the dose groups. The statistical evaluation of the implantation data indicated that no significant effects of the test article were induced at any dose levels on the total number of implantations, the frequency of dead implantations, the proportion of females with either one or more, or two or more dead implantations, or on the frequency of dead implants relative to the total number of implants in each female. In addition, no significant reduction in fertility was noted in either the test article or positive control groups. It should be noted that one vehicle control female (2nd week of mating Male # 937/

Female # 1385) was found to have all late embryonic deaths. Since this was a very unusual finding the statistical analyses were also conducted after the removal of this data from the database. Again, no statistically significant responses at any of the endpoints were observed. The positive control, TEM, induced a large and significant increase in the frequency of dead implantations, the total number of dead implantations, and in the proportion of females with either one or more or two or more dead implantations during each mating week and in the frequency of dead implants relative to the total number of implants in each female.

CONCLUSIONS:

The test article, PL88-810, was considered negative for inducing dominate lethal mutations in the post meiotic germ cells of male mice under the conditions of this assay.

DATA QUALITY:

Reliability: Reliability Code 2. See reference below.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

GENERAL COMMENTS:

The results of this assay are further supported by another GLP Dominant Lethal Study via the inhalation route.

REFERENCES:

- 1) Mutagenicity Test on PL88-810 (Araldite PT 810) in the Mouse Dominant Lethal Assay, May 23, 1989.
- 2) Study conducted by Hazleton Laboratories America, Inc., Kensington, MD.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) Sokal, R. R., and Rohlf, F. J., In ""Biometry"", Freeman, New York, 1981. (The Krushkal-Wallis Test).
- 5) Epstein, S., Arnold, E. Andrea, J., Bass, W., and Biship, Y.: Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse. Toxicol. Appl. Pharmacol., 23:288-325, 1972.
- 6) Gree, S., K.S. Lavappa, M. Manandhar, C. -J. Shew, E. Whorton, and J.A. Springer: A Guide for Mutagenicity Testing Using the Dominant Lethal Assay. Mutat. Res., 198: 167-175, 1987.

14g

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Test was performed according to OECD Guideline 479

Test Type: Sister Chromatid Exchange Assay

GLP (Y/N): Yes

Year Study Completed: 1984

Species: Hamster

Strain: Chinese

Sex: Both

Number of males per dose: 8

Number of females per dose: 8

Route of Administration: Oral by stomach tube

Doses: 35, 70, or 140 mg/kg

Exposure Period: Single exposure via oral gavage

Statistical Method: T-Test at the level of one percent. ($p < 0.01$)

Remarks for Method:

- 1) Route of administration was oral (stomach tube) and consisted of a single oral dose.
- 2) Dosages were 0.0 (negative control with arachis oil) 35, 70, 140 mg/kg in arachis oil (vehicle).
- 3) Number of animals per group was 9 females and 8 male animals in each treatment control group.
- 4) Chinese hamsters (*Cricetulus griseus*) of both sexes were used in this study.
- 5) Weight of males was 20-28 g, females was 21-28g. Age of males was 6-10 weeks, females was 4-9 weeks.
- 6) Standard diet: NAFAG No. 924. Tap water ad libitum. The animals were kept in an air-conditioned room at a temperature of 23 degrees C and a relative humidity of 56-68%. The room was illuminated for 12 hours daily.
- 7) The treatment groups and the control groups consisted of eight female and eight male animals each. The animals were treated by oral gavage and received a single dose of the test material.
- 8) As a positive control 7,12-Dimethylbenz(a)anthracene (DMBA) was administered orally at dosages of: 100 mg/kg in 20 ml/kg with 0.5% Sodium

Carboxymethylcellulose (CMC). Arachis oil at a dose of 20 ml/kg served as the negative control.

9) Bone marrow from the shafts of both femurs was suspended in 1% sodium citrate solution for hypotonic treatment, kept in a water bath at 4 to 6 degrees C for 45 min and then centrifuged for 10 min at 200 x g. The pellets were then fixed in methanol acetic acid 3:1 for a period of 30 min, resuspended, centrifuged for 5 min at 150 x g, and stored in fresh fixative overnight at 4 degrees C. Finally the pellets were again centrifuged for 5 min at 150 x g and resuspended in some 0.5 ml fixative in order to obtain a more concentrated cell suspension.

10) These specimens were pipetted onto wet slides and air dried.

11) The air dried slides then were treated with a solution of bis-benzimide (H 33258) for 15 min, rinsed in McIlvaine-buffer pH 8.0 and irradiated in this buffer at 50 degrees C with UV-light reaction in 60 degrees C 2 x SSC (standard sodium citrate) for 90 min, the slides were stained in 40% Giemsa for 20-40 min, well rinsed, cleared in Xylol and mounted in Eukitt.

12) The slides of four female and four male animals each of the treatment groups and of the control groups were examined. Twenty five differently stained metaphases of the second cell-cycle with BUdR-substitution were analyzed per animal for the number of SCE's following specific criteria.

RESULTS:

Effects on Mitosis: NA
Genotoxic Effect: Negative
Statistical Result: NA
Results Remark:

1) T-test, p was greater than or equal to 0.01.

2) In the various dose groups no significant increase of the number of SCE's was found in comparison with the negative control.

3) The positive control group showed a highly significant increase of SCE's per cell (8.91) in comparison with the negative control (5.38 SCE's/cell).

CONCLUSIONS:

The results obtained indicate that "under the given experimental conditions TK 10622 does not provoke any effect interpretable as being suggestive of a mutagenic property".

DATA QUALITY:

Reliability: Reliability Code 2. See reference below.
Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

GENERAL COMMENTS:

The oral LD50 was found to be 1672 (811-9863) mg/kg in Chinese hamsters of either sex (cf. Lab. Report: GU 2, dated August 4, 1982).

REFERENCES:

- 1) Sister Chromatid Exchange Studies on Somatic Cells of Chinese Hamsters, 2/10/84.
- 2) Study conducted by CIBA-GEIGY Limited, Basel, Switzerland.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

14h

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Test was performed according to OECD Guideline 484
Test Type: Mouse Spot Test
GLP (Y/N): Yes
Year Study Performed: 1986
Species: Mouse
Strain: See general comments
Sex: F
Number of males per dose: 0
Number of females per dose: 77
Route of Administration: Intraperitoneally
Doses: 13.5, 27.0, or 54 mg/kg.
Exposure Period: A single injection, the 10th day after conception.
Statistical Method: Chi-Square followed by McCullagh, 1983
Remarks for Method:

- 1) Test material was TK 10 622 (ARALDIT PT 810).
- 2) Male mice of "T-Stock" and female C57 BL/6 mice were used for this study. This study required cross breeding of mice.
- 3) In the mutagenicity test, each group consisted of 48 male and 96 female mice.
- 4) The vehicle and negative control was arachis oil.
- 5) Dosages were 13.5, 27.0, or 54 mg/kg.
- 6) Mature mice (males = "T-Stock"; females = C 57 BL/6; female:male ratio was 2:1), aged 3-4 months were obtained from Bomholtgard Ltd. Denmark. The bodyweight of the males was 19-30 g (mutagenicity test); the body weight of the females was not determined.
- 7) The animals were fed a standard diet of NAFAG No. 890 pellets with tap water ad libitum and were kept in an air conditioned room at a temperature of 21-23 degrees C and a relative humidity of 42-66%, illuminated for 12 hours daily.
- 8) The test article was administered intraperitoneally to groups of 77 successfully mated females. All presumable pregnant females were treated on the 10th day after conception. Treatment consisted of a single intraperitoneal

injection of the respective dose. The female animals of the control group received the vehicle only:

a. TK 10 622: was administered at dosages of 13.5, 27.0, and 54.0 mg/kg in 10 ml/kg arachis oil.

b. 10 ml/kg arachis oil served as the negative control. Manufacturer of arachis oil: Siegfried AG, Switzerland.

9) Cumulative data from positive control experiments with ethyl methane sulfonate (EMS), 100 mg/kg in 10 ml/kg 0.96% sodium chloride solution (i.p.), collected between September 1983 and September 1985, were compared to data derived from a historical vehicle control with sodium chloride solution of HBSS.

RESULTS:

Effects on Mitosis: NA

Genotoxic Effect: Negative

Statistical Result: Statistical results/conclusions not discussed in this report.

Results Remarks:

1) Of the 77 presumable pregnant females per dose group, the following numbers actually were pregnant and gave birth to litters:

Control = 56;
13.5 mg/kg = 60;
27.0 mg/kg = 57;
54.0 mg/kg = 60.

2) The average litter sizes registered were:

Control = 6.79;
Treatment Groups 13.5, 27 and 54.0 mg/kg were 7.02, 6.91 and 6.22, respectively.

3) The 370 animals from the control group and 415, 374, and 359 animals from the groups treated with 13.5, 27, and 54.0 mg/kg, respectively, were examined for color spots. The following percentages of animals with recessive (RS) and white mid-ventral (WMVS) spots were recorded from gross observations:

RS = 0.54% (Control), 0.72% (13.5 mg/kg), 1.07% (27.0 mg/kg), 0.28% (54.0 mg/kg)
WMVS = 0.54% (Control), 0.72% (13.5 mg/kg), 1.34% (27.0 mg/kg), 1.95% (54.0 mg/kg)

CONCLUSIONS:

It is concluded that under the given experimental conditions, no evidence of mutagenic effects was obtained in the offspring of pregnant mice treated with TK 10 622.

DATA QUALITY:

Reliability: Reliability Code 2. See reference below.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

GENERAL COMMENTS:

Males used in this study were T-Stock and female mice were C57 BL/6 at a ratio of 2 females /male.

REFERENCES:

- 1) Mammalian Spot Test, Mouse, 8 Weeks Old, 2/11/86.
- 2) Study conducted by CIBA-GEIGY Limited, Basel, Switzerland.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) Tarone, R.E., and Gart, J.J.: On the Robustness of Combined Tests for Trends in Proportions. Journal of the American Statistical Association, No. 75, pp 110-116 (1980).

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)**TEST SUBSTANCE:**

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Method according to Lutz, W. K. (1986); J. Cancer Res. Clin. Onc; 112, 85-91

Test Type: Potential for DNA Binding

GLP (Y/N): No

Year Study Performed: 1990

Species: Mouse

Strain: TIF:Mag F (SPF)

Sex: M

Number of males per dose: 52

Number of females per dose: 0

Route of Administration: Oral gavage

Doses: 180, 18, or 3.6 mg/kg (0.25 ml)

Exposure Period: Single oral exposure

Statistical Method: NA

Remarks for Method:

- 1) Test material was TK 10 622 (ARALDIT PT 810).
- 2) The species used in this test were male mice, strain Tif: Mag f (SPF). 52 mice were used.
- 3) The acclimatization period was at least one week.
- 4) The average weight on the day of administration of the test compound was 25g.
- 5) Standard diet: NAFAG No. 890 (Nafag, Gossau, Switzerland) and tap water ad libitum. The animals were kept in an air-conditioned room at a temperature of 22+/-1 degrees C and a relative humidity of 55+/-5%. The room was illuminated for 12 hours daily.
- 6) The test compound was suspended in 1% aqueous propylene glycol or in sesame oil to receive concentrations of about 18 mg/ml (700 microCi/ml), 1.8 mg/ml (70 microCi/ml) and 0.36 mg/ml (14 microCi/ml) , respectively. The mice received about 0.25ml (180 mg/kg, 18 mg/kg, or 3.6 mg/kg) of the suspension or mixture in oil by oral gavage.
- 7) After administration of the test compound in oil, the level of radioactivity in the blood was lower by a factor of about two than after administration in

aqueous solution. However, the time dependency of the radioactivity in the blood was similar for both application forms. This indicates a reduced absorption of the compound from the intestine after application in oil. In agreement with this finding the level of radioactivity in liver and testes after application in oil was also lower by a factor of about 2 in comparison to the organ levels after administration in aqueous solution.

RESULTS:

Effects on Mitosis: NA

Genotoxic Effect: Positive

Statistical Result: A statistical analysis of the results was not presented in this report.

Results Remark:

1) The vehicle used for the administration of the test compound had no influence on the distribution of the metabolites in the blood. Three hours after the administration, about 4% of the total radioactivity in the blood was shown to be free TriEp. The level of TGIC in the blood was around 100 micrograms/ml. Free hydrolysis products of TGIC amounted up to 10% (DiEp), 8% (MonoEp) and 17% (TriDiol) of the total radioactivity in blood. Eight hours after administration, no TriEp could be detected in the blood, at a limit of detection of < 0.1% of the total radioactivity (<4 micrograms/ml blood). At this time, free hydrolysis products of the parent compound accounted for 3% (DiEp), 1.5% (MonoEp), and 6.3% (TriDiol) of the total blood radioactivity.

2) During the first 8 hours 17% or 7% of the radiolabel was excreted in urine, after administration of the test compound in aqueous solution or in oil, respectively. Between 8 and 24 hours after the administration only minor radioactivity was excreted in the urine. The lower amount of urinary excretion after the administration in oil again supports the hypothesis that the absorption of TGIC in oil is lower compared to the absorption from an aqueous vehicle.

3) In the testes CBI values of around 0.3 resulted from administration of the test compound in aqueous solution. Again, after administration of TGIC in oil, the CBI values were lower by a factor of about 2. Since TGIC is a direct alkylating agent (Sagelsdorff and Ogorek, 1989) radioactivity on the DNA of the stomach, which is the first site of exposition after oral administration, should be the highest. In fact, CBI values of up to 10 could be calculated for stomach DNA.

4) These results indicate that the adduct formed with TGIC is a purine adduct.

5) Since TGIC can be inactivated by epoxide hydrolysis in vivo it was considered important to test whether, at a certain dose below the used 200 mg/kg, cellular defense mechanisms would be able to inactivate TGIC completely and therefore prevent DNA from alkylation. This dose could then be used as a no-effect level.

6) No radioactivity could be detected on the testes DNA at 5 mg/kg, at a limit of detection of 0.6 dpm/mg (CBI:<0.4) Therefore, if a threshold dose exists, where no TGIC-DNA adduct formation occurs, this dose must be lower than 5 mg/kg.

CONCLUSIONS:

The maximal covalent binding index (CBI) of 2 for TGIC in liver places the test compound amongst the weak genotoxic agents. This CBI value is about 10,000 times lower than the corresponding value for the strong hepatocarcinogen aflatoxin B1 (CBI of ca. 20,000) and about 200 times lower than the value for the moderate carcinogen 2-acetylaminofluorene (CBI of ca. 400) (Lutz, 1986). The presence of DNA adducts in the testes of the treated animals shows that the reactive compound is not completely inactivated by spontaneous and/or enzymatic hydrolysis of the epoxide functions. The linear dose dependency of DNA adduct formation between 5 mg/kg and 200 mg/kg suggests that no threshold dose exists, where DNA binding is prevented by metabolic inactivation of the test compound. The in vivo mutagenicity results, therefore, can likely be explained by DNA adduct formation.

DATA QUALITY:

Reliability: Reliability Code 2. See reference below.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

GENERAL COMMENTS:

This is an excellent PK Report which describes DNA binding, DNA adduct formation and the pharmacokinetic properties of Araldite PT 810.

REFERENCES:

1. Potential for DNA Binding of Araldite PT 810, 10/2/90
2. Study conducted by CIBA-GEIGY Limited, Basel, Switzerland.
3. Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

14j

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Dominant Lethal Assay Guidelines supplied by USEPA (FR.1985 and 1989) from OECD Guideline 478 (1984)
Test Type: Dominant lethal assay
GLP (Y/N): Yes
Year Study Performed: 1992
Species: Mouse
Strain: CD-1
Sex: Both
Number of males per dose: 30
Number of females per dose: 40
Route of Administration: Inhalation
Doses: 0, 2.5, 10, or 50mg TGIC/m³
Exposure Period: 6 hours per day for 5 consecutive days
Statistical Method: Weil (1970); Nonparametric via Dixon, 1990
Remarks for Method:

1) Dominant Lethal Assay Guidelines supplied by USEPA (FR. 1985 and 1989) from OECD Guideline 478 (1984). Inhalation exposure performed according to EPA Method 81-3.

2) Mice were approximately 6 weeks of age and weighed approximately 20 to 25 g when they arrived at Bushy Run. They were supplied by Charles River Breeding Laboratories, Portage, MI. All mice were acclimatized for approximately 2 weeks prior to initiation of the test. In total, there were five groups of 30 male mice/gp. The groups received: filtered air (0.0 mg TGIC/m³); 2.5; 10; or 50 mg TGIC/m³ (the vehicle and negative control, low, middle or high dose groups, respectively); or triethylenemelamine (TEM). Two of these were control groups, one received filtered air only (negative control), while the other received 0.3 mg/kg TEM (positive control) by intraperitoneal injection 48 hours prior to the commencement of the mating regimen. Approximately 24 hours after the last exposure, treated males were bred with untreated (naive) females of the same strain, one male per two females. Females were replaced weekly with a new pair of naive females for each male for a total of eight (8) consecutive weeks. All males were observed daily for clinical signs of toxicity, weighted weekly, and necropsied after the 8th week of mating. All females were observed daily from mating through sacrifice on gestational day 15. On gestational day 15, females were sacrificed and non-live and live uterine implantation sites were counted and recorded. Reproductive and gestational effects were evaluated against data generated from a concurrent positive control group of males that were exposed to

filtered air only and received 0.3 mg/kg triethylenemelamine (TEM) by intraperitoneal injection 48 hours prior to the commencement of the mating regimen.

3) A summary of clinical observations performed (clinical pathology, functional observations, etc. are provided in Table 1 of the report. The primary finding for the 50mg/m³ group are described in the results section below. No exposure-related findings were in the low or mid-dose groups or in the controls.

RESULTS:

Effects on Mitosis: None specified

Genotoxic Effect: Negative

Statistical Result: A value of 0.05 was the criterion for significance. The unit of comparison was the male, the pregnant female, or the litter (Weil, 1970).

Nonparametric data analyzed via Kruskal-Wallis/Mann-Whitney.

Results Remark:

1) During the study, the initial target doses were 2.5, 10, and 50 mg TGIC/m³ air. The actual measured doses were 1.79, 10.3, and 49.6 mg TGIC/m³, respectively. In treated males there was 10% mortality (3/30), reduced body weight gain through the second week of mating and ocular discharge or swelling, in the 50 mg/m³ dose group. According to the study authors, 50 mg/m³ was clearly above the MTD. No female mortality or changes in the rate of body weight gain were reported.

2) Effects on male fertility at 50 mg/m³ were evidenced by a reduced number of males impregnating or fertilizing females, and a reduced number of pregnant females and females with copulation plugs for the first 3 mating weeks. Effects observed during this portion of the mating regimen correspond to the effects of the test article on mature sperm and maturing spermatids, and suggest a greater toxic effect on the spermatid stage. No effects on male fertility were observed for the spermatocyte stages. Reductions in the numbers of pregnant and sperm positive females were also noted at 50 mg/m³ for mating week 6, indicating potential effects of the test article on Type B spermatogonia. There were no observed effects on male fertility associated with damage to early spermatogonia or stem cells during mating weeks 7 and 8.

3) Throughout the 8-week post-exposure mating period, there was no effect of the test substance on the numbers of resorptions/litter, the total number of implants, the numbers of viable implants, or percent postimplantation loss.

4) There were no exposure-related gross findings at necropsy in male mice.

CONCLUSIONS:

Exposure of CD-1 mice to TGIC and subsequent sequential breeding to naive females for 8 consecutive weeks resulted in general toxicity and reduced fertility due to effects on mature sperm, spermatids and spermatogonia at 50 mg/m³, and slightly reduced fertility due to the effects on early spermatids at 10 mg/m³. The NOEL for general toxicity was 10 mg TGIC/m³ of air; the NOEL for fertility effects was greater than or equal to 2.5 mg TGIC/m³; and the NOEL for dominant lethal effects was greater than 50 mg TGIC/m³. There was no dominant lethal effect on offspring of TGIC exposed males.

DATA QUALITY:

Reliability: Reliability Code 1;

Data Reliability Remarks: This 583 page EPA and OECD GLP Report provides the necessary data to allow a reasonable assessment of the dominant lethal potential of the test article. See reference below. Furthermore, results from a separate 500 plus page EPA/OECD GLP report in which TGIC (5%) was administered via inhalation as a partially reacted Powder Coating, at concentrations of 115, 975, and 1575 mg/m³, concluded that: "The "no observed effect level" (NOEL) for general toxicity was 115 mg/m³. The NOEL for effects on fertility was at least 1575 mg/m³. The NOEL for dominant lethal effects was at least 1575 mg/m³." These data further support the conclusion that TGIC does not produce dominant lethal effects.

GENERAL COMMENTS:

This particular study does not fit neatly into any of the categories of test type provided in the HPV Tracker software. Therefore, after discussions with EPA, it was decided that the data best fits in this "Genetic Toxicity In Vivo" category.

REFERENCES:

- 1) Dominant Lethal Assay of Inhaled PL90-810 Dust in CD-1 Mice. Prepared by T. L. Neepser-Bradley of Bushy Run Research Center, Export, PA for Ciba-Geigy Corporation, Hawthorne, NY. May 12, 1992.
- 2) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

14k

14 Genetic Toxicity in Vivo (Chromosomal Aberrations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Dominant Lethal Assay Guidelines supplied by USEPA (FR.1985 and 1989) from OECD Guideline 478 (1984)
Test Type: Dominant lethal assay
GLP (Y/N): Yes
Year Study Performed: 1989
Species: Mouse
Strain: ICR
Sex: Both
Number of males per dose: 20
Number of females per dose: 40
Route of Administration: Oral
Doses: 0.0; 137.5; 275; or 550 mg TGIC (in oil) /kg BW
Exposure Period: Once per day for 5 days
Statistical Method: Chi-square; ANOVA; log transformation; and t-tests
Remarks for Method:

- 1) Twenty male mice/group received TGIC via oral gavage at the dosages described above. A negative control group (peanut oil only), and a positive control group (triethylenemelamine) or TEM, administered intraperitoneally at a dosage of 0.5mg/kg BW, were also included in this study.
- 2) Approximately 18 hours after dosing each male was housed with two unexposed (naive) females and allowed to mate.
- 3) Males remained with females for up to 5 days, at which time the females were removed and the males rested for 2 days. This process was repeated 2 more times with naive females, for a total three breeding episodes.
- 4) Females were sacrificed and examined 14 days after confirmation of a copulatory plug, or 14 days from the mid point of the 5 day breeding exposure.
- 5) The results of this exposure and mating protocol are described in the Results Section below.

RESULTS:

Effects on Mitosis: None reported
Genotoxic Effect: Negative

Statistical Result: No statistically significant responses at any of the endpoints was observed.

Results Remark:

- 1) No adverse health signs were noted for any of the female mice;
- 2) No deaths or impacts on body weights were noted for male mice;
- 3) Arched backs, scruffy coats and diarrhea were noted in several mice from the negative control, low dose and high dose groups.
- 4) During the first week of mating, 1 male from the vehicle control group, and 3 males from the high dose group were found dead. No other deaths, toxic effects or clinical impacts were noted during the remainder of the study.

CONCLUSIONS:

The test article, PL88 - 810 (TGIC), was considered negative for inducing dominant lethal mutations in the post-meiotic germ cells of male mice under the conditions of this assay.

DATA QUALITY:

Reliability: Reliability Code 2:

Data Reliability Remarks: This EPA/OECD GLP Report provides the necessary data to allow a reasonable assessment of the dominant lethal potential of the test article. See reference and General Comments below.

GENERAL COMMENTS:

The basic conclusion of this report i.e., TGIC administered orally at dosages up to 550 mg/kg body weight did not induce dominant lethal effects in male mice, was further supported by data generated in more detailed and comprehensive inhalation study which is also provided in this dossier. The method described in this report does not appear to be as detailed and comprehensive as that described in the OECD protocol.

REFERENCES:

- 1) Mutagenicity Test on PL88-810 in the Mouse Dominant Lethal Assay. Prepared by Hazleton Laboratories America, Inc, for Ciba-Geigy Corporation, Hawthorne, NY. May 23, 1989.
- 2) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

15a

15 Genetic Toxicity in Vitro (Gene Mutations):

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: None cited

Test Type: Chromosome Aberration Study

System of Testing: Non-bacterial

GLP (Y/N): No

Year Study Performed: 1985

Species: Primary cultures - human lymphocytes

Metabolic Activation: With and without metabolic activation (MA) - rat livers microsomal fraction S9 using Aroclor 1254

Concentration: With MA 0.625, 1.25, 2.5, 5.0, or 10 ug/ml; Without MA 0.0625, 0.125, 0.25, 0.5, or 1.0 ug/ml

Statistical Method: Not specified

Remarks for Method:

- 1) TK 10622 (ARALDIT) PT 810) was tested for mutagenic effects on human lymphocytes in vitro. The experiments were performed without microsomal activation at concentrations of 0.0625, 0.125, 0.25, 0.5. or 1.0 micrograms/ml, and with microsomal activation at concentrations of 0.625, 1.25, 2.5, 5.0 and 10.0 micrograms/ml.
- 2) This test system permits the detection of structural chromosome aberrations in human lymphocytes in vitro induced by the test substance or by its metabolites. To ensure that any mutagenic effects of metabolites of the test substance formed in mammals are also detected, a parallel series of experiments is performed, in which its metabolic turnover is simulated in vitro by the addition of an activation mixture containing rat liver microsomes and co-factors to the cell culture.
- 3) One hundred metaphase plates from the vehicle control, from the cultures treated with the various concentrations of TK 10 622 and from the Positive controls were examined.
- 4) Test material was TK 10622 (ARALDIT PT 810).
- 5) The fourteen doses used in the Cytotoxicity Study ranged from 0.12 to 1000 micrograms/ml. In the Mutagenicity Study, doses ranged from 0.0625 to 1.0 micrograms/ml without activation, and 0.0625 to 10 micrograms/ml, with activation.

6) The test article was solubilized in DMSO, which served as the vehicle. A 1% suspension of the test article in DMSO was added to the culture media.

7) Preparation of the microsomal activation mixture: Rat liver microsomal fraction S9 was prepared from Aroclor (Analabs Inc., North Haven, Connecticut, U.S.A.) induced livers of male RAI rats. The co-factors used were NADP and Isocitric acid. 1.0 ml activation mixture contained: 0.15 ml S9 fraction and 0.2 ml of the solution with the co-factors and 0.65 ml medium. In the experiments in which the substance was metabolically activated, 1.0 ml of the activation mixture was added to 9.0 ml of cell suspension.

8) Cytotoxicity test: A preliminary cytotoxicity test was performed to determine the concentrations to be used in the mutagenicity assay. The concentration selected as the highest for the mutagenicity assay causing approximately 50% suppression of mitotic activity in comparison with the control after a 3-hour treatment followed by a 24-hour recovery phase. The human blood in this experiment was obtained from a normal donor by venipuncture. The white cells were separated by density-gradient centrifugation using Ficoll-Paque a (Pharmacia Fine Chemicals AB, Uppsala, Sweden) and maintained in blood culture medium (Chromosome Medium IA, Gibco AG, Basel, Switzerland). The -pre-incubation time before treatment was 46 hours. The substance dissolved in DMSO was added (1:100) to the cell suspension in chromosome medium IA. The cells were exposed for three hours to fourteen concentrations ranging from 0.12 to 1000) micrograms/ml of the test substance. After removal of the test substance, the cells were washed and incubated in chromosome medium for 24 hours. The percentages of mitotic suppression in comparison with the controls were evaluated by counting at least 1000 cells per concentration. This preliminary toxicity test was performed with and without metabolic activation. The concentration calculated to produce about a 50% suppression of mitotic activity in comparison with the control was used as highest dose in the mutagenicity experiments together with four concentrations corresponding to factors of 0.5, 0.25, 0.0625.

9) Mutagenicity test (treatment and chromosome preparation): The mutagenicity tests were carried out by treating human lymphocytes with the selected concentrations (0.0625, 0.125, 0.25, 0.5, 1.0 micrograms/ml without microsomal activation, and 0.625, 1.25, 2.5, 5.0, 10.0 micrograms/ml with metabolic activation). The white blood cells were prepared in the same manner as in the toxicity test. About 46 hours before exposure to the test substance, a series of Falcon flasks was seeded with human lymphocytes. Subsequently, the cells were treated for three hours, both in the presence and in the absence of rat-liver S9 activation system, with the five pre-selected concentrations of the test substance, with the positive control, or with the vehicle as negative control. In the experiments in which the substance was metabolically activated, 1.0 ml of an activation mixture was added to 9.0 ml of cell suspension. 1.0 ml activation mixture contained: 0.15 ml S9 fraction of liver from rats induced with Aroclor 1254 (Analabs, Inc., North Haven, Connecticut, U.S.A.) and 0.2 ml of a solution of cofactors and 0.65 ml medium. Mitomycin C (KYOWA HAKKO KOGYO Co. Ltd., Japan) 0.8 mg/ml, a mutagen not requiring S9 activation, and cyclophosphamide (ASTA-WERKE, Germany) 10.0) mg/ml, which requires activation, were used as positive controls.

After treatment, the cells were washed twice with 10 ml Banks BSS to remove the test substance, resuspended in chromosome medium and allowed to grow for 43.5 hours.

Two and a half hours prior to harvesting, the cultures were treated with Colcemide (0.4 micrograms /ml). The experiment was terminated by hypotonic treatment (0.075 M KCl solution) of the cells, followed by fixation

(methanol:acetic acid, 3:1). Drop preparations were made by the air-drying technique.

10) Scoring of the slides: 100 complete metaphase figures altogether from cultures of two Icon flasks in the vehicle control and in the treated groups re-examined for the following aberrations:

a) specific aberrations: breaks, exchanges, deletions, fragments and minutes;

b) unspecific aberrations: gaps, premature chromosome condensation and chromosome decay;

c) numerical aberrations (metaphases with $>2n$ chromosomes).

RESULTS:

Result: Negative

Cytotoxic Concentrations: All concentrations tested above 10ug/ml with MA; and 1.0 without MA

Genotoxic Effect: Unconfirmed

Statistical result: Not Reported

Results Remark:

1) In the experiment performed without microsomal activation, the chromosome displays from the cultures treated with the vehicle alone, as well as with the various concentrations of TK 10 622 revealed no specific chromosomal aberrations.

2) In the experiment performed with microsomal activation, the chromosome displays from the vehicle control and from the cultures treated with the concentrations of 0.625, 1.25 and 2.5 micrograms/ml showed no specific chromosomal aberrations. The cultures treated with the concentration of 5.0 micrograms/ml revealed one metaphase with an iso- chromatid break. At the concentration of 10.0 mg/ml one metaphase with a double minute was registered.

3) The incidence of specific aberrations in the cultures treated with TK 10622 is within the frequency generally observed in the control cultures and can therefore be considered spontaneous in origin.

4) The treatment of the cultures with mitomycin-C, at 0.8 mg/ml and cyclophosphamide, at 10 mg/ml, respectively (positive controls) was followed by a high incidence of specific chromosomal aberrations (16% and 24%).

CONCLUSIONS:

It is concluded that under the given experimental conditions, no evidence of mutagenic effects was obtained in human lymphocytes in vitro treated with TK 10622 (ARALDIT PT 810).

DATA QUALITY:

Reliability: Reliability Code 2; See reference below.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

- 1) Chromosome Studies on Human Lymphocytes in Vitro Using TK 10622 (TGIF), Test No 850071, November 12, 1985.
- 2) CIBA-GEIGY Limited, Basel, Switzerland.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

15b

15 Genetic Toxicity in Vitro (Gene Mutations):

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD 401, represented by Hazleton Protocol #E-401, edition 4.

Test Type: Ames test

System of Testing: Bacterial

GLP (Y/N): Yes

Year Study Performed: 1987

Species: Salmonella typhimurium

Metabolic Activation: TA-1535, TA-1537, TA-1538, TA-98, TA-100

Concentration: 1.0, 10, 100, 500, 1000, 2500, 5000, and 10000 ug/plate

Statistical Method: Not Specified

Remarks for Method:

1) The Salmonella typhimurium strains used in this assay were obtained from Dr. Bruce Ames, University of California at Berkeley (Ames et al., 1975). The following strains are used: TA-1535, TA-1537, TA-1538, TA-98, TA-100.

2) S9 Homogenate: A 9000 x g supernatant prepared from Sprague-Dawley adult male rat liver induced by Aroclor 1254 (described by Ames et al., 1975) was purchased commercially and used in this assay.

3) Positive Control Articles: Strain specific positive controls and positive controls to ensure the efficacy of the S9 mixture were assayed concurrently with the test material. Positive controls were: for all strains with metabolic activation, 2-Anthramine; without activation, Sodium Azide for TA-1535 and TA-100; 2-Nitrofluorene for TA-1538 and TA-98; and Quinacrine for TA1537.

4) Mutation assays were conducted at 8 doses from 1.0 to 10,000 micrograms per plate. The mutation assays were conducted using three plates per dose level.

5) Araldite PT 810 was examined for mutagenic activity in the Ames Salmonella/Microsome assays using Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, TA-100. The assays were conducted using three plates per dose level in the presence and absence of a metabolic activation system. The entire assay was performed twice as requested by the sponsor.

RESULTS:

Result: Positive

Cytotoxic Concentration: NA

Genotoxic Effect: Dose-response
Statistical Result: Not Specified
Results Remark:

1) The results of the assays conducted on the test material at dose levels ranging from 1.0 to 10,000 micrograms per plate in the absence and the presence of metabolic activation were positive with the strains TA-1535, TA-98, and TA-100. The results with the strain TA-1538 were also positive in the absence of metabolic activation. In the presence of metabolic activation, however, increases in the numbers of revertants were observed but these increases were not sufficient for a positive evaluation.

2) An independent replicate of this test showed positive results with strains TA-1535, TA-98, and TA-100 both with and without metabolic activation. With strain TA-138, increases in the number of revertants were observed with both non-activation and activation, but these increases were not sufficient for a positive evaluation.

3) The positive control treatments in both the non-activation and S-9 activation assays induced large increases in the revertant numbers with all the indicator strains, which demonstrates the effectiveness of the S-9 activation system and ability of the test system to detect known mutagens.

CONCLUSIONS:

The test material, Araldite PT 810, exhibited activity with the strains TA-1535, TA-98, and TA-100 in both the non-activation and the activation part of both experiments and with the strain TA-1538 in the non-activation part of the first trial of the assays conducted in this evaluation. Therefore, Araldite PT 810 was considered mutagenic to *Salmonella typhimurium* indicator organisms under these test conditions according to our evaluation criteria.

DATA QUALITY:

Reliability: Reliability Code 2; See reference below.
Data Reliability Remarks: Basic data provided; comparable to guideline/standards.
See reference below.

REFERENCES:

- 1) Mutagenicity test on ARALDITE PT 810 in the Ames Salmonella/ Microsome Reverse Mutation Assay, December 7, 1987.
- 2) Hazleton Biotechnologies, Landjuweel 11, 3905 PE Veenendaal, The Netherlands.
- 3) Ames, B.N, McCann, J. and Yamasaki, E.: Methods for Detecting Carcinogens and Mutagens with the Salmonella/mammalian-Microsome Mutagenicity Test. Mutation Res., 31:347-364, 1975.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

15c

15 Genetic Toxicity in Vitro (Gene Mutations):

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Based on KAKUNAGA (1973).

Test Type: Cell Transformation Assay

System of Testing: Non-bacterial

GLP (Y/N): Yes

Year Study Performed: 1983

Species: Mouse embryo fibroblasts BALB/3T3, clone A31-1-1

Metabolic Activation: NA

Concentration: 8.75, 17.5, 35, 70, or 140 nanograms/ml

Statistical Method: Tarone and Gart, 1980

Remarks for Method:

- 1) Test material was TK 10 622 (ARALDIT PT 810).
- 2) Test was performed on mouse embryo fibroblasts BALB/3T3, clone A31-1-1.
- 3) Number of cultures per group was 15.
- 4) The test article was dissolved in DMSO.
- 5) Dosages were 8.75, 17.50, 35, 70, and 140 nanograms /ml in transformation test.
- 6) TK 10 622 (ARALDIT PT 810) was tested for transformation-inducing effects on mouse fibroblasts (BALB/3T3) in vitro. The investigations were performed with concentrations of 140, 70, 35, 17.5 and 8.75 nanograms/ml.
- 7) The transformation assay was performed on BALB/3T3 cells treated with the selected concentrations. The procedure employed is based on that reported by KAKUNAGA (1973).
48 hours before exposure to the test substance, a series of petri dishes (60 x 15 mm) were seeded with 5×10^5 cubed cells per dish (density 10 cubed cells /ml; 5 ml/dish) and incubated. Fifteen dishes were then treated for each of the following conditions: five pre-selected concentrations of the test substance; two positive controls (methylcholanthrene at concentrations of 1.0 microgram/ml and 3.0 microgram /ml); a negative control containing the vehicle, and an untreated negative control. The petri dishes were incubated of 72 h. After removal of the test substance, the cells were washed and incubated for 4 weeks in the growth medium, which was replenished on the tenth and the seventeenth

day. The experiment was terminated by fixing the cell monolayers with the methanol and staining with Giemsa. The stained colonies of transformed cells were examined under the microscope and counted with the naked eye. Parallel to the transformation assay, a cell-viability control was carried out. For this purpose, 200 cells per 5 ml petri dish were seeded and treated as described above. Three dishes each were used for the different concentrations of the test substance and for the negative and positive controls. The incubation time for the viability control was three days after treatment. The values obtained from the viability control are used to normalize the results from the transformation test (number of transformed cells/ cells plated), i.e., to preclude errors due to the assumption of 100% viability of the cells seeded in cultures for the transformation test. Thus, the calculated values correspond to the number of foci per 10, 000 viable cells, giving the transformation frequency.

8) The significance of differences between the treated and control cultures was tested by calculation of the fiducial limits for p according to the binomial-distribution model.

RESULTS:

Result: Negative

Cytotoxic Concentration: 140 ng/ml

Genotoxic Concentration: Unconfirmed

Statistical Result: Statistical methods were discussed in the text of this report, but p-values were not assigned to the results. P values were $P < 0.05$.

Results Remark:

The transformation test was carried out with 140 ng/ml as the highest concentration and four additional, lower concentrations, decreasing by a factor of 0.5. All five concentrations, as well as the solvent and untreated controls did not give rise to the development of foci.

By contrast, in the positive controls treated with methylcholanthrene (1.5 and 3.0 microgram /ml) development of foci was detected in 15 of 15 and 13 of 13 dishes respectively, giving transformation-frequency values of 22.1 and 73.2. Statistical comparison of these values with the controls revealed a highly significant difference.

CONCLUSIONS:

"It is concluded that under the given experimental conditions no effects were obtained." These data were interpreted as suggestive that TK 10622 did not exhibit transformative properties.

DATA QUALITY:

Reliability: Reliability Code 2; See reference below.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

1) BALB /3T3 Cell Transformation Assay (In vitro test for transformation inducing properties in mammalian fibroblasts), 6/27/83.

2) Study conducted by CIBA-GEIGY Limited, Basel, Switzerland.

- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) Tarone, R.E., and Gart, J.J.,: On the robustness of combined tests for trend in proportions. Journal of the American Statistical Association 75, 110-116 (1980).
- 5) Kakunaga, T., A Quantitative System for Assay of Malignant Transformation by Chemical Carcinogens Using A Clone Derived From the BALB/3T3 Mouse. Int. Journal of Cancer 12, 463-73, 1973.

15d

15 Genetic Toxicity in Vitro (Gene Mutations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

MEHTOD:

Method/Guideline followed: Based on KAKUNAGA (1973).

Test Type: Mammalian cell gene mutation assay

System of Testing: Non-bacterial

GLP (Y/N): Yes

Year Study Performed: 1986

Species: Mouse embryo fibroblasts BALB/3T3, clone A31-1-1

Metabolic Activation: Rat liver microsomal fraction S9 from Aroclor 1254 induced male rats

Concentration: 0.3125, 0.625, 1.25, 2.5, or 5.0 ug/ml

Statistical Method: Tarone and Gart, 1980

Remarks for Method:

- 1) Test material was TK 10 622 (ARALDIT PT 810).
- 2) Test was performed on mouse embryo fibroblasts BALB/3T3, clone A31-1-1.
- 3) Number of cultures per group was 15.
- 4) The test article was dissolved in DMSO.
- 5) Dosages were 0.3125, 0.625, 1.25, 2.5, or 5 micrograms/ml in transformation test.
- 6) TK 10 622 (ARALDIT PT 810) was tested for transformation-inducing effects on mouse fibroblasts (BALB/3T3) in vitro. The investigations were performed with concentrations of 0.3125, 0.625, 1.25, 2.5, or 5 micrograms/ml.
- 7) The transformation assay was performed on BALB/3T3 cells treated with the selected concentrations. The procedure employed is based on that reported by KAKUNAGA (1973).
- 8) 48 hours before exposure to the test substance, a series of petri dishes (60 x 15 mm) were seeded with 5×10^5 to the third cells per dish (density 10^5 cubed cells /ml; 5 ml/dish) and incubated. Fifteen dishes were then treated for each of the following conditions: five pre-selected concentrations of the test substance; two positive controls (2-acetylaminofluorene (Fluka AG, Buchs SG, Switzerland) 50 and 100 microgram/ml); a negative control containing the solvent, and an untreated negative control. The duration of treatment was 25 hours in the presence of the activation mixture. After removal of the test

substance, the cells were washed and incubated for 4 weeks in the growth medium, which was replenished twice weekly. The experiment was terminated by fixing the cell monolayers with methanol and staining with Giemsa. The stained colonies of transformed cells were examined under the microscope and counted with the naked eye.

9) Parallel to the transformation assay, a cell-viability control was carried out. For this purpose, 300 cells per Petri dish in the presence of activation mixture were seeded and treated as described above. Three dishes each were used for the different concentrations of the test substance and for the negative and positive controls. The incubation time for the viability control was five days after treatment of the cultures. The values obtained from the viability control are used to normalize the results from the transformation test (number of transformed cells/ cells plated), i.e., to preclude errors due to the assumption of 100% viability of the cells seeded in cultures for the transformation test. Thus, the calculated values correspond to the number of foci per 10,000 viable cells, giving the transformation frequency.

RESULTS:

Result: Negative

Cytotoxic Concentration: NA

Genotoxic Effect: Unconfirmed

Statistical result: Statistical methods were discussed in the text of this report, but p-values were not assigned to the results. P values were $P < 0.05$.

Results Remark:

1) The significance of differences between the treated and control cultures was tested by calculation of the fiducial limits for p according to the binomial distribution model. The number of dishes without colonies was compared with the number showing one or more colonies.

2) In the transformation test, altogether three foci in three of 15 dishes with transformed cells were found in the solvent control. In the untreated control altogether nine colonies in seven of 15 dishes were observed giving a transformation-frequency value of 4.82. At the various concentrations of the test substance (TK 10 622) from 15 dishes each four with colonies of transformed cells were found at the lowest concentration and seven, four, four and four at the further four concentrations up to the highest. The corresponding transformation-frequency values were 1.51, 4.66, 1.85, 1.65, and 2.33.

3) Statistical comparison of the results in the various concentration groups with the solvent control revealed no significant differences.

4) By contrast, in the positive controls treated with 2-acetylamino-fluorene (50 and 100 micrograms/ml) development of foci was detected in 15 of 15 and 10 of 15 dishes respectively, giving transformation-frequency values of 67.95 and 680.0. Statistical comparison of these values with the control revealed a highly significant difference at the concentration of 50 micrograms/ml.

CONCLUSIONS:

It is concluded that under the given experimental conditions no effects were obtained that must be interpreted as suggestive of a transformative property of TK 10 622 and its metabolites.

DATA QUALITY:

Reliability: Reliability Code 2; See reference below.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

1. Transformation/ Liver Microsome Test (In vitro test for transformation-inducing properties in mammalian fibroblasts with metabolic activation.), 7/25/86.
2. Study conducted by CIBA-GEIGY Limited, Basel, Switzerland.
3. Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
4. Tarone, R.E., and Gart, J.J.: On the robustness of combined tests for trends in proportions. Journal of the American Statistical Association 75, 110-116 (1980).
- 5) Kakunaga, T., A Quantitative System for Assay of Malignant Transformation by Chemical Carcinogens Using A Clone Derived From the BALB/3T3 Mouse. Int. Journal of Cancer 12, 463-73, 1973.

15e

15 Genetic Toxicity in Vitro (Gene Mutations):

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Other-See general Comments below.

Test Type: Ames Test

System of Testing: Bacterial

GLP: Yes

Year study performed: 1988

Species: Salmonella typhimurium

Metabolic Activation: Male rat liver induced by a single dose of Aroclor 1254 at a rate of 500 mg/kg

Concentration: 8, 40, 200, 1000, and 5000 ug/plate

Statistical Method: Method was not cited in this report.

Remarks for Method:

1) Test was conducted according to Safepharm Definitive Protocol Number TX 654 and was designed to assess the mutagenic potential of the test material using a bacterial / microsome test system. The study was based on the in vitro technique described by Ames and his co-workers (1,2,3) and Garner et al (4) in which mutagenic activity is assessed by exposing histidine auxotrophs of Salmonella typhimurium to various concentrations of the test material.

2) Tester strains were Salmonella Typhmuriuim (TA1535, TA1537, TA98 and TA100) and Escherichia Coli (WP2uvrA). These strains were obtained from the British Industrial Biological Research Association on 14th August 1987 and were stored at -196 degrees C in a Statebourne liquid N2 freezer, model SXR 34. Prior to being used, characterization checks were carried out to determine the amino acid requirement, presence of rfa and R factors and the spontaneous reversion rate.

3) Topic G was accurately weighed and dissolved in 10% DMSO and appropriate dilutions made. The use of a detergent in the vehicle was necessary to maintain the test material in suspension.

4) Negative and positive controls were used in parallel with the test material. A solvent treatment group was used as the negative control and the positive control materials were as follows:

N-Methyl-N-nitro-N-nitrosoguanidine (MNNG) 2 ug/plate for TA1535 andTA100

9-Aminoacridine (9AA) 50 or 100 ug/plate for TA1537

4-Nitro-O -phenylenediamine (4NOPD) 10 ug/plate for TA98

4-Nitroquinoline N-oxide (4NQO) 3.3 ug/plate for WP2uvrA.

5) In addition to the material 2-Aminoanthracene (2AA) which is non-mutagenic in the absence of metabolizing enzymes was used at 3.3 ug/plate (10 ug/plate for WP2uvrA) in the S-9 series of plates.

RESULTS:

Result: Positive

Cytotoxic Concentration: None Reported

Genotoxic Concentration: Dose-response

Statistical Result: Not described in this report.

Results Remark:

1) The overnight culture of each strain was found to be in the required range of 10 to the seventh (10E7) to 10 to the 9th (10E9) bacteria per ml and the spontaneous reversion rate for each was found to be within the expected range.

2) Toxicity to all strains of bacteria used was exhibited at varying doses of Tepic-G. The expression of toxicity by Tepic-G was variable both between bacterial strains and between experiments.

3) A significant dose related, reproducible increase in the numbers of revertant colonies of bacteria was recorded for all of the strains of bacteria used except TA1537, both with and without metabolic activation.

CONCLUSIONS:

The test material, TEPIC-G, was found to be mutagenic under the conditions of this test.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

GENERAL COMMENTS:

Safepharm Definitive Protocol Number TX 653.

REFERENCES:

1)Tepic-G: Japanese MITI/MHW/MOL/MAFF "AMES TEST" / Using Salmonella Typhmurium and Escherichia Coli , Project Number 14/16, November 28, 1988.

2)Study conducted by Safepharm Laboratories Limited, Derby, UK.

3)Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

4)Ames, B.N., Durston, W.E., Yamasaki, E., and Lee, F.D. ,Proc. Nat. Acad. Sci. USA (1970), 70, 2285.

5)Ames, B.N., McCann, J. and Yamasaki, E., Mutation Research (1975) , 31,347.

6)McCann, J. Coi, E., and Yamasaki, E., and Ames, B.E., Proc. Nat. Acad. Sci. USA (1975), 75, 5135.

7)Garner, R.C., Miller, E.C., and Miller, J.A., Cancer Res. (1972), 33,2058.

15f

15 Genetic Toxicity in Vitro (Gene Mutations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Other-see general comments below.

Test Type: Ames test

System of Testing: Bacterial

GLP (Y/N): Yes

Year study performed: 1988

Species: Salmonella typhimurium

Metabolic Activation: Male rat liver induced by a single dose of Aroclor 1254 at a rate of 500 mg/kg

Concentration: 312.5, 525, 1250, 2500, and 5000 ug/plate

Statistical Method: Method was not cited in this report.

Remarks for Method:

- 1) Test was conducted according to Safepharm Definitive Protocol Number TX 653 and was designed to assess the mutagenic potential of the test material using a bacterial / microsome test system. The study was based on the in vitro technique described by Ames and his co-workers (1,2,3) and Garner et al (4) in which mutagenic activity is assessed by exposing histidine auxotrophs of Salmonella typhimurium to various concentrations of the test material.
- 2) Tester strains were Salmonella Typhimurium (TA1535, TA1537, TA98 and TA100) and Escherichia Coli (WP2uvrA). These strains were obtained from the British Industrial Biological Research Association on 14th August 1987 and were stored at -196 degrees C in a Statebourne liquid N2 freezer, model SXR 34. Prior to being used, characterization checks were carried out to determine the amino acid requirement, presence of rfa and R factors and the spontaneous reversion rate.
- 3) Topic G was accurately weighed and dissolved in 10% DMSO and appropriate dilutions made. The use of a detergent in the vehicle was necessary to maintain the test material in suspension.
- 4) Negative and positive controls were used in parallel with the test material. A solvent treatment group was used as the negative control and the positive control materials were as follows:

N-Methyl-N-nitro-N-nitrosoguanidine (MNNG) 2 ug/plate for TA1535 and TA100

9-Aminoacridine (9AA) 50 or 100 ug/plate for TA1537

4-Nitro-O-phenylenediamine (4NOPD) 10 ug/plate for TA98

4-Nitroquinoline N-oxide (4NQO) 3.3 ug/plate for WP2uvrA.

5) In addition to the material 2-Aminoanthracene (2AA) which is non-mutagenic in the absence of metabolizing enzymes was used at 3.3 ug/plate (10 ug/plate for WP2uvrA) in the S-9 series of plates.

RESULTS:

Result: Positive

Cytotoxic Concentration: None Reported

Genotoxic Effect: Dose-response

Statistical Result: Not described in this report.

Results Remarks:

1) The overnight culture of each strain was found to be in the required range of 10 to the seventh (10E7) to 10 to the 9th (10E9) bacteria per ml and the spontaneous reversion rate for each was found to be within the expected range.

2) Toxicity to all strains of bacteria used was exhibited at varying doses of Tepic-G. The expression of toxicity by Tepic-G was variable both between bacterial strains and between experiments.

3) A significant dose related, reproducible increase in the numbers of revertant colonies of bacteria were recorded for all of the strains of bacteria used except TA1537, both with and without metabolic activation.

CONCLUSIONS:

The test material, TEPIC-G, was found to be mutagenic under the conditions of this test.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

GENERAL COMMENTS:

Safepharm Definitive Protocol Number TX 653.

REFERENCES:

1) Tepic-G: Japanese MITI/MHW/MOL/MAFF "AMES TEST" / Using Salmonella Typhmurium and Escherichia Coli , Project Number 14/15, November 28, 1988.

2) Study conducted by Safepharm Laboratories Limited, Derby, UK.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

4) Ames, B.N., Durston, W.E., Yamasaki, E., and Lee, F.D. ,Proc. Nat. Acad. Sci. USA (1970), 70, 2285.

5) Ames, B.N., McCann, J. and Yamasaki, E., Mutation Research (1975) , 31,347.

6) McCann, J. Coi, E., and Yamasaki, E., and Ames, B.E., Proc. Nat. Acad. Sci. USA (1975), 75, 5135.

7) Garner, R.C., Miller, E.C., and Miller, J.A., Cancer Res. (1972), 33,2058.

15g

15 Genetic Toxicity in Vitro (Gene Mutations):

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guidelines Followed: Method was not cited in this report.

Test Type: Unscheduled DNA synthesis

System of Testing: Non-bacterial

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Human fibroblasts

Metabolic Activation: None required for this test.

Concentration: 2.7, 9, 30, 100, 250, or 400 ug/ml.

Statistical Method: T -Tests and Interval Comparisons

Remarks for Method:

- 1) Test material was TK 10 622 (ARALDIT PT 810).
- 2) Doses used in the Unscheduled DNA Synthesis (DNA Repair Test) were 2.7, 9, 30, 100, 250, or 400 ug/ml.
- 3) The vehicle used was DMSO (Dimethylsulfoxide, Merck).
- 4) A Cytotoxicity Test was performed to determine the highest concentration to be used in the DNA Repair Assay. The concentration best suited as the highest in the DNA Repair Test was determined by a reference to three criteria:
 1. a sufficiently large number of cells must adhere to the cover-slips;
 2. at least 25% of the cells must show viability upon examination by means of the vital staining technique; and
 3. a corresponding percentage of the cells must be in good condition upon morphological examination.

If no toxic effect is observed at any concentration, the highest concentration to be used in the DNA repair assay will be determined according to the solubility limit of the test substance. In this case, the highest concentration tested exceeded the solubility of the test substance in the culture medium or be a maximum of 10 mg/ml.

- 5) A series of compartments in multiplates containing glass coverslips is seeded with 4 x 10000 cells per compartment. (1 ml medium compartment) and cultivated overnight. On the following morning, the test substance was dissolved in DMSO and eleven stock solutions were prepared by serial dilution with the vehicle. From each, a volume of 10 ul was added to two compartments containing 1 ml medium. In addition, a negative control containing the vehicle only was run.

After an incubation period of 5 hours, the medium was removed and the cells were washed twice with BSS and stained with Trypan blue solution (.2%) for 5 minutes. After washing with BSS, the cells were fixed and the percentage of unstained cells evaluated by counting 100 cells.

6) The DNA Repair Assay is likewise performed. The procedure employed for the preparation of the compartments is the same as described in the previous toxicity test. The compartments are treated under each of the following conditions: 6 pre-selected concentrations of the test substance; a positive control (4-nitroquinoline-n-oxide, 4NQO, FLUKA, 5 uM); a negative control containing the vehicle (DMSO) and an untreated negative control.

7) From the results obtained in the toxicity test, the highest usable concentration in the DNA repair test was found to be 400 ug/ml. Five additional, lower concentrations, were identified, covering a 2-log range, the lowest being 2.7 ug/ml.

8) From the positive control substance and from the test substance stock solutions were prepared. From the latter, five additional concentrations were prepared by serial dilution with the vehicle. From each of the solutions, 10 ul were added to four compartments containing 1 ml medium. In the case of negative controls, corresponding volumes of the vehicle and of the culture medium were added.

9) Immediately after addition of the test substance, 3H-thymidine was added (6-3H-thymidine, THE RADIOCHEMICAL CENTRE, Amersham, England, specific activity 23 Curies/mmol, Batch: 150). 2 uCi in the ul were added to 1 ml medium in each compartment. At the end of the incubation period of 5 hours the cells were washed twice with BSS and fixed with ethanol / acetic acid, 3/1, v/v. The cover slips were mounted on microscope slides and prepared for autoradiography. The exposure time was 6 days. The autoradiographs were stained with hemotoxylin-eosine.

RESULTS:

Result: Negative

Cytotoxic Concentration: Concentrations greater than 400 ug/ml

Genotoxic Effect: Unconfirmed

Statistical result: None reported

Results Remark:

1) Cytotoxicity Test: In a preliminary toxicity test, eleven concentrations of TK 10 622 (ARALDIT PT 810) from 7.81 to 1800 ug/ml were tested to determine the highest applicable concentration in the DNA repair assay. From the results obtained, the highest concentration in the DNA repair assay was determined to be 400 ug/ml.

2) DNA Repair Test: The DNA repair assay was carried out with concentrations of 2.7, 9, 30, 350 or 400 ug/ml. Comparison of the mean number silver grains per nucleus in the vehicle control and after treatment with TK 10 622 revealed no marked differences. Also the percentage of nuclei with more than 5 silver grains was not significantly enhanced.

3) Concurrent ""positive control"" experiments with 4NQO (5 uM) yielded a marked increase in the number of silver grains per nucleus. The mean value was 15.08 (vehicle control: 0.29). The percentage of nuclei with more than five silver grains was 100% (vehicle control 0.0%).

CONCLUSIONS:

It is concluded that under the given experimental conditions, no evidence of induction of DNA damage by TK 10 622 was obtained that could be interpreted as suggestive of genotoxic properties of the substance.

DATA QUALITY:

Reliability: Reliability Code 2.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

1. Test of TK 10622 (Araldite PT 810): Test System: Autoradiographic DNA Repair Test on Human Fibroblasts, 5/2/88.
2. Study conducted by CIBA-GEIGY Limited, Basel, Switzerland.
3. Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

15h

15 Genetic Toxicity in Vitro (Gene Mutations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 471 - Test was performed according to OECD and MITI Guidelines

Test Type: Ames test

System of Testing: Bacterial

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Salmonella typhimurium

Metabolic Activation: With & without metabolic activation - TA 1535, TA 1537, TA 98, TA 100 and E. Coli (WP2uvrA)

Concentration: -

Statistical Method: Not specified

Remarks for Method:

- 1) Test was conducted according to Safepharm Definitive Protocol Number TX 653 and was designed to assess the mutagenic potential of the test material using a bacterial / microsome test system. The study was based on the in vitro technique described by Ames and his co-workers (1,2,3) and Garner et al (4) in which mutagenic activity is assessed by exposing histidine auxotrophs of Salmonella typhimurium to various concentrations of the test material.
- 2) Tester strains were Salmonella Typhmuriium (TA1535, TA1537, TA98 and TA100) and Escherichia Coli (WP2uvrA). These strains were obtained from the British Industrial Biological Research Association on 14th August 1987 and were stored at -196 degrees C in a Statebourne liquid N2 freezer, model SXR 34. Prior to being used, characterization checks were carried out to determine the amino acid requirement, presence of rfa and R factors and the spontaneous reversion rate.
- 3) Tepic G was accurately weighed and dissolved in 10% DMSO and appropriate dilutions made. The use of a detergent in the vehicle was necessary to maintain the test material in suspension.
- 4) Negative and positive controls were used in parallel with the test material. A solvent treatment group was used as the negative control and the positive control materials were as follows:

N-Methyl-N-nitro-N-nitrosoguanidine (MNNG) 2 ug/plate for TA1535 andTA100

9-Aminoacridine (9AA) 50 or 100 ug/plate for TA1537

4-Nitro-O -phenylenediamine (4NOPD) 10 ug/plate for TA98

4-Nitroquinoline N-oxide (4NQO) 3.3 ug/plate for WP2uvrA.

5) In addition to the material 2-Aminoanthracene (2AA) which is non-mutagenic in the absence of metabolizing enzymes was used at 3.3 ug/plate (10 ug/plate for WP2uvrA) in the S-9 series of plates.

RESULTS:

Results: Positive

Cytotoxic Concentration:

Genotoxic Effect: Dose-response

Statistical Result: Methods not cited in this study

Results Remark:

1) The overnight culture of each strain was found to be in the required range of 10 to the seventh degree and 10 to the 9th degree bacteria per ml and the spontaneous reversion rate for each was found to be within the expected range.

2) Toxicity to all strains of bacteria used was exhibited at varying doses of Tepic-G. The expression of toxicity by Tepic-G was variable both between bacterial strains and between experiments.

3) A significant dose relate, reproducible increase in the numbers of revertant colonies of bacteria were recorded for all of the strains of bacteria used except TA1537, both with and without metabolic activation.

CONCLUSIONS:

The test material, TEPIC-G, was found to be mutagenic under the conditions of this test.

DATA QUALITY:

Reliability: Reliability Code 1 - See references below

Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below.

REFERENCES:

1) Tepic-G: Japanese MITI/MHW/MOL/MAFF "AMES TEST" / Using Salmonella Typhmurium and Escherichia Coli , Project Number 14/16, November 28, 1988.

2) Study conducted by Safepharm Laboratories Limited, Derby, UK.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

4) Ames, B.N., Durston, W.E., Yamasaki, E., and Lee, F.D. ,Proc. Nat. Acad. Sci. USA (1970), 70, 2285.

5) Ames, B.N., McCann, J. and Yamasaki, E., Mutation Research (1975) , 31,347.

6) McCann, J. Coi, E., and Yamasaki, E., and Ames, B.E., Proc. Nat. Acad. Sci. USA (1975), 75, 5135.

7) Garner, R.C., Miller, E.C., and Miller, J.A., Cancer Res. (1972), 33,2058.

15 Genetic Toxicity in Vitro (Gene Mutations)**TEST SUBSTANCE:**

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Method 471 - Other-See general Comments below.

Test Type: Ames test

System of Testing: Bacterial

GLP (Y/N): Yes

Year Study Performed: 1988

Species: Salmonella typhimurium

Metabolic Activation: With & without metabolic activation - TA 1535, TA 1537, TA 98, TA 100 and E. Coli (WP2uvrA)

Concentration: -

Statistical Method: None cited

Remarks for Method:

1) Test was conducted according to Safepharm Definitive Protocol Number TX 653 and was designed to assess the mutagenic potential of the test material using a bacterial / microsome test system. The study was based on the in vitro technique described by Ames and his co-workers (1,2,3) and Garner et al (4) in which mutagenic activity is assessed by exposing histidine auxotrophs of Salmonella typhimurium to various concentrations of the test material.

2) Tester strains were Salmonella Typhmurium (TA1535, TA1537, TA98 and TA100) and Escherichia Coli (WP2uvrA). These strains were obtained from the British Industrial Biological Research Association on 14th August 1987 and were stored at -196 degrees C in a Statebourne liquid N2 freezer, model SXR 34. Prior to being used, characterization checks were carried out to determine the amino acid requirement, presence of rfa and R factors and the spontaneous reversion rate.

3) Topic G was accurately weighed and dissolved in 10% DMSO and appropriate dilutions made. The use of a detergent in the vehicle was necessary to maintain the test material in suspension.

4) Negative and positive controls were used in parallel with the test material. A solvent treatment group was used as the negative control and the positive control materials were as follows:

N-Methyl-N-nitro-N-nitrosoguanidine (MNNG) 2 ug/plate for TA1535 andTA100

9-Aminoacridine (9AA) 50 or 100 ug/plate for TA1537

4-Nitro-O -phenylenediamine (4NOPD) 10 ug/plate for TA98

4-Nitroquinoline N-oxide (4NQO) 3.3 ug/plate for WP2uvrA.

5) In addition to the material 2-Aminoanthracene (2AA) which is non-mutagenic in the absence of metabolizing enzymes was used at 3.3 ug/plate (10 ug/plate for WP2uvrA) in the S-9 series of plates.

RESULTS:

Result: Positive
Cytotoxic Concentration: -
Genotoxic Effect: Dose-response
Statistical Result: None cited in this study
Results Remark:

1) The overnight culture of each strain was found to be in the required range of 10 to the seventh degree and 10 to the 9th degree bacteria per ml and the spontaneous reversion rate for each was found to be within the expected range.

2) Toxicity to all strains of bacteria used was exhibited at varying doses of Tepic-G. The expression of toxicity by Tepic-G was variable both between bacterial strains and between experiments.

3) A significant dose relate, reproducible increase in the numbers of revertant colonies of bacteria were recorded for all of the strains of bacteria used except TA1537, both with and without metabolic activation.

CONCLUSIONS:

The test material, TEPIC-G, was found to be mutagenic under the conditions of this test.

DATA QUALITY:

Reliability: Reliability Code 1 - See references below
Data Reliability Remarks: OECD/GLP Protocol and Report - See reference below.

REFERENCES:

- 1) Tepic-G: Japanese MITI/MHW/MOL/MAFF "AMES TEST" / Using Salmonella Typhmurium and Escherichia Coli , Project Number 14/16, November 28, 1988.
- 2) Study conducted by Safepharm Laboratories Limited, Derby, UK.
- 3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).
- 4) Ames, B.N., Durston, W.E., Yamasaki, E., and Lee, F.D. ,Proc. Nat. Acad. Sci. USA (1970), 70, 2285.
- 5) Ames, B.N., McCann, J. and Yamasaki, E., Mutation Research (1975) , 31,347.
- 6) McCann, J. Coi, E., and Yamasaki, E., and Ames, B.E., Proc. Nat. Acad. Sci. USA (1975), 75, 5135.
- 7) Garner, R.C., Miller, E.C., and Miller, J.A., Cancer Res. (1972), 33,2058.

15j

15 Genetic Toxicity in Vitro (Gene Mutations)

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Not cited in this report

Test Type: DNA Damage and Repair Assay

System of Testing: Non-bacterial

GLP (Y/N): Unknown

Year Study Performed: 1988

Species: Human Fibroblasts

Metabolic Activation: -

Concentration: 2.7, 9, 30, 100, 250, or 400 ug/ml.

Statistical Method: Not cited

Remarks for Method:

- 1) Test material was TK 10 622 (ARALDIT PT 810).
- 2) Doses used in the DNA Repair Test were 2.7, 9, 30, 100, 250, or 400 ug/ml.
- 3) The vehicle used was DMSO (Dimethylsulfoxide, Merck).
- 4) A Cytotoxicity Test was performed to determine the highest concentration to be used in the DNA Repair Assay. The concentration best suited as the highest in the DNA Repair Test was determined by a reference to three criteria:

1. a sufficiently large number of cells must adhere to the cover-slips;
2. at least 25% of the cells must show viability upon examination by means of the vital staining technique; and
3. a corresponding percentage of the cells must be in good condition upon morphological examination.

If no toxic effect is observed at any concentration, the highest concentration to be used in the DNA repair assay will be determined according to the solubility limit of the test substance. In this case, the highest concentration tested exceeded the solubility of the test substance in the culture medium or be a maximum of 10 mg/ml.

- 5) A series of compartments in multiplates containing glass coverslips is seeded with 4 x 10000 cells per compartment. (1 ml medium compartment) and cultivated overnight. On the following morning, the test substance was dissolved in DMSO and eleven stock solutions were prepared by serial dilution with the

vehicle. From each, a volume of 10 ul was added to two compartments containing 1 ml medium. In addition, a negative control containing the vehicle only was run. After an incubation period of 5 hours, the medium was removed and the cells were washed twice with BSS and stained with Trypan blue solution (.2%) for 5 minutes. After washing with BSS, the cells were fixed and the percentage of unstained cells evaluated by counting 100 cells.

6) The DNA Repair Assay is likewise performed. The procedure employed for the preparation of the compartments is the same as described in the previous toxicity test. The compartments are treated under each of the following conditions: 6 preselected concentrations of the test substance; a positive control (4-nitroquinoline-n-oxide, 4NQO, FLUKA, 5 uM); a negative control containing the vehicle (DMSO) and an untreated negative control.

7) From the results obtained in the toxicity test, the highest usable concentration in the DNA repair test was found to be 400 ug/ml. Five additional, lower concentrations, were identified, covering a 2-log range, the lowest being 2.7 ug/ml.

8) From the positive control substance and from the test substance stock solutions were prepared. From the latter, five additional concentrations were prepared by serial dilution with the vehicle. From each of the solutions, 10 ul were added to four compartments containing 1 ml medium. In the case of negative controls, corresponding volumes of the vehicle and of the culture medium were added.

9) Immediately after addition of the test substance, 3H-thymidine was added (6-3H-thymidine, THE RADIOCHEMICAL CENTRE, Amersham, England, specific activity 23 Curies/mmol, Batch: 150). 2 uCi in the ul were added to 1 ml medium in each compartment. At the end of the incubation period of 5 hours the cells were washed twice with BSS and fixed with ethanol / acetic acid, 3/1, v/v. The cover slips were mounted on microscope slides and prepared for autoradiography. The exposure time was 6 days. The autoradiographs were stained with hematoxylin-eosine.

RESULTS:

Result: Negative

Cytotoxic Concentration: Concentrations above 400ug/ml

Genotoxic Effect: Unconfirmed

Statistical Result: None cited for this study

Results Remark:

1) Cytotoxicity Test: In a preliminary toxicity test, eleven concentrations of TK 10 622 (ARALDIT PT 810) from 7.81 to 1800 ug/ml were tested to determine the highest applicable concentration in the DNA repair assay. From the results obtained, the highest concentration in the DNA repair assay was determined to be 400 ug/ml.

2) DNA Repair Test: The DNA repair assay was carried out with concentrations of 2.7, 9, 30, 350 or 400 ug/ml. Comparison of the mean number silver grains per nucleus in the vehicle control and after treatment with TK 10 622 revealed no marked differences. Also the percentage of nuclei with more than 5 silver grains was not significantly enhanced.

3) Concurrent "positive control" experiments with 4NQO (5 uM) yielded a marked increase in the number of silver grains per nucleus. The mean value was

15.08 (vehicle control: 0.29). The percentage of nuclei with more than five silver grains was 100% (vehicle control 0.0%).

CONCLUSIONS:

It is concluded that under the given experimental conditions, no evidence of induction of DNA damage by TK 10 622 was obtained that could be interpreted as suggestive of genotoxic properties of the substance.

DATA QUALITY:

Reliability: Reliability Code 2. See reference below.

Data Reliability Remarks: Basic data provided; comparable to guideline/standards. See reference below.

REFERENCES:

1. Test of TK 10622 (Araldit PT 810): Test System: Autoradiographic DNA Repair Test on Human Fibroblasts, 5/2/88.
2. Study conducted by CIBA-GEIGY Limited, Basel, Switzerland.
3. Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

16a

16 Repeat Dose Toxicity:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Repeated Dose (13 Week) Toxicity and Fertility Study - OECD Method 408; Adopted May 12, 1981
GLP (Y/N): Yes
Year Study Performed: 1995
Species: Rat
Strain: Sprague-Dawley Crl CD (SD) BR Strain
Sex: Both
Number of males per dose: 10
Number of females per dose: 20
Route of Administration: Oral
Exposure Period: 94
Frequency of Treatment: Daily
Dose: 10, 30, or 100 ppm
Control Group: Yes
Post observation period: None specified
Statistical Method: See remarks below.
Remarks for Method:

- 1) Test substance was Araldite PT 810, batch number 407923.48, manufactured on 11/5/94 and stored at 4 degrees centigrade.
- 2) The identity of the test substance was independently confirmed by the testing laboratory.
- 3) The vehicle used was A04C 2.5 ground diet, batch numbers 40927 and 41114 (U.A.R., 91360 Villemisson-sur-Orge, France).
- 4) The diet was mixed; tested for homogeneity, stability and TGIC concentration on weeks 1, 4, 5, 8, 9, and 12); and stored at 4 degrees centigrade.
- 5) One hundred and thirty three Sprague Dawley rats (45 male and 88 female) of the Crl CD (SD) BR strain were supplied by Charles River France (76410 Saint-Aubin-les-Elbeuf, France).
- 6) Rats were acclimatized for a minimum of 8 days prior to being placed on study. They were randomly assigned to treatment groups and identified by ear tattoo.

7) At the beginning of the treatment period males were approximately 6 weeks old and had a mean body weight of 204 grams.

8) Upon arrival at the lab, animals were placed in a disinfected room, quarantined and given a clinical examination. Temperature was 21 +/- 2 degrees centigrade, relative humidity was 50 +/- 20%, light/dark cycle was 12hr/12hr, and ventilation was 12 cycles/hr of filtered, non-recycled air. ""There were no deviations in temperature and relative humidity which could have influenced the outcome of the study.""

9) Animals had free access to food and water. ""There were no known contaminants in the diet, water or saw dust bedding at levels likely to have influenced the outcome of the study.""

10) After 64 days of treatment males were placed with females (1 male and 2 females) overnight. Females were placed with the same male for 7 night or until mating was confirmed.

11) The following parameters were measured: clinical signs, clinical chemistry, sperm count, pathology mortality, body weight, food consumption and mean food intake (mg/kg/day), as well as the other parameters required by this guideline. See report for details of these evaluations.

RESULTS:

NOAEL Precision: =

NOAEL dose: 30

Unit: mg/kg in feed

NOAEL Effect: Lower body weight gain for the Toxicity Evaluation.

LOAEL Precision: >

LOAEL dose: 100

Unit: mg/kg in feed

LOAEL Effect: None identified.

Actual dose received by dose level by sex: M=0.72, 2.08, or 7.32 mg/kg/day; F=0 mg/kg/day

Toxic response: Test substance was well received at 10 and 30 ppm. Slightly lower body weight gain was recorded during the first 6 weeks of dosing at 100 ppm. A slight, but dose-related decrease in the mean number of spermatozoa was noted in the TGIC treated groups. No treatment-related infertility was noted in males and no influences on embryonic or pup development were observed.

Therefore, 30 ppm is the NOEL and 100 ppm is the NOAEL.

Statistical result: Statistical methods were discussed, but analyses of the data were not provided.

Results Remark:

1) The chemical composition of the test article was confirmed at the laboratory prior to initiation of the in vivo studies.

2) The concentration, homogeneity and stability of the test article in the diet were monitored and reported. This data, along with food consumption and body weight, was used to calculate the actual doses received during the study.

3) Results summary for the Toxicology Study:

Clinical examinations:

No treatment-related clinical signs and no mortalities occurred during the treatment period. Slightly lower body weight gain was noted over the first 6

weeks of dosing in males given 100 ppm (-16%). Thereafter, the body weight gain of this group was similar to that of controls. The body weight gain of males given 10 or 30 ppm was similar to that of controls. No statistically significant differences from controls were observed in food consumption for any male treatment groups.

The achieved dosages were on average, 0.72, 2.08 or 7.32 mg/kg/day in the males given 10, 30 or 100 ppm, respectively. The achieved dosages decreased throughout of the treatment period (in mean -60% between weeks 1 and 13). The efficiency of food utilization was similar in all treated groups.

Laboratory investigations:

Slightly lower leucocyte and lymphocyte counts were noted in 2/10 males given 100 ppm. No significant differences from controls were noted in blood biochemistry and urinalysis parameters.

Pathology:

No treatment-related differences from controls were recorded in the organ weights. Reddish coloration of mesenteric lymph nodes in association with hemosiderosis and congestion were found in some individuals given 100 ppm.

Analysis of sperm:

Slightly lower number of spermatozoa was observed with a dose-related frequency in all treated groups.

The mean spermatozoa viability was similar in male treatment groups when compared to the control group.

Results summary for the Fertility Study:

Maternal data:

No clinical signs and no unscheduled mortalities occurred during the study period. No abortions occurred in any female. The body weight gain and the food consumption of females was similar in all groups during pregnancy and lactation periods. No relevant macroscopic findings were made at necropsy.

Reproductive data in males:

The mating index of males was 100% in all groups. No treatment-related infertility was recorded in any male group.

Litter data for the hysterectomy subgroup:

The gestation index was 100% in all groups. The mean number of corpora lutea and implantation sites and therefore the pre-implantation loss were similar in all groups. The rate of resorption and the post-implantation loss were similar in all groups. There were no dead fetuses were noted in any group. The mean number, the mean fetal body weight and the sex-ratio of live fetuses were similar in all groups. No external anomalies or malformations were observed in fetuses of any group.

Litter data for the delivery subgroup:

At birth, the mean number of live born pups was similar in all groups. The viability index of pups on day 4 post-partum, and on day 21 post-partum (or lactation index) was considered to be similar in all groups. The mean body weight of pups was similar in all groups, over the period of study (Day 1 to Day 21 post-partum). No toxicologically significant clinical observations were noted for pups in any groups. The physical development of pups as assessed by: pinna unfolding, hair growth, tooth eruption, eye opening and auditory canal opening, was similar in all groups. The reflex development of pups as assessed

by: surface righting, cliff avoidance and air righting, was similar in all groups. See report for details of these evaluations.

CONCLUSIONS:

The administration of the test article Araldite PT 810 (TGIC), by dietary admixture for 13 weeks to male Sprague Dawley rats was well tolerated at doses of 10 or 30 ppm (0.72 or 2.08 mg/kg/day). Slightly lower (approximately 10%) body weight gain was recorded for the 100 ppm (7.32 mg/kg/day) group. A slight, but dose-related decrease in the mean number of spermatozoa was observed in the TGIC treated groups. No treatment-related infertility was noted in males and no influence on embryonic or pup development was observed after mating with untreated females. Consequently, 30 ppm was considered as the no observed effect level (NOEL). At 100 ppm, the lower number of spermatozoa did not impair the fertility of the treated males and therefore this dose level was considered to be the no observed adverse effect level (NOAEL).

DATA QUALITY:

Reliability: Reliability Code 1.

Data Reliability Remarks: The Report and Protocol followed OECD and GLP Guidelines. See reference below.

GENERAL COMMENTS:

Because of the overlap of the two endpoints discussed herein, this same 13-Week Toxicity Study and Fertility Study In Male Rats is listed in the Repeated Dose Toxicity Section of this dossier.

REFERENCES:

- 1) Fabreguettes, C., 13-Week Toxicity Study and Fertility Study By Oral Route (Dietary Admixture) In Male Rats; Test Substance was Araldite PT 810 (TGIC) [1,3,5 - Triglycidyl isocyanurate]; Centre International de Toxicologie, BP 563 - Miserey - 27005 Evreux - France and completed on December 12, 1995. Volumes 1 and 2; pages 1-466; Laboratory Study Number 11099 TCR.
- 2) Bartlette, M.S.; Proceedings of the Royal Society of America; Volume 160, pp 268-82, (1937).
- 3) Dunn J. O.; Multiple Comparisons Using Rank Sums. Techno-metrics, Volume 6, Number 3, pp 241-52, (1964).
- 4) Dunnett, C. W.; A Multiple Comparison Procedure For Comparing Several Treatments With A Control. American Statistical Association Journal, pp 1096-1121, (1965).
- 5) Fisher, R. A.; Statistical Method For Research Workers (5th edition). Edinburgh; Oliver and Boyd (1934).
- 6) Mann, H. B., and D. R. Whitney; On a Test of Whether One or Two Random Variables is Stochastically Larger than the Other. Annals of Mathematical Statistics; Volume 18, pp 50-60, (1947).
- 7) Smirnov, N. V., Tables for Estimating the Goodness of Fit of Empirical Distributions; Annals of Mathematical Statistics, Volume 19 pp 279-81 (1948).

8) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

16b

16 Repeat Dose Toxicity:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: OECD Guideline 451 (Adopted May 12, 1981)
GLP (Y/N): Yes
Year Study Performed: 1999
Species: Rat
Strain: Sprague-Dawley Crl CD (SD) BR Strain
Sex: M
Number of males per dose: 50
Number of females per dose: 0
Route of Administration: Oral
Exposure Period: 693
Frequency of treatment: Ad libitum in diet
Doses: 0, 10, 30, 100, and 300 ppm in dietary admixture
Control Group: Yes
Post observation period: None
Statistical Method: Peto et. Al., 1980
Remarks for Method:

- 1) On the first day of treatment, animals were approximately 8 weeks old, and had a mean body weight of 319 grams (range of 241 g to 364 g) for the "Principal" animals and 319 grams (range of 286 g to 344 g) for the "Satellite" animals.
- 2) Nominal dosages were 0, 10, 30, 100, and 300 ppm TGIC admixed into the diet. There were 50 Principal rats assigned to each of the 5 dose level groups. In addition, 10 rats were assigned to each of the 0, 100, or 300 ppm dose levels as Satellite groups. These animals were included in the study in order to assess toxicity of the test article during the first 6 months of treatment. The total number of animals used in the study was 280.
- 3) Animals had free access to food and water. Formulation information and chemical analyses, as well as homogeneity and stability studies for the dietary admixture were performed and archived by the laboratory. "No contaminants were known to have been present in the diet or drinking water or sawdust at levels which may be expected to have interfered with, or prejudiced the outcome of the study."
- 4) Due to the lack of a method to analyze TGIC in serum, all blood samples intended for this purpose were cancelled.

5) The study was scheduled to continue for 104 weeks. However, excessive mortality in the 300 ppm group caused treatment of this group to be stopped after 63 weeks. In order to maintain the integrity of the study, it was decided to terminate the study if the survival rate of any group approached 40%.

6) Aspects of the study not discussed above were conducted in compliance with OECD Guideline 451.

7) A total of 250 male Sprague-Dawley rats were randomly allocated to four treated and one control group of 50 males. Treated males received the test substance, TGIC (1, 3, 5 - triglycidyl isocyanurate) by dietary admixture at the constant concentrations of 10, 30, 100 or 300 ppm for 63 weeks (300 ppm group) or 98/99 weeks (10, 30 and 100 ppm groups). Control males received the untreated diet (A04 C rodent maintenance diet, type 2.5, UAR) for 98/99 weeks. The treatment groups in this study as well as the accompanying satellite study, together with the duration of treatment, are summarized in the table below:

The animals were checked daily for clinical signs and mortality. After six months of treatment, the animals were palpated regularly in order to monitor palpable masses. Body weight and food consumption were recorded once and twice a week respectively during the first 13 weeks of treatment and then once a month. Achieved dosages were calculated throughout the treatment period and the efficiency of food utilization was estimated from the food conversion ratio during the period of maximal growth of the animals. Blood pressure was recorded in 20 control animals and all surviving, animals of the 300 ppm group on one occasion in weeks 59/60. The Differential White Blood Cell Count (DWBC) was investigated in weeks 13, 26, 52 and 78 in the control and highest dose-level group; hematological investigations were carried out on all surviving animals at the end of the treatment period. DWBC was also evaluated in all moribund animals.

Any animal found dead or killed prematurely during the treatment period was subjected to a full macroscopic postmortem examination and a full list of tissues was preserved for microscopic examination. Due to the high rate of mortality noted in the 300 ppm group (44% in week 62) and the rapid clinical degradation of these animals, the treatment of this group was stopped in week 63 and the animals were killed. The study was originally scheduled to continue for at least 104 weeks. However, at the request of the Sponsor's Monitoring Scientist and, since a survival rate of 40% was observed in the low dose-level group in week 98, the study was terminated in weeks 98/99.

At the end of the treatment period, all surviving animals were killed and submitted to a detailed macroscopic postmortem examination. Tissue specimens and any masses or lesions were preserved. A microscopic examination was performed on all macroscopic lesions, masses and almost all tissues in control, 100 and 300 ppm groups, and on all macroscopic lesions, masses, kidneys, liver and lungs in the 10 and 30 ppm groups.

RESULTS:

NOAEL Precision: =

NOAEL dose: 100

Unit: mg/kg in feed

NOAEL Effect: Slightly lower food consumption, resulting in terminal mean body weight which was 9% lower than controls. Noncarcinogenic at all dosage levels.

LOAEL Precision: >

LOAEL dose: 100

Unit: mg/kg in feed

LOAEL Effect: LOAEL not fully defined. 100 ppm=NOAEL, while 300 ppm (the next highest dosage level) exceeded the MTD.

Actual dose received by dose level by sex: See "Results Remarks"

Toxic Response:

1) At 100 ppm, slightly lower food consumption (maximum = 11%) was noted.

2) "At 100 ppm, a lower mean body weight gain (33% when compared to controls) was recorded during the first two weeks of dosing: thereafter, the absolute body weight gain was often slightly lower than that of controls, but the body weight gain evolution over the different periods was similar to that of controls. Over the whole treatment period, the mean body weight gain was similar to that of controls. Consequently, the lower values noted at the beginning period were attributed to adaptation of the animals to the treated diet, without any toxicological consequence."

3) "At 300 ppm a mean body weight loss or a lower mean body gain was recorded during the treatment period with marked degradation over the last nine months of dosing. These differences from controls, correlated with a lower mean food consumption, were attributed to treatment with the test substance."

Statistical result: Utilizing (Peto et. al., 1980), "it was concluded that there was no treatment-related effect". A trend was positive if the P value was less than 0.05 (rare finding) or 0.01 (common finding).

Results Remarks:

Actual doses received were:

0.43 mg/kg/day (range = 0.85 to 0.32 mg/kg/day) for the 10 ppm concentration

1.30 mg/kg/day (range = 2.65 to 1.01 mg/kg/day) for the 30 ppm concentration

4.36 mg/kg/day (range = 8.47 to 3.41 mg/kg/day) for the 100 ppm concentration

13.6 mg/kg/day (range = 20.2 to 12.4 mg/kg/day) for the 300 ppm concentration

Clinical signs:

=====

Signs of poor clinical condition (round back, piloerection and emaciation associated in some animals with swollen and/or hard abdomen, coldness to the touch, hypokinesia, dyspnea, pallor of eyes and body extremities, chromodacryorrhea) were noted in the 300 ppm group and attributed to treatment with the test substance.

All the other clinical signs noted in treated groups were similar to those of control group.

Palpable Masses:

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The incidence, time of onset, multiplicity, location and size of palpable masses were similar in all treated and control groups and consistent with those commonly recorded in rats of this strain and age.

Morbidity and Mortality:

=====

At 300 ppm, there was a rapid onset of mortality and low terminal survival rate. The cause of death was possibly a histamine-related hypotension.

At 10, 30 and 100 ppm, the onset of mortality, the nature and frequency of the factors contributing to death or premature killing were similar to those in the controls and similar to those commonly recorded in rats of this strain and age and did not show any indications of being dose- or treatment-related.

Food Consumption:

=====

Slight to markedly lower food consumption was recorded in males in the 100 or 300 ppm dosage groups.

Body Weight:

=====

At 100 ppm, a slightly lower terminal body weight was noted (-9%). At 300 ppm, a body weight loss or a lower body weight gain was recorded during the treatment period with a marked degradation over the last nine months of dosing.

Achieved Dosages:

=====

The achieved dosages, based on the nominal concentrations of 10, 30, 100 and 300 ppm, were as follows:

- * 0.43 mg/kg/day (0.85 mg/kg/day to 0.32 mg/kg/day) for the 10 ppm concentration,
- * 1.30 mg/kg/day (2.65 mg/kg/day to 1.01 mg/kg/day) for the 30 ppm concentration,
- * 4.36 mg/kg/day (8.47 mg/kg/day to 3.41 mg/kg/day) for the 100 ppm concentration,
- * 13.6 mg/kg/day (20.2 mg/kg/day to 12.4 mg/kg/day) for the 300 ppm concentration.

Efficiency of Food Utilization:

=====

The efficiency of food utilization was markedly lower in the 300 ppm group than in the control or other treated groups during the first four weeks of treatment.

Blood Pressure:

=====

There were no differences in blood pressure measurements in any of the animals in the control or treated groups.

Hematology:

=====

For the 300 ppm group (samples were collected during weeks 13, 26, 52 and 63).

A higher neutrophil percentage and a lower lymphocyte percentage were noted in week 52.

In week 63, at the time of final sacrifice, a slightly lower total leucocyte count, mainly attributable to a lower lymphocyte count, was noted.

No biologically relevant abnormalities were noted in animals killed prematurely.

For the 10, 30 and 100 ppm group (blood samples were collected during weeks 78 and 98/99 and all animals killed prematurely).

No treatment-related differences from control animals were noted.

MACROSCOPIC EXAMINATION:

=====

Non-neoplastic Findings:

The incidence and nature of the non-neoplastic changes observed in all organs were similar in control and treated animals and showed no indication of treatment or dose-relationship. These changes were typical for rats of this strain and age.

Neoplastic Findings:

The masses found in some organs and tissues were equally distributed between control and treated animals and showed no influence of treatment, either in size or multiplicity.

MICROSCOPIC EXAMINATIONS:

=====

Non-neoplastic Findings:

In the 300 ppm group, the following findings were attributed to treatment with the test substance:

- * high incidence of mastocytosis, hemosiderosis and sinusal hemorrhage in the mesenteric lymph nodes,
- * high incidence of lymphoid depletion in the spleen,
- * moderate dilatation of some intestinal segments,
- * hyopsecretion together with small tubulo-alveolar units in the prostate.

In the other treated groups, the incidence, severity and morphological characteristics of the non-neoplastic microscopic findings showed no indication of treatment or dose-relationship and were similar to spontaneous lesions described for rats of this strain and age.

Neoplastic Findings:

The incidence and morphological types of neoplastic lesions were similar in control and treated animals and showed no indication of treatment or dose-relationship.

The test substance showed neither a carcinogenic potential, nor an effect on the incidence of spontaneously occurring tumors at 300 ppm (up to week 63) or 100 ppm, 30 and 10 ppm (up to week 98/99). Moreover, the test substance did not induce a decrease in the latency of tumor appearance.

CONCLUSIONS:

"The dose level of 300 ppm (13.6 mg/kg/day) clearly exceeded the maximum tolerated dose (MTD). On the basis of the results generated in the course of this study, the NOAEL is considered to be 100 ppm (4.36 mg/kg/day) and the NOEL is considered to be 30 ppm (1.36 mg/kg/day). There was no carcinogenic effect at any dose."

DATA QUALITY:

Reliability: Reliability Code 1;

Data Reliability Remarks: "OECD/GLP Protocol and Report - See reference number 3.

REFERENCES:

1) Carcinogenicity In Male Rats; Test Substance: TGIC (1,3,5 - Triglycidylisocyanurate); Author: Catherine Fabreguettes; Study conducted by: Centre International de Toxicologie, BP 563 - Miserey - 27005 Evreux - France and completed on June 4, 1999. Volumes 1-6; pages 1-1487; Laboratory Study Number 11117 TCR.

2) Peto et. Al., 1980.

3) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

16c

16 Repeat Dose Toxicity:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Five - Day Inhalation Toxicity Study - Method/Guideline was not cited in this report.

GLP (Y/N): Yes

Year Study Performed: 1991

Species: Mouse

Strain: CD-1 mice

Sex: M

Number of males per dose: 12

Number of females per dose: 0

Route of Administration: Nose-only inhalation

Exposure Period: 5

Frequency of Treatment: 6 hours/day; 5 days/wk

Doses: 0.01, 0.04, or 0.14 mg/l

Control Group: Yes

Post observation period: 17 days post-dosing

Statistical Method: F-max' test for homogeneity

Remarks for Method:

1. A significant number of male Crl: CD-1 (ICR) BR strain mice were obtained from Charles River (UK) Limited, Manston, Kent.
2. The test material was administered by nose-only inhalation to 3 groups each of 12 male cd-1 mice for 5 consecutive days.
3. The mean achieved atmosphere concentrations were .01, .04, and .14 mg/litre.
4. A control group of 12 males was exposed to air only.
5. At the start of this five-day range-finding study, animals weighed 23-30g and were approximately six to seven weeks of age.
6. The animals were housed in a single air-conditioned room maintained at a temperature of 18-22 degrees C and a relative humidity of 40-70%.
7. Exposure Schedule.

Four groups, each of 12 male mice, were treated according to the following schedule:

Group Number	Target Atmosphere Concentration	Mean Achieved Atmosphere Concentration	Treatment Period
1	0		
2	0.01	0.00	5 days
3	0.05	0.01	5 days
4	0.20	0.04	5 days

RESULTS:

NOAEL Precision: >=

NOAEL dose: 10

Unit: ug/L(air)

NOAEL Effect: Clinical Observations: ptosis and/or red/brown staining of fur (unlikely to be of toxicological significance) were noted on treatment days 2 and 3.

LOAEL Precision: >=

LOAEL dose: 10

Unit: ug/L(air)

LOAEL Effect: NONE

Actual dose received by dose level by sex: 0.01, 0.04 or 0.14 mg/L (air)

Toxic Response:

High Dose: 75% mortality

Intermediate Dose: 17% mortality; decreased body weight gain, and reduced lung weight

Low Dose: No effects. See NOAEL Effect.

Statistical result: Statistical Method: one way analysis of variance incorporating 'F-max' test for homogeneity of variance

Probability values were calculated at

P < 0.001 ***

P < 0.01 **

P < 0.05 *

P >= 0.05

Results Remarks:

1. Mortality Data: With the exception of the two animals sacrificed from each dose group for the cytotoxicity study, there were twelve deaths over the study period.

Four high dose animals were killed in extremis on day 4 prior to the exposure period and a further 5 animals were found dead over the following two days. Two intermediate dose animals died on day 5; one died during the exposure period and the other was found dead approximately 2 « hours post dosing. There was one death in the low dose group on day 1 but this was unrelated to treatment with the test material.

2. Clinical Observations: Wet fur was commonly observed in all treatment groups, including controls during exposure. This is a normal finding associated with the restraint procedure and is not indicative of toxicity. However, high dose animals showed hunched posture, pilo-erection, lethargy, ptosis, decreased respiratory rate, noisy or gasping respiration, pallor of the extremities, ataxia, distended abdomen, dehydration and emaciation. The sole survivor from this group continued to show signs of hunched posture, pilo-erection, noisy respiration, and decreased respiratory rate throughout the recovery period.

Clinically observable signs of toxicity were also apparent in the intermediate dose group although the severity was considerably reduced compared with the high dose. Observations included hunched posture, pilo-erection, lethargy, decreased respiratory rate, noisy or gasping respiration, ptosis, and red/brown staining of the fur. Signs of toxicity regressed during the treatment free period to such an extent that the animals were comparable with controls by day 15. No clinically observable abnormalities were detected in the low dose group which could be considered attributable to toxicity.

3. Bodyweight: All treatment groups, including controls, showed individual bodyweight losses by day 2 but these were considered to be a consequence of the restraint procedure and not dose related. However, the losses seen in the high dose animals were more pronounced than those of the control group and all animals continued to show bodyweight losses until day 5. The one surviving male continued to lose weight until day 16 at which time a slight gain was then evident over the following seven days. Individual intermediate dose animals also showed bodyweight losses over the treatment period. Bodyweight gain remained reduced during the treatment free period and frequent losses were still apparent during this time. No adverse effects were detected in the low dose group.

4. Water Consumption: No overt intergroup differences were detected.

5. Necropsy; Macroscopic abnormalities detected in the decedents from the high dose group included dark or abnormally red lungs, pale liver, pale kidneys and congestion of the small intestine. The two animals sacrificed on day 5 for the cytotoxicity study showed dark or reddened lungs. The two decedents from the intermediate dose group also showed dark or reddened lungs and one individual showed an abnormally pink pancreas. One cytotoxicity animal also showed red lungs. No further macroscopic abnormalities were detected in the remaining animals necropsied on day 23. No convincing treatment -related effects were apparent in the low dose group, although one animal did show slightly reddened lungs.

6. Organ Weights: Due to the substantially reduced group size, statistical analysis of organ weight data was not performed on the high dose group. A statistically significant reduction in absolute and relative lung weight was detected in the intermediate dose animals in comparison with controls. No apparent adverse effects were detected in the low dose group.

7. Cytotoxicity: Tepic SP caused no depression of the cytotoxic ration in the germ cells of male mice given a 5-day repeat exposure by the inhalation route.

CONCLUSIONS:

1) The inhalation of Tepic SP by male mice for a period of five consecutive days at a maximum concentration of 0.14 mg/l resulted in deaths and toxicologically significant changes at 0.04 and 0.14 mg/l.

2) Animals exposed to 0.14 mg/l showed severe signs of toxicity over the treatment period. Clinically observable signs were apparent with respiratory effects of noisy or gasping respiration and decreased respiratory rate. All animals showed marked bodyweight reductions and only one male survived until the end of the study. The majority of decedents from this group showed macroscopic abnormalities of the respiratory tract with red or dark lungs commonly observed.

3) Signs of toxicity were also apparent in animals exposed to 0.04 mg/l, although these were less severe than those of the high dose. Respiratory

abnormalities were detected clinically and bodyweight gain was reduced with sporadic losses noted throughout the treatment free period. No macroscopic abnormalities were detected in the lungs of animals necropsied on day 23, however, both absolute and relative lung weights were significantly reduced in comparison with controls.

4) No toxicologically significant effects were detected in the 0.01 mg/l dose group.

Daily six hour exposure to Tepic SP, at mean achieved atmosphere concentrations of up to 0.14 mg/liter for five consecutive days in the male mouse resulted in deaths and toxicologically significant changes at concentrations of 0.04 and 0.14 mg/l. No such changes were detected at 0.01 mg/l.

DATA QUALITY:

Reliability: Reliability Code 2;

Data Reliability Remarks: The protocol and report appear to be comprehensive and consistent with international guidelines. This study was conducted by an internationally recognized laboratory and was certified as a GLP study for the EEC, US, and Japan. Study quality appears to be acceptable.

REFERENCES:

1) Five Day Repeat Exposure Inhalation Toxicity Study in the Male Mouse Using TEPIC SP; Study conducted by: Safepharm Laboratories Limited, Derby, DE1 2BT, UK, and completed on September 24, 1991.

2) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

17a

17 Reproduction Toxicity:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.
ADDITIVES: None
SOLVENT CARRIERS: None
CONTAMINANTS: None
CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: This study used the 1992 EPA approved Method and was similar to OECD Method 483
Test Type: In Vivo Chromosome Aberration and Cytogenetics Assay.
GLP (Y/N): Yes
Year Study Performed: 1992
Species: Mouse
Strain: Mammal Strain: CD-1
Sex: M
Number of males per dose: 10
Number of females per dose: 0
Route of Administration: Inhalation (with oral control)
Exposure Period: 5
Frequency of treatment: 6 hr/day; 5 days/wk
Doses: Pure TGIC at a dose of 7.8 mg/m³ via inhalation; Pure TGIC at 115 mg/kg/day via oral gavage; 10% TGIC powder at 100 and 255 mg/m³ via inhalation.
Control Group: Yes
Premating exposure period for female: NA
Premating exposure period for male: NA
Statistical Method: See below.
Remarks for Method:

This study utilized a combination of test articles, dosages and routes of exposure to evaluate the chromosome damaging potential of TGIC and powder coating formulations containing 10% TGIC. The experimental design is best described by the following information:

Group 1 was a negative control group which was exposed to pure air via nose only inhalation;

Group 2 received pure TGIC via inhalation at a dose of 7.8 mg/m³;

Group 3 was exposed to a Powder Coating formulation which contained 10% TGIC. Exposure was via inhalation at a dose of 95.3 mg/m³;

Group 4 was exposed to a Powder Coating formulation which contained 10% TGIC. Exposure was via inhalation at a dose of 255.3 mg/m³;

Group 5 was exposed to pure TGIC at a dose of 115 mg/kg. The exposure route was via oral gavage;

Group 6 was an oral positive control group in which animals were exposed to cyclophosphamide via gavage; and

Group 7 was a positive control group for the cytogenetics assay. Animals in this group were exposed to Mitomycin -C intraperitoneally at a dosage of 3 mg/kg.

RESULTS:

Parental Precision/NOAEL: >
Parental NOAEL dose: 8
Parental NUnit used: mg/m3(air)
Parental NOAEL effect assessed: NA
Parental Precision/LOAEL: >
Parental LOAEL dose: 8
Parental LUnit used: mg/m3(air)
Parental LOAEL effect assessed: NA
F1 Precision/NOAEL: >
F1 NOAEL dose: 0
F1 NUnit used: mg/m3(air)
F1 NOAEL effect assessed: NA
F1 Precision/LOAEL: >
F1 LOAEL Dose: 0
F1 LUnit used: mg/m3(air)
F1 LOAEL effect assessed: NA
F2 Precision/NOAEL: >
F2 NOAEL dose: 0
F2 NUnit used: mg/m3(air)
F2 NOAEL effect assessed: NA
F2 Precision/LOAEL: >
F2 LOAEL dose: 0
F2 LUnit used: mg/m3(air)
F2 LOAEL effect assessed: NA
Actual dose received by dose level by sex: See Method discussion above.
Parental/F1 data: None
Offspring Data: None
Statistical Result: The cytotoxic ratios for Groups 5 and 7 were significant at $p < 0.01$ and $p < 0.001$, respectively. Total aberrations for Groups 3, 5, and 7 were significant at $p < 0.05$, 0.01 and 0.001, respectively.

Results Remarks:

No deaths occurred during the study and no adverse effects on body weight were detected. There were "no treatment-related effects" noted during the study. "There was no significant reduction in the cytotoxic ratio in the cyclophosphamide dose group, whereas in the Mitomycin-C dose group there was a highly significant reduction" in the cytotoxic ratio.

CONCLUSIONS:

TGIC, either in the technical form or as a 10% powder, did not induce significant toxicity or clastogenicity in the spermatogonial cells of mice exposed via the inhalation route. TGIC Technical given by the oral route induced a marked toxic effect in the spermatogonial cells of mice and also gave an equivocal response in terms of chromosome aberrations.

DATA QUALITY:

Reliability: Reliability Code 1;
Data Reliability Remarks: See Klimisch reference below

GENERAL COMMENTS:

This particular study does not fit neatly into any of the categories of test type provided in the HPV Tracker software. Therefore, after discussions with EPA, it was decided that the data may fit in this reproductive toxicity category.

This study provides data to suggest the oral high dose (115 mg/kg/day) systemic toxicity of TGIC, and data to conclude that relatively high workplace inhalation concentrations of TGIC (7.8 mg/m³) do not induce clastogenicity or chromosome aberrations.

REFERENCES:

- 1) TGIC Technical and TGIC 10% Powder: Chromosome Analysis in Mouse Spermatogonial Cells, Comparative Inhalation Study. Study conducted for Nissan Chemical Industries, Ltd. Tokyo, Japan by Safepharm Laboratories Limited, Derby, UK; May, 1992.
- 2) Number of cells with aberrations and total number of aberrations were calculated using Fishers Exact Test.
- 3) Cytotoxic ratios were compared using a Chi² Test and if necessary a one-way analysis of variance.
- 4) Klimisch, H.J. et.al., A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data; Regulatory Toxicology and Pharmacology 25, 1-5 (1997).

17b

17 Reproduction Toxicity:

TEST SUBSTANCE:

PURITY: Technical Grade TGIC: Technical grade TGIC contains approximately 76 to 80% of the α -isomer, and approximately 20 to 24% of the β -isomer. The relative amount of the isomers in technical grade TGIC is not influenced by the method of manufacture. Excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8) may be present at concentrations up to 100 ppm.

ADDITIVES: None

SOLVENT CARRIERS: None

CONTAMINANTS: None

CHEMICAL FORMULA: C12 H15 N3 O6

METHOD:

Method/Guideline Followed: Repeated Dose (13 Week) Toxicity and Fertility Study - OECD Method 408; Adopted May 12, 1981

Test Type: Fertility

GLP (Y/N): Yes

Year Study Performed: 1995

Species: Rat

Strain: Sprague-Dawley

Sex: M

Number of males per dose: 10

Number of females per dose: 0

Route of Administration: Oral

Exposure Period: 94

Frequency of treatment: Daily

Doses: M=0.72, 2.08, or 7.32 mg/kg/day; F=0 mg/kg/day

Control Group: Yes

Premating exposure period for female: None

Premating exposure period for male: NA

Statistical Method: See Remarks below.

Remarks for Method:

- 1) Test substance was Araldite PT 810, batch number 407923.48, manufactured on 11/5/94 and stored at 4 degrees centigrade.
- 2) The identity of the test substance was independently confirmed by the testing laboratory.
- 3) The vehicle used was A04C 2.5 ground diet, batch numbers 40927 and 41114 (U.A.R., 91360 Villemisson-sur-Orge, France).
- 4) The diet was mixed; tested for homogeneity, stability and TGIC concentration on weeks 1, 4, 5, 8, 9, and 12); and stored at 4 degrees centigrade.
- 5) One hundred and thirty three Sprague Dawley rats (45 male and 88 female) of the Crl CD (SD) BR strain were supplied by Charles River France (76410 Saint-Aubin-les-Elbeuf, France).
- 6) Rats were acclimatized for a minimum of 8 days prior to being placed on study. They were randomly assigned to treatment groups and identified by ear tattoo.

7) At the beginning of the treatment period males were approximately 6 weeks old with a mean body weight of 204 grams.

8) Upon arrival at the lab, animals were placed in a disinfected room, quarantined and given a clinical examination. Temperature was 21 +/- 2 degrees centigrade, relative humidity was 50 +/- 20%, light/dark cycle was 12hr/12hr, and ventilation was 12 cycles/hr of filtered, non-recycled air. ""There were no deviations in temperature and relative humidity which could have influenced the outcome of the study.""

9) Animals had free access to food and water. "There were no known contaminants in the diet, water or saw dust bedding at levels likely to have influenced the outcome of the study."

10) After 64 days of treatment males were placed with females (1 male and 2 female) overnight. Females were placed with the same male for 7 night or until mating was confirmed.

11) The following parameters were measured: clinical signs, clinical chemistry, sperm count, pathology mortality, body weight, food consumption and mean food intake (mg/kg/day), as well as the other parameters required by this guideline. See report for details of these evaluations.

RESULTS:

Parental Precision/NOAEL: =

Parental NOAEL dose: 30

Parental NUnit used: mg/kg in feed

Parental NOAEL effect assessed: Decreased numbers of spermatazoa

Parental Precision/LOAEL: >

Parental LOAEL dose: 100

Parental LUnit used: mg/kg in feed

Parental LOAEL effect assessed: None identified

F1 Precision/NOAEL: >

F1 NOAEL dose: 0

F1 NUnit used: mg/kg in feed

F1 NOAEL effect assessed: NA

F1 Precision/LOAEL: >

F1 LOAEL Dose: 0

F1 LUnit used: mg/kg in feed

F1 LOAEL effect assessed: NA

F2 Precision/NOAEL: >

F2 NOAEL dose: 0

F2 NUnit used: mg/kg in feed

F2 NOAEL effect assessed: NA

F2 Precision/LOAEL: >

F2 LOAEL dose: 0

F2 LUnit used: mg/kg in feed

F2 LOAEL effect assessed: NA

Actual dose received by dose level by sex: M=0.72, 2.08, or 7.32 mg/kg/day; F=0 mg/kg/day

Parental/F1 data: No treatment-related infertility was noted in males and no influence on embryonic or pup development was observed.

Offspring Data: None

Statistical result: Statistical methods were discussed, but analyses of the data were not provided.

Results Remarks:

- 1) The chemical composition of the test article was confirmed at the laboratory prior to initiation of the in vivo studies.
- 2) The concentration, homogeneity and stability of the test article in the diet were monitored and reported. This data, along with food consumption and body weight, was used to calculate the actual doses received during the study.
- 3) Results summary for the Toxicology Study:

Clinical examinations:

No treatment-related clinical signs and no mortalities occurred during the treatment period. Slightly lower body weight gain was noted over the first 6 weeks of dosing in males given 100 ppm (-16%). Thereafter, the body weight gain of this group was similar to that of controls. The body weight gain of males given 10 or 30 ppm was similar to that of controls. No statistically significant differences from controls were observed in food consumption for any male treatment groups.

The achieved dosages were on average, 0.72, 2.08 or 7.32 mg/kg/day in the males given 10, 30 or 100 ppm, respectively. The achieved dosages decreased throughout of the treatment period (in mean -60% between weeks 1 and 13). The efficiency of food utilization was similar in all treated groups.

Laboratory investigations:

Slightly lower leucocyte and lymphocyte counts were noted in 2/10 males given 100 ppm. No significant differences from controls were noted in blood biochemistry and urinalysis parameters.

Pathology:

No treatment-related differences from controls were recorded in the organ weights. Reddish coloration of mesenteric lymph nodes in association with hemosiderosis and congestion were found in some individuals given 100 ppm.

Analysis of sperm:

Slightly lower number of spermatozoa was observed with a dose-related frequency in all treated groups.

The mean spermatozoa viability was similar in male treatment groups when compared to the control group.

Results summary for the Fertility Study:

Maternal data:

No clinical signs and no unscheduled mortalities occurred during the study period. No abortions occurred in any female. The body weight gain and the food consumption of females was similar in all groups during pregnancy and lactation periods. No relevant macroscopic findings were made at necropsy.

Reproductive data in males:

The mating index of males was 100% in all groups. No treatment-related infertility was recorded in any male group.

Litter data for the hysterectomy subgroup:

The gestation index was 100% in all groups. The mean number of corpora lutea and implantation sites and therefore the pre-implantation loss were similar in all groups. The rate of resorption and the post-implantation loss were similar in all groups. There were no dead fetuses were noted in any group. The mean

number, the mean fetal body weight and the sex-ratio of live fetuses were similar in all groups. No external anomalies or malformations were observed in fetuses of any group.

Litter data for the delivery subgroup:

At birth, the mean number of live born pups was similar in all groups. The viability index of pups on day 4 post-partum, and on day 21 post-partum (or lactation index) was considered to be similar in all groups. The mean body weight of pups was similar in all groups, over the period of study (Day 1 to Day 21 post-partum). No toxicologically significant clinical observations were noted for pups in any groups. The physical development of pups as assessed by: pinna unfolding, hair growth, tooth eruption, eye opening and auditory canal opening, was similar in all groups. The reflex development of pups as assessed by: surface righting, cliff avoidance and air righting, was similar in all groups. See report for details of these evaluations.

CONCLUSIONS:

The administration of the test article Araldite PT 810 (TGIC), by dietary admixture for 13 weeks to male Sprague Dawley rats was well tolerated at doses of 10 or 30 ppm (0.72 or 2.08 mg/kg/day). Slightly lower (approximately 10%) body weight gain was recorded for the 100 ppm (7.32 mg/kg/day) group. A slight, but dose-related decrease in the mean number of spermatozoa was observed in the TGIC treated groups. No treatment-related infertility was noted in males and no influence on embryonic or pup development was observed after mating with untreated females. Consequently, 30 ppm was considered as the no observed effect level (NOEL). At 100 ppm, the lower number of spermatozoa did not impair the fertility of the treated males and therefore this dose level was considered to be the no observed adverse effect level (NOAEL).

DATA QUALITY:

Reliability: Reliability Code 1. (See Reference No. 7 below)
Data Reliability Remarks: The Report and Protocol followed OECD and GLP Guidelines.

GENERAL COMMENTS:

Because of the overlap of the two endpoints discussed herein, this 13-Week Toxicity Study and Fertility Study In Male Rats is also listed in the Repeated Dose Toxicity Section of this dossier.

REFERENCES:

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