

Robust Summaries

CAS# 136-23-2

201-14986B

Zinc, bis(dibutylcarbamoedithioato-S,S')-, (T-4)-

Molecular Formula: C18-H36-N2-S4-Zn
Molecular Weight: 474.13

1.1 GENERAL SUBSTANCE INFORMATION

- A. Type of Substance: Organic
- B. Physical State: White Solid
- C. Purity: 96-99 % Typical for Commercial Products

1.2 SYNONYMS

Zinc Dibutyldithiocarbamate
ZDBC
Butazate®
Butyl Zimate®
Butasan®
Zinc, N,N-dibutyldithiocarbamate
Butyl Ziram®
ZnBDC
Perkacit ZDBC®

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PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value: 105 – 112 °C
Decomposition: No
Sublimation: No
Method: ASTM Standard Test Method D-1519
GLP: Yes
Remarks: Capillary Method for determining the initial and final melting point of organic compounds. Melt onset at 105 °C, final melt at 110-112 °C
Reference: ASTM Standard Methods of Analysis
Reliability: (1) Valid without restriction

*2.2 BOILING POINT

Value: 296 °C
Pressure: 29 mm Hg
Decomposition: Yes
Method: Instrumental – Du Pont 2100 TGA
GLP: No
Remarks: Residue after decomposition = 2%
Reference: R.T. Vanderbilt Analytical Lab Report 07 Jan 1998
Reliability: (1) Valid without restriction

†2.3 **DENSITY (relative density)**

Type: Density
Value: 1.24
Temperature: 20 °C
Method: Other: Density of solids by displacement of liquid
GLP: No
Remarks: Density of solids by displacement of liquid
Reference: FF97.8-1 Flexsys Standard Methods of Analysis
Reliability: (1) Valid without restriction

*2.4 **VAPOUR PRESSURE**

Value: 1.06E-009 mm Hg
Temperature: 25 °C
Method: calculated
Other: Modified Grain method
GLP: No
Remarks: Estimation method based on molecular structure and measured melting point and water solubility values.
Reference: EPIWIN/MPBPWIN v1.40
Reliability: (2) Valid with restrictions – Modelling data

*2.5 **PARTITION COEFFICIENT $\log_{10}P_{ow}$**

Log Pow: 7.04
Temperature: None
Method: calculated
Other: SRC LogKow (KowWin) Program 1995
GLP: No
Remarks: Estimation method based on molecular structure fragments, measured melting point and water solubility.
Reference: EPIWIN/KOWWIN v1.66
Reliability: (2) Valid with restrictions – Modelling data

*2.6 **WATER SOLUBILITY**

A. Solubility

Value: 13 ppm (0.0013%)
Temperature: 21 °C
Description: Of very low solubility
Method: Fifty milligrams of the test compound was dispersed in 200 ml deionized water and stirred for 24 hours at room temperature (70 °C). After 24 hours, the dispersion was filtered through a 0.2 micron filter to remove solids. 100 grams of the filtrate was evaporated to dryness in a tared beaker. After drying, the residue weight was determined.
GLP: No
Remarks: Test compound is very hydrophobic and resists wetting.

Reference: Flexsys AP 2003.105, 10/07/2003
Reliability: (1) Valid without restriction

B. pH Value, pKa Value

pH Value: Not Applicable
pKa value: Not Applicable

2.11 OXIDISING PROPERTIES

†2.12 OXIDATION: REDUCTION POTENTIAL

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

B. Other data – Henry's Law Constant

Results: 5.078E-008 atm-m³/mole
Remarks: Calculated at 25 °C
Reference: Environ Toxicol Chem 10: 1283-93 (1991)
EPIWIN/HENRYWIN v3.10
Remarks: Estimation method based on molecular structure fragments, measured melting point and water solubility.
Reliability: (2) Valid with restrictions – Modelling data

3. ENVIRONMENTAL FATE AND PATHWAYS

***3.1.1 PHOTODEGRADATION**

Type: Air
Light source: Sunlight
Temperature: 25 °C
Direct photolysis:
Half life: 0.691 hours
Indirect Photolysis:
Rate constant (radical): 185.6527 E-12 cm³/molecule-sec
Method: calculated
Atmospheric Oxidation Program/SAR Methods, 1995
GLP: No
Test substance: Other: SAR
Remarks: Estimation method based on molecular structure fragments, measured melting point and water solubility. Rapid atmospheric degradation of test substance in vapor phase by reaction with photochemically produced hydroxyl radicals. Particulate phase test substance may be physically removed from air by both wet and dry deposition. If released to air, test substance is expected to exist in both vapor and particulate phases.

Reference: Meylan, WH and Howard, PH, Chemosphere 26: 1193-99, 1999
EPIWIN/AOPWIN v1.90
Reliability: (2) Valid with restrictions - Modelling data

*3.1.2 STABILITY IN WATER

Type: Abiotic (hydrolysis)
Half life: pH dependent – see below
Degradation: 50% after 0.25 hours @ pH 3.8
50% after 9.1 hours @ pH 5.7
50% after 121 hours @ pH 7.0
50% after 433 hours at pH 8.0
Method: Hydrolysis as a Function of pH
GLP: No data
Test substance: Zinc Dimethyldithiocarbamate (ZDMC), a structurally similar zinc-containing dithiocarbamate also used as a rubber additive.
Remarks: Dithiocarbamate salts are known to rapidly hydrolyze under acidic conditions. Breakdown products detected during hydrolysis experiments are the starting amine (dibutylamine in the case of ZDBC) and carbon disulfide.
Reference: Van Leeuwen, C.J (1986)
Reliability: (2) Valid with restrictions – data from a structurally similar compound and general class of compounds which have been extensively tested for environmental effects

*3.2 MONITORING DATA (ENVIRONMENTAL)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

*3.3.1 TRANSPORT

Type: Adsorption
Media: Soil/Sediment
Method: SRC Structure estimation method based on molecular connectivity indices, 1992
Results: $K_{oc} = 2.289E+004$; $\log K_{oc} = 4.360$
Remarks: Estimation method based on molecular structure fragments, measured melting point and water solubility.
Reference: EPIWIN/PCKOCWIN v1.66
Reliability: (2) Valid with restrictions – Modelling data

Type: Volatility
Media: Water
Method: Estimation Method, 1990
Results: Volatilization half-life from model river: $2.452E+004$ hours
Volatilization half-life from model lake: $2.677E+005$ hours

Remarks: Model river = 1 m deep flowing at 1 m/sec and wind velocity of 3 m/sec.
Model lake = 1 m deep flowing at 0.05 m/sec and wind velocity of 0.5 m/sec.
Estimation method based on molecular structure fragments, measured melting point and water solubility.

Reference: Handbook of Chemical Property Estimation Methods, 1990

Reliability: (2) Valid with restrictions – Peer-reviewed published data from a generally accepted and validated estimation method

*3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Media: Air-biota-sediment-soil-water
Method: Fugacity level III
EPIWIN v3.10

Results:

	Mass Amount (%)	Half-life (hrs)	Emissions (kg/hr)
Air	0.184	1.38	1000
Water	12.1	208.00	1000
Soil	31.4	208.00	1000
Sediment	56.3	832.00	0

Persistence time estimated to be 334 hours

Remarks: Estimation method based on molecular structure fragments, measured melting point and water solubility.

Reference: EPISUTTE/EPIWIN v3.10

Reliability: (2) Valid with restrictions – Modelling data

*3.5 BIODEGRADATION

Type: Anaerobic
Inoculum: Adapted
Concentration of the chemical: no data
Medium: Water-sediment
Degradation: Without sediment: 17% CO₂ production after 50 days
With sediment: 68% CO₂ production after 50 days

Results: Inherently biodegradable
Method: EPA 835.4400(162-3) equivalent
GLP: No data
Test substance: Structurally similar compound Zinc Dimethyldithiocarbamate (ZDMC), also known as the pesticide Ziram

Remarks: 14C-labeled Ziram was assayed for biodegradation in surface water, water with sediment, and mud. Approximately 23% of the total 14C-activity in the mud was recovered as a bound residue.

Reference: Van Leeuwen, C.J., Rijkswaterstaat Communications (1986)

Reliability: (2) Valid with restrictions - data from a structurally similar compound which has been extensively tested for environmental effects

3.6 BOD5, COD OR RATIO BOD5/COD

3.7 BIOACCUMULATION

Species: Trout and Guppy (measured); Estimation
BCF: <100
Type of test: Calculated and Measured
GLP: No data
Test substance: Structurally similar compound Zinc Dimethyldithiocarbamate (ZDMC), also known as the pesticide Ziram
Remarks: Measured values of 90 for trout, 4.7 for guppy (Van Leeuwen)
Estimated value of 59 based on water solubility (Kenaga, E.E.)
14C-labeled ZDMC was rapidly disseminated throughout rainbow trout tissues. Whole-body accumulation was low, and whole-body elimination was rapid, with 45% of the initial radioactivity from ZDMC retained at the end of the 16-day depuration period. Pigmented tissues appeared to be the major distribution sites.
Estimated value of 59 based on water solubility (Kenaga, E.E.)
Reference: Van Leeuwen, C.J (1986); Kenaga, E.E. (1980)
Reliability: (2) Valid with restrictions - data from a structurally similar compound which has been extensively tested for environmental effects

4. ECOTOXICITY

*4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type of test: Static
Closed system
Species: *Salmo gairdneri* (Rainbow Trout)
Exposure period: 96 hours
Concentration: 0, 100, 180, 320, 560 and 1000 mg/l, plus solvent control
Results: LC₅₀ (24h) = 750 mg/l
LC₅₀ (48h) = 560 mg/l
LC₅₀ (96h) = 520 mg/l
NOEC = 320 mg/l
LOEC = 560 mg/l
Analytical monitoring: No
Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, 1975
GLP: Yes
Test substance: As prescribed by 1.1-1.4, purity: >96%
Remarks: Test fish were obtained from Spring Creek Hatchery in Lewistown, Montana. Test fish were held in culture tanks on a 16-hour daylight photoperiod and observed for at least 14 days prior to testing. A daily record of fish observations was maintained during the holding period, during which time the fish were fed a standard diet of commercial fish food until 48 hours prior to testing, when feeding was stopped. A 72-hour range-finding test preceded the definitive study. Test fish used had a mean weight of 0.84g and a mean standard length of 38 mm. The test was

conducted in 5 gallon glass vessels containing 15 liters of ABC well water. The 0-hour measured control water parameters of this dilution water were dissolved oxygen 9.1 mg/l and pH 8.0. The test vessels were kept in a water bath at 12 °C. Test fish were acclimated to the dilution water and test temperature, and held without food for 48 hours prior to testing. Nanograde Acetone was used as the solvent and as the solvent control. Test concentrations were obtained by transferring appropriate weights of test compound directly into the test chambers, followed by 7.5 ml of nanograde acetone to facilitate dissolution. The solvent control received an aliquot of 7.5 ml of acetone equivalent to that of the highest test concentration. A white precipitate was observed in all test compound solutions. Ten fish per concentration were placed in the testing vessels within 20 minutes of the addition of the test material aliquots. All concentrations were observed once every 24 hours for mortality and abnormal effects. Dissolved oxygen values (9.2 to 7.7 mg/l, or 85-71% saturation, respectively) and pH ranges (8.0 to 8.1) were monitored during the testing and remained within acceptable limits and were comparable to those of the control vessel (9.1 to 8.1 for DO, 8.0 to 8.1 for pH). As a quality check, test fish were challenged with Antimycin A. The estimated 96Hr LC50 and 95% confidence limits were within the 95% confidence limits reported in the literature, indicating that the fish were in good condition. NOTE: Because of the possibility of rapid hydrolysis of the test material, a stipulation was written into the protocol mandating that no more than 20 minutes could elapse between addition of test fish and chemical addition. The 24 and 48-hour LC50 values and corresponding confidence limits were determined by an LC50 computerized program developed by Stephan et. al. (1978). This program calculated the LC50 statistic and its 95% confidence limits using the binomial, moving angle and probit methods because no one method is appropriate for all possible sets of data. The method of calculation selected was that which gave the narrowest confidence limits for each separate analysis. The no-effect concentration based on the lack of mortality and abnormal effects was 320 mg/l after 96 hours. The abnormal effects of surfacing and dark discoloration progressed from 1000 mg/l initially to 560 mg/l after 96 hours.

Reference: Monsanto AB-83-014 Analytical Bio-Chemistry Labs 07/21/83
Reliability: (4) Unassignable – while the addition of acetone solvent directly to the test aquaria rather than to the test compound is a major protocol deviation, the results suggest that the test compound does not exhibit significant toxicity to freshwater fish unless it is dissolved in a suitable solvent beforehand.

Type of test: Static
Closed system
Species: *Salmo gairdneri* (Rainbow Trout)
Exposure period: 96 hours
Concentration: 0, 0.10, 0.18, 0.32, 0.56 and 1.0 mg/l, plus solvent control
Results: LC₅₀ (24h) = 0.42 mg/l

	LC ₅₀ (48h) = 0.32 mg/l
	LC ₅₀ (96h) = 0.23 mg/l
	NOEC = 0.10 mg/l
	LOEC = 0.18 mg/l
Analytical monitoring:	No
Method:	EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, 1975
GLP:	Yes
Test substance:	Other: Structurally similar compound Zinc Diethyldithiocarbamate (ZDEC), purity: >97%
Remarks:	Test fish were obtained from Spring Creek Hatchery in Lewistown, Montana. Test fish were held in culture tanks on a 16-hour daylight photoperiod and observed for at least 14 days prior to testing. A daily record of fish observations was maintained during the holding period, during which time the fish were fed a standard diet of commercial fish food until 48 hours prior to testing, when feeding was stopped. A 72-hour range-finding test preceded the definitive study. Test fish used had a mean weight of 1.2 g and a mean standard length of 41 mm. The test was conducted in 5 gallon glass vessels containing 15 liters of ABC well water. The 0-hour measured control water parameters of this dilution water were dissolved oxygen 8.7 mg/l and pH 8.0. The test vessels were kept in a water bath at 12°C. Test fish were acclimated to the dilution water and test temperature, and held without food for 48 hours prior to testing. Nanograde Acetone was used as the solvent and as the solvent control. The solvent control received an aliquot (5.0 ml) of acetone equivalent to that used in the highest test concentration. Ten fish per concentration were placed in the testing vessels within 20 minutes of the addition of the test material aliquots. All concentrations were observed once every 24 hours for mortality and abnormal effects. Dissolved oxygen values (8.7 to 7.0 mg/l, or 81-65% saturation, respectively) and pH ranges (8.0 to 8.2) were monitored during the testing and remained within acceptable limits and were comparable to those of the control vessel (8.7 to 7.3 for DO, 8.0 to 8.1 for pH). As a quality check, test fish were challenged with Antimycin A. The estimated 96Hr LC50 and 95% confidence limits were within the 95% confidence limits reported in the literature, indicating that the fish were in good condition. NOTE: Because of the possibility of rapid hydrolysis of the test material, a stipulation was written into the protocol mandating that no more than 20 minutes could elapse between addition of test fish and chemical addition. The 24 and 48-hour LC50 values and corresponding confidence limits were determined by an LC50 computerized program developed by Stephan et. al. (1978). This program calculated the LC50 statistic and its 95% confidence limits using the binomial, moving angle and probit methods because no one method is appropriate for all possible sets of data. The method of calculation selected was that which gave the narrowest confidence limits for each separate analysis. The no-effect concentration based on the lack of mortality and abnormal effects was 0.10 mg/l after 96 hours. The abnormal effects of mortality, surfacing,

loss of equilibrium and dark discoloration progressed from 1.0 mg/l initially to 0.18 mg/l after 96 hours.

Reference: Monsanto ABC 30801, Analytical Bio-Chemistry Labs 09/16/83

Reliability: (2) Valid with restrictions – data from a structurally similar compound

Type of test: static
Closed system

Species: *Lepomis macrochirus* (Bluegill Sunfish)

Exposure period: 96 hours

Concentration: 0, 100, 180, 320, 560 and 1000 mg/l, plus solvent control

Results: LC₅₀ (24h) >1000 mg/l
LC₅₀ (48h) = 880 mg/l
LC₅₀ (96h) = 880 mg/l
NOEC = 560 mg/l
LOEC = 1000 mg/l

Analytical monitoring: No

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, 1975

GLP: Yes

Test substance: As prescribed by 1.1-1.4, purity: >96%

Remarks: Test fish were obtained from Osage Catfisheries in Osage Beach, Missouri. Test fish were held in culture tanks on a 16-hour daylight photoperiod and observed for at least 14 days prior to testing. A daily record of fish observations was maintained during the holding period, during which time the fish were fed a standard diet of commercial fish food until 48 hours prior to testing, when feeding was stopped. A 96-hour range-finding test preceded the definitive study. Test fish had a mean weight of 0.17 g and a mean standard length of 20 mm. The test was conducted in 5 gallon glass vessels containing 15 liters of ABC well water. The 0-hour measured control water parameters of this dilution water were dissolved oxygen 8.4 mg/l and pH 8.0. The test vessels were kept in a water bath at 22 °C. Test fish were acclimated to the dilution water and test temperature, and held without food for 48 hours prior to testing. Nanograde Acetone was used as the solvent and as the solvent control. Test concentrations were obtained by transferring appropriate weights of test compound directly into the test chambers, followed by 7.5 ml of nanograde acetone to facilitate dissolution. The solvent control received an aliquot of 7.5 ml of acetone equivalent to that of the highest test concentration. A white precipitate was observed in all test compound solutions. Ten fish per concentration were placed in the testing vessels within 20 minutes of the addition of the test material aliquots. All concentrations were observed once every 24 hours for mortality and abnormal effects. Dissolved oxygen values (8.4 to 5.0 mg/l, or 95-57% saturation, respectively) and pH ranges (8.0 to 8.1) were monitored during the testing and remained within acceptable limits and were comparable to those of the control vessel (8.4 to 5.5 for DO, 8.0 for pH). As a quality check, test fish were challenged with Antimycin A. The estimated 96Hr LC50 and 95% confidence limits were within the 95% confidence limits

reported in the literature, indicating that the fish were in good condition.
NOTE: Because of the possibility of rapid hydrolysis of the test material, a stipulation was written into the protocol mandating that no more than 20 minutes could elapse between addition of test fish and chemical addition. The 24 and 48-hour LC50 values and corresponding confidence limits were determined by an LC50 computerized program developed by Stephan et. al. (1978). This program calculated the LC50 statistic and its 95% confidence limits using the binomial, moving angle and probit methods because no one method is appropriate for all possible sets of data. The method of calculation selected was that which gave the narrowest confidence limits for each separate analysis. The no-effect concentration based on the lack of mortality and abnormal effects was 560 mg/l after 96 hours. The abnormal effects of mortality and surfacing were confined to the highest concentration of 1000 mg/l.

Reference: Monsanto AB-83-013 Analytical Bio-Chemistry Labs 07/27/83
Reliability: (4) Unassignable – while the addition of acetone solvent directly to the test aquaria rather than to the test compound is a major protocol deviation, the results suggest that the test compound does not exhibit significant toxicity to freshwater fish unless it is dissolved in a suitable solvent beforehand.

Type of test: static
Closed system

Species: *Lepomis macrochirus* (Bluegill Sunfish)

Exposure period: 96 hours

Concentration: 0, 0.056, 0.10, 0.18, 0.32, 0.56 and 1.0 mg/l, plus solvent control

Results: LC₅₀ (24h) = 0.45 mg/l
LC₅₀ (48h) = 0.34 mg/l
LC₅₀ (96h) = 0.40 mg/l
NOEC = 0.18 mg/l
LOEC = 0.32 mg/l

Analytical monitoring: No

Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, 1975

GLP: Yes

Test substance: Other: Structurally similar compound Zinc Diethyldithiocarbamate (ZDEC), purity: >97%

Remarks: Test fish were obtained from Osage Catfisheries in Osage Beach, Missouri. Test fish were held in culture tanks on a 16-hour daylight photoperiod and observed for at least 14 days prior to testing. A daily record of fish observations was maintained during the holding period, during which time the fish were fed a standard diet of commercial fish food until 48 hours prior to testing, when feeding was stopped. A 96-hour range-finding test preceded the definitive study. Test fish had a mean weight of 0.09 g and a mean standard length of 17 mm. The test was conducted in 5 gallon glass vessels containing 15 liters of ABC well water. The 0-hour measured control water parameters of this dilution water were dissolved oxygen 8.6 mg/l and pH 8.1. The test vessels were kept in a water bath at 22 °C. Test fish were acclimated to the dilution water and

test temperature, and held without food for 48 hours prior to testing. Nanograde Acetone was used as the solvent and as the solvent control. The solvent control received an aliquot (5.0 ml) of acetone equivalent to that used in the highest test concentration. Ten fish per concentration were placed in the testing vessels within 20 minutes of the addition of the test material aliquots. All concentrations were observed once every 24 hours for mortality and abnormal effects. Dissolved oxygen values (8.6 to 7.2 mg/l, or 98-82% saturation, respectively) and pH ranges (7.9 to 8.3) were monitored during the testing and remained within acceptable limits and were comparable to those of the control vessel (8.6 to 7.3 for DO, 8.1-7.9 for pH). As a quality check, test fish were challenged with Antimycin A. The estimated 96Hr LC50 and 95% confidence limits were within the 95% confidence limits reported in the literature, indicating that the fish were in good condition. NOTE: Because of the possibility of rapid hydrolysis of the test material, a stipulation was written into the protocol mandating that no more than 20 minutes could elapse between addition of test fish and chemical addition. The 24 and 48-hour LC50 values and corresponding confidence limits were determined by an LC50 computerized program developed by Stephan et. al. (1978). This program calculated the LC50 statistic and its 95% confidence limits using the binomial, moving angle and probit methods because no one method is appropriate for all possible sets of data. The method of calculation selected was that which gave the narrowest confidence limits for each separate analysis. The no-effect concentration based on the lack of mortality and abnormal effects was 0.18 mg/l after 96 hours. The abnormal effects of mortality, quiescent behaviour, loss of equilibrium and dark discoloration progressed from 1.0 mg/l initially to 0.32 mg/l after 96 hours.

Reference: Monsanto ABC30800, Analytical Bio-Chemistry Labs 09/16/83
Reliability: (2) Valid with restrictions – data from a structurally similar compound

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

*A. *Daphnia*

Type of test: Static
Closed system
Species: *Daphnia magna*
Exposure period: 48 hours
Concentrations: 0, 0.056, 0.10, 0.18, 0.32, 0.56 and 1.0 mg/l, plus solvent control
Results: EC₅₀ (24h) >1.0 mg/l
EC₅₀ (48h) = 0.74 mg/l
NOEC = 0.056 mg/l
Analytical monitoring: No
Method: EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, 1975
GLP: Yes
Test substance: As prescribed by 1.1-1.4, purity: >96 %

Remarks: The *Daphnia magna* used in the test were cultured at the ABC facilities. Adult *Daphnia* were fed the algae *Selenastrum capricornutum* at least every three days prior to testing and supplemented with a suspension of trout chow. The bioassay was conducted in duplicate in 250 ml glass beakers containing 200 ml of ABC well water. Ten *Daphnia*, first instar less than 24 hours old, were selected for each test vessel. Vessels were kept at 20 °C in a temperature-controlled area. Lighting was maintained at 50-70 foot-candles on a 16-hour daylight photoperiod. An initial range-finding experiment was carried out to determine the exposure concentrations for the definitive test. Acetone was used as the solvent for the test solutions, and the experiment included both a control and a solvent control. The concentrated working standard solution was prepared by dissolving 0.20g of the test compound in 10 ml nanograde acetone. The solvent control received an aliquot of 0.10 ml of acetone equivalent to that of the highest test concentration. *Daphnia* in all concentrations were observed once every 24 hours for mortality and abnormal effects. Dissolved oxygen (DO) levels (7.6 to 8.7 mg/l, 83-95% saturation) and pH (8.2 to 8.6) were monitored throughout the testing and were considered adequate and equivalent to those measurements in the control chamber (7.6 to 8.5 mg/l for DO, 8.2 to 8.5 for pH). NOTE: Because of the possibility of rapid hydrolysis of the test material, a stipulation was written into the protocol mandating that no more than 20 minutes could elapse between addition of test fish and chemical addition. The 24 and 48-hour LC50 values and corresponding confidence limits were determined by an LC50 computerized program developed by Stephan et. al. (1978). This program calculated the LC50 statistic and its 95% confidence limits using the binomial, moving angle and probit methods because no one method is appropriate for all possible sets of data. The method of calculation selected was that which gave the narrowest confidence limits for each separate analysis.

Reference: Monsanto AB-83-015 Analytical Bio-Chemistry Labs 07/20/83

Reliability: (1) Valid without restriction

*4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

Species: *Chorella pyrenoidosa* (Green algae)

Endpoint: Respiration and Growth rate

Exposure period: 96 hours

Concentration: 0 to 10 mg/ml, plus solvent control

Results: EC₅₀ 96hr = 1.2 mg/l growth rate, >10 mg/ml respiration (ZDMC)
EC₅₀ 96hr = 1.1 mg/l growth rate (ZDEC)

Analytical monitoring: No

Method: OECD Guideline 201, 1984
Closed system

GLP: Yes

Test substance: Other: Structurally similar compound Zinc Dimethyldithiocarbamate (ZDMC), also known as the pesticide Ziram, purity: 95% and Zinc Diethyldithiocarbamate (ZDEC)

Remarks: The bioassay was conducted in a temperature-controlled room maintained at 20 °C. Test solutions (100 ml) with an initial cell density of approximately 10(8) cells/l (-1) were added to 200ml Erlenmeyer flasks. The flasks were stoppered with cotton and placed on a shaker under fluorescent light. Cells were counted using a Coulter Counter. Tests were carried out in triplicate in infuse bottles. Samples were taken via syringe to determine algal density. In order to compare EC50 values when similar tests were analyzed in different ways, the values were calculated for both the average specific growth rate, as defined in OECD Guideline 201, and for the specific growth rate as defined by Kooyman et. al. (1983). The effect on photosynthesis was also studied in a radiometric assay. Inhibition of respiration was studied using a 50 ml suspension of 10(10) cells/l (-1) together with radiolabeled sodium bicarbonate solution and a four hour incubation period. Dissolved radiolabeled sodium bicarbonate was removed via centrifugation. Acetone was used to prepare the stock solutions and for the solvent control. Stock solutions were prepared fresh daily. The EC50 values and their 95% confidence limits were calculated using the method of Litchfield and Wilcoxon (1949). Dithiocarbamates and dithiocarbamate salts are generally recognized as being toxic to green algae.

Reference: Van Leeuwen, C.J. *Rijkskwaterstaat Communications* 44, The Netherlands, 1986

Reliability: (2) Valid with restrictions - data from a structurally similar compound which has been extensively tested for environmental effects.

5. TOXICITY

*5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Type: LD₅₀
Species/strain: Rats, Sprague-Dawley Albino
Value: >5000 mg/kg b.w.
Discriminating dose: Not determined

Sex: Male/female
of Animals: 10
Vehicle: Corn Oil
Doses: 5000 mg/kg b.w.
Method: Other: 21 CFR Part 58, Single Oral Dose 1982
GLP: Yes
Test substance: As prescribed by 1.1-1.4, purity: 99.9 %
Remarks: Ten adult albino rats, 5 males and 5 females purchased from Sasco, Inc. were used for this study. Body weight ranges for the test animals were 224 – 312g for males and 169-213g for females. The test animals were administered a single dose of the test substance as a 434 mg/ml suspension in corn oil via oral intubation. Volume administered to each rat was adjusted according to body weight. Clinical observations were made three times within the first eight hours after dosing, and twice daily

thereafter until sacrifice. Body weights were recorded on days 0, 7 and 14. On day 15, all rats were sacrificed and necropsied. There were no clinical observations of toxicity other than diarrhea in three males and all females on day of dosing, but this effect was thought to be induced by the corn oil rather than the test substance. All rats survived until sacrifice. No abnormalities were observed in any test animal on necropsy.

Results:	<u>Dose mg/kg</u>	<u>Mortalities-Male</u>	<u>Mortalities-Female</u>	<u>Combined</u>
	5000	0/5	0/5	0/10

Reference: Monsanto ML-82-055 EHL/DMEH, 08/16/1982

Reliability: (1) Valid without restriction

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type:	LD ₅₀
Species/strain:	Rabbits, New Zealand Albino
Sex:	Male/female
# of Animals:	10
Vehicle:	None
Doses:	2000 mg/kg b.w.
Exposure Time:	24 Hours
Value:	>2000 mg/kg bow.
Method:	Other: 21 CFR Part 58, Single Oral Dose 1982
GLP:	Yes
Test substance:	As prescribed by 1.1-1.4, purity: 99.9 %
Remarks:	Ten young adult rabbits, five males and five females, were purchased from Isaac's Farm in Litchfield, IL, for this study. Mean body weight of males was 2.56 kg, and females 2.69 kg. The skin on the dorsal surface of each animal was shaved with an electric clipper and abraded with a hypodermic needle prior to administration of the test substance. Abrasions were sufficiently deep to penetrate the stratum corneum, but not deep enough to cause bleeding. All test animals received a single dermal exposure of 2000 mg/kg b.w. on the dorsal surface. The test material, moistened with physiological saline, was held in place by means of an occlusive wrap of latex rubber and secured by bandaging and elastic tape. The occlusive wrap was removed after 24 hours and the excess material was wiped from the test animal. Clinical observations were made three times during the first eight hours after dosing, and twice daily thereafter until sacrifice. Body weights were recorded on days 0, 7 and 14. All animals were sacrificed and necropsied on day 15. All test animals survived until necropsy. Mean body weights at the end of the study were 2.87 kg for males, and 3.05 kg for females. The only clinical abnormality observed was erythema in the exposed area of four animals (three males and one female) on the day after dosing. At necropsy, pale renal coloration was observed in one male, but this was not considered to be

related to the test material. No abnormalities of any type were observed in the viscera of the other nine animals.

Results:	<u>Dose mg/kg</u>	<u>Mortalities-Male</u>	<u>Mortalities-Female</u>	<u>Combined</u>
	2000	0/5	0/5	0/10

Reference: Monsanto ML-82-055 EHL/DMEH, 08/16/1982

Reliability: (1) Valid without restriction

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Species/Strain: Rabbits, New Zealand Albino

Results: Slightly irritating

Classification: Not irritating

Method: Draize, J.H., Woodard, G., and Calvery, H.O., 1944

GLP: Yes

Test substance: As prescribed by 1.1-1.4, purity: 99.9 %

Remarks: Six young adult rabbits were purchased from Isaac's Farm in Litchfield, IL, for this study. Mean body weights of test animals ranged from 2.91 – 3.20 kg. The skin on the dorsal surface of each animal was shaved with an electric clipper and abraded with a hypodermic needle prior to administration of the test substance. Abrasions were sufficiently deep to penetrate the stratum corneum, but not deep enough to cause bleeding. A mass of 0.5g of the test material, moistened with physiological saline, was applied to each of two intact and two abraded sites on each animal. The test material was applied to the skin under 1" square gauze patches and held in contact with the skin by means of an occlusive wrap of latex rubber secured by bandaging and elastic tape. The occlusive wrap and gauze patches were removed after 24 hours, and the excess test material was wiped from the treated sites of each animal. The initial (day 1) observation for skin irritation was made approximately one hour after removal of the wrappings. Dermal irritation was scored by the Draize Method, and results were recorded on the first and third days after topical application. The Primary Irritation Index was calculated by averaging the mean scores at 24 and 72 hours. The Primary Irritation Index was found to be 0.1 on a scale of 0.0-8.0. All signs of skin irritation had subsided by the third day after test material administration.

Reference: Monsanto ML-82-055 EHL/DMEH, 08/16/1982

Reliability: (2) Valid with restrictions – Differs from current testing guidelines by using abraded skin surface, a 24-hr contact period rather than a 4-hr contact period, and PII calculated using 24- and 72-hr observations instead of 24-, 48- and 72-hr time points.

5.2.2 EYE IRRITATION/CORROSION

Species/strain: Rabbits, New Zealand Albino

Results: Slightly irritating

Classification:	Not irritating
Method:	Draize, J.H., Woodard, G., and Calvery, H.O., 1944
GLP:	Yes
Test substance:	As prescribed in 1.1-1.4, purity: 99.9 %
Remarks:	Six young adult rabbits were purchased from Isaac's Farm in Litchfield, IL for this study. Body weights of test animals ranged from 2.57 – 2.83 kg. Thirty-nine (39) mg of the test substance was instilled into the conjunctival sac of the right eye of each animal by gently pulling the lower eyelid away from the eyeball to form a cup. Eyelids were held together for approximately one second. The topical aesthetic proparacaine hydrochloride (0.5%) was applied to both eyes of all test animals. Observations for signs of irritation were conducted on days 1, 2 3 after dosing. The untreated eye of each animal served as a negative control. On the first day after exposure, sterile fluorescein sodium was applied to the eyes. After approximately 10 seconds, the excess fluorescein was flushed from the eyes with physiological saline, and an ultraviolet light was used to determine whether staining persisted. The Draize Method was used for scoring eye irritation. The average Draize score for 24, 48 and 72 hours was calculated for each animal and then averaged over the six animals. The average Draize score was 0.3 on a scale from 0-110. All signs of irritation had subsided by the second day after exposure.
Reference:	Monsanto ML-82-055 EHL/DMEH, 08/16/1982
Reliability:	(1) Valid without restriction

*5.4 REPEATED DOSE TOXICITY

Species/strain:	Rats, Wistar
Sex:	Male/Female
Route of Administration:	Dietary
Exposure period:	17 Weeks
Frequency of treatment:	Daily
Post exposure observation period:	No data
Dose:	0, 100, 500 or 2500 ppm
Control group:	Yes (concurrent vehicle)
NOEL:	500 ppm [41-47 mg/kg/day]
LOEL:	2500 ppm
Results:	Lower mean body weights were seen in female high-dose animals, and the differences were statistically significant from day 9 and onward. Mean body weights of mid-dose and high-dose male rats were also slightly lower, but only to a statistically significant degree on days 13, 16, 20 and 27, and only in mid-dose animals. There were no statistically significant differences in mean body weights in the low-dose animals of either sex. Food consumption was reduced for both sexes in the high-dose group only. Water intake was not reduced in any group or sex. Hemoglobin concentration was significantly higher than controls at week 2 for mid-dose males and for high-dose females. No such changes were observed at subsequent examinations. The proportion of neutrophils was significantly greater and the proportion of lymphocytes was significantly lower in high-dose females at week 6. These changes were reversed at week 17. In the

results from serum analyses, statistically significant differences were limited to a rise in glutamic-pyruvic transaminase and a fall in lactate dehydrogenase at week 6 in high-dose males. No abnormal urinary constituents were found in any treated animals, nor were urinary protein levels different from controls. Some scattered significant differences were noted in the volume and specific gravity of urine in the dilution test at weeks 2 and 6, but not at week 17. The number of cells in the urine tended to be lower in treated animals in general, but this difference was only significantly different in a few cases. There were a number of small, but statistically significant differences in organ weights and organ/body weight ratios: Week 2 heart weight and relative heart weight were reduced in high-dose females. Relative caecum weight was significantly higher in high-dose males and females and in mid-dose males. Relative liver weights in high-dose males and females were slightly higher than controls, but this difference was only statistically significant in the males. Week 6 brain weights were lower in high-dose males. Relative weights of the caecum and gonads were also lower in these animals. At week 17, relative weights of both kidneys and livers were higher in both sexes of high-dose animals. High-dose males had higher relative weights of the small intestine and caecum, while high-dose females had lower brain, heart, small intestine and caecum weights. Relative heart weight and relative adrenal gland weight was significantly increased in both mid- and high-dose females. No histological changes related to dose or duration of treatment were seen in any of the tissues examined. The authors concluded that the no-untoward-effect level in this study was 500 ppm, which translates to 41 mg/kg/day for males and 47 mg/kg/day for females. Groups of 15 male and 15 female rats obtained from a specified pathogen-free colony were given diets containing 0, 100, 500 or 500 ppm of the test substance for 17 weeks. Additional groups of five male and five female rats of similar body weight were given diets containing 0, 500 or 2500 ppm of the test substance for 2 or 6 weeks. All animals were weighed initially, and on days 1, 2, 6, 9, 13, 16 and 20 of treatment, and thereafter weekly at intervals of up to 17 weeks. Food and water consumption were measured over a 24-hr period preceding each weighing. Urine was collected from each rat during the last week of its treatment and examined for appearance, microscopic constituents and content of albumin, glucose, ketones, bile salts and blood. During those same times, renal concentrating and diluting ability was assessed by measuring specific gravity and volume of urine produced during a 6-hr period of water deprivation and in a 2-hr period following a water load of 25 mg/kg. In addition, at weeks 6 and 17, the same measurements were made on the urine produced during a 4-hr period following 16 hours without water. The number of cells in the urine was counted using the 2-hr sample. At the end of the appropriate period of feeding, the rats were sacrificed following a 24-hr fasting period. Blood samples were analyzed for hemoglobin concentration, packed cell volume, and counts of erythrocytes and total and differential leucocytes. Serum was analyzed for the activities of glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase and lactate dehydrogenase, and for its contents of urea and glucose. An

Method:

autopsy was conducted on each animal, during which any macroscopic abnormalities were noted, and the brain, heart, liver, stomach, small intestine, caecum, spleen, kidneys, adrenal glands, gonads, pituitary and thyroid glands were weighed. Samples of these organs, and of lung, salivary gland, trachea, esophagus, aorta, thymus, lymph nodes, bladder, colon, rectum, pancreas, uterus, spinal cord and skeletal muscle were preserved in 10% buffered formalin. Paraffin wax sections of all of these tissues were stained for microscopic examination, but only slides from the high-dose animals, half of the control animals, half of the mid-dose animals and half of the low-dose animals were actually examined, along with all tissues from animals that showed abnormalities on autopsy.

GLP: No data
Test substance: As prescribed by 1.1-1.4, purity: >96 %
Reference: Gray, T.J.B., *et al.*, Food Cosmet. Toxicol. 16, 237-242, 1978
Reliability: (1) Valid without restriction

*5.5 GENETIC TOXICITY *IN VITRO*

A. BACTERIAL TEST

Type: Ames Bacterial Reverse Mutation Assay
System of testing: *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100
Concentration: 0, 25, 50, 100 and 250 µg/plate
Metabolic activation: With and without
Results:
Cytotoxicity conc.: With metabolic activation: 250 µg/plate
Without metabolic activation: 250 µg/plate
Precipitation conc.: Not determined
Genotoxic effects:
With metabolic activation: Negative
Without metabolic activation: Negative
Method: Ames *et al.* Mutation Res. 31: 347-364 (1975)
GLP: No data
Test substance: As prescribed in 1.1-1.4, purity: >96%
Remarks: The test compound was evaluated for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations. The *Salmonella typhimurium* strains used for this experiment were obtained from Dr. Bruce Ames. The activation system used was S-9 homogenate from Aroclor 1254-induced adult male Sprague-Dawley rat livers. The pooled livers from three rats were used for each S-9 preparation, and the S-9 was kept at -80 °C. The metabolizing system contained 10% S-9 and cofactors according to the Ames method. The toxicity of ZDBC was determined in advance on a complete medium, and the doses to be tested for mutagenicity were chosen with regard to this toxic level. The mutagenesis assay was carried out as the plate-incorporation test according to the Ames protocol. The chemicals used as positive controls for the non-activation assays included methylnitrosoguanidine (MNNG), 2-nitrofluorene (NF) and quinacrine mustard (QM). Positive control chemicals used for the activation assays

were 2-anthramine (ANTH), 2-acetylaminofluorine (AAF) and 8-aminoquinoline (AMQ). ZDBC was toxic to tester strains TA1535, TA98 and TA100 at 250 µg/plate without S-9 mix. With metabolic activation, a dose of 250 µg/plate ZDBC was toxic to TA98 and TA100.

Non-activation results: No mutagenic activity in any indicator organism at any dose.

Activation results: No mutagenic activity in any indicator organism at any dose.

Reference: Hedenstedt *et al.* Mutation Research 68, 313-325 (1979)
Reliability: (1) Valid without restriction

Type: Ames Bacterial Reverse Mutation Assay
System of testing: *Salmonella typhimurium* TA-1535, TA-1537, TA-1538, TA-98, TA-100
Concentration: 25, 79, 250, 790 and 2500 µg/plate
Metabolic activation: With and without

Results:

Cytotoxicity conc.: With metabolic activation: 250 µg/plate
Without metabolic activation: 250 µg/plate

Precipitation conc.: Not determined

Genotoxic effects:

With metabolic activation: Negative
Without metabolic activation: Negative

Method: UKEMS Basic Mutagenicity Test Guidelines, 1990
OECD 471

GLP: Yes

Test substance: As prescribed in 1.1-1.4, purity: >96%

Remarks: The test compound was evaluated for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations. The test design included a preliminary toxicity test and a mutation assay using the standard pour-plate procedure, followed by an independent repeat experiment. The solvent used was DMSO, and DMSO was also used for the solvent control. The activation system used was S-9 homogenate from Aroclor 1254-induced adult male Sprague-Dawley rat livers. Chemicals used as positive controls were sodium azide and benzo[a]pyrene. Inhibition of growth in all strains was seen at the 2500 µg/plate level and also in TA-100 at the 250 and 790 µg/plate levels. An additional assay in TA-100 was performed at lower concentrations (2.5, 7.9, 25, 79 and 250 µg/plate) in view of the toxicity seen in the first experiment using this tester strain.

Non-activation results: No mutagenic activity in any indicator organism at any dose.

Activation results: No mutagenic activity in any indicator organism at any dose.

Reference: Tinkler, *et al.* Food and Chemical Toxicology 36, 849-866 (1998)
Reliability: (1) Valid without restriction

B. NON-BACTERIAL *IN VITRO* TEST

Type: Mouse Lymphoma Forward Mutation Assay
 System of testing: L5178Y
 Concentration: 2.5, 5.0, 7.5, 10.0 and 15.0 µg/ml
 Metabolic activation: With and without
 Results:
 Cytotoxicity conc.: With metabolic activation: 7.5 µg/ml
 Without metabolic activation: 5.0 µg/ml
 Precipitation conc.: Not determined
 Genotoxic effects:
 With metabolic activation: Negative
 Without metabolic activation: Negative
 Method: UKEMS Basic Mutagenicity Test Guidelines, 1990
 OECD 476
 GLP: Yes
 Test substance: As prescribed in 1.1-1.4, purity: >98%
 Remarks: Mutagenic potential was assessed in mouse lymphoma cells heterozygous at the thymidine kinase gene locus (TK +/-) in accord with the relevant UKEMS guidelines (soft agar cloning technique). The study included two independent experiments, in both the presence and absence of an S-9 mix derived from Aroclor 1254-treated rats, and using EMS and DMBA as positive controls and DMSO as solvent control. The test substance was dissolved in DMSO and tested at concentrations of 0.25, 0.5, 0.75, 1.0 and 1.5 µg/ml. Due to the low cytotoxicity seen, a second experiment was run using concentrations of 0.5, 1.0, 1.5, 2.0 and 2.5 µg/ml. or greater. Cytotoxicity was still low, so a third experiment was run using concentrations of 2.5, 5.0, 7.5, 10.0 and 15.0 µg/ml. No genetic effects were attributed to the presence of the solvent. EMS and DMBA were used as reference mutagens and induced mutation frequencies within the expected range.

	Conc.	Total growth	Mutant clones	Mutant frequency x10(-5)
Non-Activation				
Solvent Control	---	100	58	10.2
EMS		31	200	75.9
ZDBC	2.5 µg/ml	80	56	10.7
	5.0 µg/ml	13	42	10.1
	7.5 µg/ml	2	37	10.9
	10.0 µg/ml	---	---	---
	15.0 µg/ml	---	---	---
Activation with S-9				
Solvent Control	---	100	70	12.1
DMBA		10	115	27.1
ZDBC	2.5 µg/ml	78	96	15.2
	5.0 µg/ml	47	84	11.0
	7.5 µg/ml	5	48	12.6
	10.0 µg/ml	---	---	---
	15.0 µg/ml	---	---	---

The test substance was considered to be not active in the L5178Y Mouse Lymphoma Assay.

Reference: Tinkler, *et al.* Food and Chemical Toxicology 36, 849-866 (1998)

Reliability:	(1) Valid without restriction
Type:	Mammalian Cell Forward Mutation Gene Mutation Assay
System of testing:	Human Lymphocytes
Concentration:	24Hr and 48Hr cultures w/o S-9 mix: 0, 5.0, 10.0, 20.0 µg/ml 24Hr cultures with S-9 mix: 0, 10.0, 20.0, 50.0 µg/ml 48Hr cultures with S-9 mix: 0, 10.0, 50.0, 100.0 µg/ml
Metabolic activation:	With and without
Results:	
Cytotoxicity conc.:	With metabolic activation: Without metabolic activation:
Precipitation conc.:	Not Determined
Genotoxic effects:	With metabolic activation: Weak positive Without metabolic activation: Weak positive
Method:	UKEMS Basic Mutagenicity Test Guidelines, 1990 OECD 476
GLP:	Yes
Test substance:	As prescribed in 1.1-1.4, purity: >98%
Remarks:	The human lymphocyte cytogenetics assay was performed in accordance with the current UKEMS guidelines. The assay included two independent experiments in both the presence and absence of an S-9 mix of Aroclor-induced rat liver cells. Positive controls were chlorambucil (CB) and cyclophosphamide (CP). DMSO was the solvent control. Pairs of replicate cultures were harvested at to different times: for activated treatments, a 3-hr exposure period was followed by 21 or 45 hours of growth in culture medium; for non-activated treatment, exposure was continuous for 24 or 28 hours. ZDBC was tested at the indicated concentrations. These concentrations were selected following a preliminary evaluation of toxicity, and 200 metaphases were scored for aberrations. Statistically significant increases in aberrant cell frequency were seen following ZDBC exposure at cells harvested at 24 hours. This was seen in both experiments, both with and without activation. However, these increases were small – in some cases not sufficiently large to exceed the historical solvent control range of the testing laboratory (0-5% including gaps). At the 48-hour harvest, the single case of statistically significant increase in the frequency of aberrant cells was not considered biologically significant. When gap-type aberrations were taken into account, a generally similar pattern of small increases over control values was seen. The reproducibility of the effect seen in the presence of S-9 mix at the 24-hr harvest time was considered evidence of weak clastogenic activity. An apparent increase in the incidence of polyploidy and endoreduplication in ZDBC-treated cultures was observed. Since these effects were not determined quantitatively, no definitive conclusion can be drawn. Overall, it was concluded that ZDBC showed weak clastogenicity in this assay at exposure levels, which reduced cell division (mitotic index), by some 0-60%.

24 Hour cultures without S-9 mix

Treatment	µg/ml	% aberrations	MI
DMSO	--	0.5	7.0
ZDBC	5.0	2.0	7.0
ZDBC	10.0	2.0	7.9
ZDBC	20.0	3.5	5.6
CB	2.0	16.0	5.6

24 Hour cultures with S-9 mix

Treatment	µg/ml	% aberrations	MI
DMSO	--	0.0	10.5
ZDBC	10.0	3.5	8.1
ZDBC	20.0	4.5	6.5
ZDBC	50.0	3.5	4.0
CP	6.0	20.5	5.6

48 Hour cultures without S-9 mix

Treatment	µg/ml	% aberrations	MI
DMSO	--	1.0	7.2
ZDBC	5.0	1.0	7.8
ZDBC	10.0	1.0	7.9
ZDBC	20.0	3.0	7.5
CB	2.0	7.5	4.6

48 Hour cultures with S-9 mix

Treatment	µg/ml	% aberrations	MI
DMSO	--	0.0	6.8
ZDBC	10.0	0.0	8.7
ZDBC	50.0	1.0	10.6
ZDBC	100.0	0.5	6.2
CP	6.0	5.0	4.4

Reference: Tinkler, *et al.* Food and Chemical Toxicology 36, 849-866 (1998)

Reliability: (1) Valid without restriction

*** 5.6 GENETIC TOXICITY *IN VIVO***

Type: Mammalian Erythrocyte Micronucleus Test

Species/strain: Mouse, CD-1

Sex: Male/Female

Route of Administration: Gavage

Exposure period: 0, 24, 48 and 72 hours

Doses: 200, 1000 or 5000 mg/kg

Results:

Effect on mitotic index or P/N ratio: Negative

Genotoxic effects: Negative

Method: UKEMS Basic Mutagenicity Test Guidelines, 1990
OECD 474

GLP: Yes
 Test substance: As prescribed in 1.1-1.4, purity: 98 %
 Remarks: The micronucleus test was performed in groups of five CD-1 mice per sex in accordance with current UKEMS guidelines. The test material was formulated in corn oil and administered (single dose to each animal) by oral gavage. Doses were selected following a preliminary toxicity test. Bone marrow from mice receiving the low and mid-level doses was collected at sacrifice 24 hours after dosing. Control and high-dose mice were sacrificed 24, 48 and 72 hours after dosing and bone marrow preparations were made at these times. After appropriate slide staining, a minimum of 2000 erythrocytes (polychromatic and mature) from each animal were examined microscopically for the presence of micronuclei. The ratio of polychromatic to mature cells was then calculated, as an indicator of possible bone marrow toxicity, and the frequency of micronucleated polychromatic erythrocytes (per 1000) was determined as the critical indicator of chromosome-damaging effect. The known clastogen ambucil (30 mg/kg) was employed as the positive control. ZDBC was dosed at 200, 1000 and 5000 mg/kg. No significant adverse reactions were observed at any dose. There was no evidence of effect in the bone marrow. However, the maximum dose tested was both high and the maximum normally employed in this type of assay. No significant difference in frequency of micronucleated polychromatic erythrocytes between ZDBC and the vehicle control was found at any of the dosages or harvest times. It was concluded that ZDBC was negative in this study at dose levels up to 5 g/kg of body weight.

Frequencies of micronucleated polychromatic erythrocytes for the test substance ZDBC:

ZDBC, 24-hour exposure

Sex	200 mg/kg	1000 mg/kg	5000 mg/kg
Male	0.9 +/- 1.1	0.9 +/- 1.2	1.1 +/- 0.8
Female	1.4 +/- 0.5	1.8 +/- 1.3	1.2 +/- 0.4

ZDBC, 48-hour exposure

Sex	200 mg/kg	1000 mg/kg	5000 mg/kg
Male	Not tested	Not tested	0.2 +/- 0.4
Female	Not tested	Not tested	1.0 +/- 1.2

ZDBC, 72-hour exposure

Sex	200 mg/kg	1000 mg/kg	5000 mg/kg
Male	Not tested	Not tested	0.8 +/- 0.8
Female	Not tested	Not tested	0.2 +/- 0.4

Reference: Tinkler, *et al.* Food and Chemical Toxicology 36, 849-866 (1998)
 Reliability: (1) Valid without restriction

Type: Liver Unscheduled DNA Synthesis (UDS) Assay

Species/strain: Rat, Sprague-Dawley (CD)
 Sex: Male
 Route of Administration: Oral gavage
 Exposure period: 2 and 16 hours
 Doses: 0, 1000, 1500 and 2000 mg/kg
 Results:
 Effect on mitotic index or P/N ratio:
 Genotoxic effects: Negative
 Method: UKEMS Basic Mutagenicity Test Guidelines, 1990
 OECD 486
 GLP: Yes
 Test substance: As prescribed in 1.1-1.4, purity: 98 %
 Remarks: The rat liver UDS assay was performed to provide further data on the genotoxic potential of ZDBC *in vivo*. Investigation of this different cell population was considered to provide a valuable supplement to the mouse micronucleus data, since the exposure of the bone marrow cells to the test material was not proven in the micronucleus test. The effect of ZDBC treatment *in vivo* on the DNA of rat hepatocytes was investigated following acute oral administration to male rats at three different doses. Test material doses were suspended in corn oil. In each of two separate experiments, three test groups (4 rats per group) plus two control groups (vehicle and positive) were given a single oral treatment. Positive controls were 500 mg/kg methylmethanesulfonate (MMS) and 200 mg/kg 2-acetyl aminofluorene (2-AAF). In the first experiment, all rats were sacrificed 2 hours after dosing; in the second, sacrifice took place 16 hours after dosing. Hepatocytes were isolated by liver perfusion and cultured in medium supplemented with tritiated thymidine. The amount of unscheduled DNA synthesis was assessed by autoradiography using standard techniques: Fifty cells per slide from each of 2 slides per animal were evaluated. Nuclear grain count (NG), cytoplasmic grain count (CG) and net nuclear grain count (NNG calculated as NG-CG) were determined for each scored cell. The results from the ZDBC-treated animals compared statistically to those from concurrent vehicle controls using Students t-test. Rats dosed with ZDBC showed no adverse reaction to treatment. Hepatocyte viabilities were generally high among control rats and those dosed at 1000 or 1500 mg/kg (73-93%). In rats dosed at the highest level, they appeared slightly lower (69-78%). Statistical analysis revealed no significant differences between test and control groups for NG, NNG or percent of cells in repair (%IR). No individual test animal gave an NNG value greater than 0 on both slide preparations scored for grain counts.

Hepatocytes taken 2 hours post dose

mg/kg	NG	CG	NNG	%IR
0 (corn oil)	3.51	5.37	-1.85	2.25
1000	4.25	6.31	-2.07	2.75
1500	5.47	9.25	-3.78	3.00
2000	5.14	7.49	-2.35	2.50
MMS	11.01	4.47	6.54	57.50

Hepatocytes taken 16 hours post dose

mg/kg	NG	CG	NNG	%IR
0 (corn oil)	7.04	9.81	-2.77	5.50
1000	6.05	9.41	-3.36	5.00
1500	6.81	9.95	-3.14	4.00
2000	9.35	11.29	-1.94	11.50
2-AAF	22.75	10.55	12.19	76.25

It was concluded that ZDBC gave negative results in the *in vivo* rat liver USD assay.

Reference: Tinkler, *et al.* Food and Chemical Toxicology 36, 849-866 (1998)

Reliability: (1) Valid without restriction

5.7 CARCINOGENICITY

Species/strain: Mice, B6C3F1 and B6AKF1

Sex: Male/Female

Route of Administration: Oral intubation on days 7-28, oral feed for remainder
Single subcutaneous injection on Day 28

Exposure period: 18 months

Frequency of treatment: Daily for one study, once for other study

Post-exposure observation: Not determined

Doses: Gavage = 1000 mg/kg b.w. Feed = 2600 ppm
Injection = 1000 mg/kg as 0.05 ml of suspension

Control group: Yes, Other: Positive Control

Results: In a National Cancer Institute study, 18 virgin male and 18 virgin female mice from two hybrid strains were dosed with the test substance. Two types of studies were run simultaneously. One group of 36 mice received a single subcutaneous injection administered in the nape of the neck at the 28th day of age, with no exposure to the test substance thereafter. The second group of 26 mice received a daily oral intubation dose of the test article administered from the 7th to 28th days of age, and then daily in their feed mix thereafter. All compounds administered orally as positive controls were carcinogenic, while only two of the positive controls (urethane, ethyleneimine) administered subcutaneously had carcinogenic activity. There were no statistically significant increases in tumor incidences observed and no significant adverse affects were seen that could be attributed to the test substance.

Method: Litton Bionetics Research Labs Protocol

GLP: No data

Test substance: As prescribed by 1.1-1.4, purity: >96%

Remarks: Study was undertaken to determine the carcinogenic potential of 130 chemicals that had been used in the formulations of insecticides, herbicides and fungicides.

Reference: Litton Bionetics/NCI Report # PB223-159 (1968)

Reliability: (2) Valid with restrictions. Intubation/feed part of this study followed generally accepted parameters for a 1968 carcinogenicity assessment, but not all test parameters comply with current guidelines. No GLP

data. The reliance on a single subcutaneous injection as adequate for the other portion of this study is questionable.

Species/strain: Mice, C57BL/6 and C3H/Anf
Sex: Male and Female
Route of Administration: Oral intubation for 3 weeks
Dietary for 17 months
Duration of the test: 18 months
Exposure period: From 7 days old until sacrifice
Frequency of treatment: Daily
Number of animals: 72 (18 mice/sex/strain)
Doses: 4.6 mg/kg bw (15 ppm)
Control group: Yes, positive controls, negative/vehicle-only controls
Results: The maximum tolerated dose for testing was determined by a sequence of studies during which the maximal levels resulting in no mortality was determined for a single dose, for six daily doses, and then for nineteen daily doses. 7-day old mice were fed the test article in 0.5% gelatin vehicle until they were 28 days old. After weaning at 4 weeks, the test compound was mixed directly into their food. Animals were sacrificed after 18 months on test. The postmortem procedure included an external examination and a thorough examination of thoracic and abdominal cavities, with histologic examination of major organs and of all grossly visible lesions. The cranium was not dissected. The entire carcass and all internal organs were fixed and saved. Blood smears were made on all mice before sacrifice, and then examined in cases showing splenomegaly or lymphadenopathy. Statistical analysis included the chi-square test for heterogeneity of proportions after adjustment of stratification (Armitage, 1966), ordinary chi-square tests, regression analyses, the Mantel-Haenszel procedure, and the weighted geometric mean. Seven different chemicals were used as positive controls and were administered via intubation: Ethylcarbamate (158 mg/kg), Ethyleneimine (4.64 mg/kg), Amitrol (1000 mg/kg), Aramite (464 mg/kg), Dihydrosafrole (464 mg/kg), Isosafrole (215 mg/kg) and Safrole (464 mg/kg). The positive control chemicals produced the expected incidence and types of tumors in the test animals. Oral administration of the test compound at the maximum tolerated dose did not cause a significant increase in instances of tumors, types of tumors or total tumors in either male or female mice, and was judged to be non-carcinogenic under the conditions of this study.
Method: Other: National Institutes of Health/National Cancer Institute/Litton Bionetics Protocol, 1967
GLP: No data
Test substance: As prescribed by 1.1-1.4, purity: 97%
Remarks: The test substance was one of 48 compounds evaluated in this experiment. All compounds were selected due to use as insecticides, herbicides or fungicides.
Reference: Innes, J.R.M. et. al., J. Natl. Cancer Inst., 42: 1101-1114, 1969
Reliability: (1) Valid without restriction

***5.8 TOXICITY TO REPRODUCTION**

Type: One-generation study
Species/strain: Rat, Wistar
Sex: Male/Female
Route of Administration: Oral feed
Exposure period: 2 years
Frequency of treatment: Daily
Post exposure observation period: No data
Premating exposure period: No data
Duration of the test:
Doses: No data
Control group: No data
NOEL Parental:
NOEL F1 Offspring:
NOEL F2 Offspring:
Results:
 General parental toxicity:
 Toxicity to offspring:
Method: No data – complete report not available
GLP: No data
Test substance: As prescribed in 1.1-1.4, purity: >96 %
Remarks: A two-year chronic feeding study on Wistar rats conducted by The Institute de Medicine Legal de Marseille was reported in the Japanese journal Kobunshi Kato. Under investigation were rubber accelerators commonly used in the production of latex examination gloves and other skin-contact latex products. The report indicated that testing of ZDBC showed no effects on neither the reproductive functions of the rats nor were any effects related to ZDBC exposure seen in their descendants.
Reference: Sakaramoto, Y. Kobunshi Kato 26: 358-362 (1977)
Reliability: (4) Not assignable; – data taken from a secondary literature source.

Species/strain: Rats, Wistar
Sex: Male/Female
Route of Administration: Dietary
Exposure period: 17 Weeks
Frequency of treatment: Daily
Post exposure observation period: No data
Dose: 0, 100, 500 or 2500 ppm
Control group: Yes (concurrent vehicle)
NOEL: 2500 ppm (for reproductive organ effects)
Results: See Section 5.4, Repeat Dose, 17-week dietary study for other details.

<u>Sex/dose</u>	<u>Week</u>	<u># animals</u>	<u>mean gonad weight</u>	<u>mean terminal body wt.</u>
M-0	2	5	1.13 g/100g bw	155 g
M-500	2	5	1.34 g/100g bw	141 g

M-2500	2	5	1.30 g/100g bw	144 g
F-0	2	5	84 mg/100g bw	132 g
F-500	2	5	81 mg/100g bw	128 g
F-2500	2	5	84 mg/100g bw	126 g
M-0	17	5	0.80 g/100g bw	432 g
M-100	17	5	0.76 g/100g bw	457 g
M-500	17	5	0.81 g/100g bw	423 g
M-2500	17	5	0.86 g/100g bw	403 g
F-0	17	5	0.49 mg/100g bw	254 g
F-100	17	5	0.50 mg/100g bw	259 g
F-500	17	5	0.51 mg/100g bw	248 g
F-2500	17	5	0.54 mg/100g bw	219 g

There were no statistically significant differences between treated and control animals in either the absolute gonad weights or the gonad/body weight ratios at Weeks 2 and 17 of the study. Statistical analysis was performed using Student's t-test to determine significant difference from controls.

Method:

Groups of 15 male and 15 female rats obtained from a specified pathogen-free colony were given diets containing 0, 100, 500 or 500 ppm of the test substance for 17 weeks. Additional groups of five male and five female rats of similar body weight were given diets containing 0, 500 or 2500 ppm of the test substance for 2 or 6 weeks. All animals were weighed initially, and on days 1, 2, 6, 9, 13, 16 and 20 of treatment, and thereafter weekly at intervals of up to 17 weeks. Food and water consumption were measured over a 24-hr period preceding each weighing. At the end of the appropriate period of feeding, the rats were sacrificed following a 24-hr fasting period. An autopsy was conducted on each animal, during which any macroscopic abnormalities were noted, and the brain, heart, liver, stomach, small intestine, caecum, spleen, kidneys, adrenal glands, gonads, pituitary and thyroid glands were weighed. Samples of these organs, and of lung, salivary gland, trachea, esophagus, aorta, thymus, lymph nodes, bladder, colon, rectum, pancreas, uterus, spinal cord and skeletal muscle were preserved in 10% buffered formalin. Paraffin wax sections of all of these tissues were stained for microscopic examination, but only slides from the high-dose animals, half of the control animals, half of the mid-dose animals and half of the low-dose animals were actually examined, along with all tissues from animals that showed abnormalities on autopsy. See Section 5.4, Repeat Dose, 17-week dietary study for other details.

GLP:

No data

Test substance:

As prescribed by 1.1-1.4, purity: >96 %

Reference:

Gray, T.J.B., *et al.*, Food Cosmet. Toxicol. 16, 237-242, 1978

Reliability:

(2) Valid with restrictions – evaluation of male and female reproductive organs from a valid repeat-dose study may be used to satisfy this endpoint if a valid developmental study exists

Type: Two-generation reproduction and developmental neurotoxicity study
Species/strain: Rats, Sprague-Dawley Crl:CD BR
Sex: Male/Female
of animals: 30/sex/dose
Route of Administration: Dietary/Oral feed
Frequency of treatment: Daily
Doses: 0, 72, 207 and 540 ppm
Control group: Yes
NOEL Parental: 72 ppm
NOEL Reproduction: 207 ppm
NOEL F1 Offspring: 207 ppm
NOEL F2 Offspring: 207 ppm
NOEL Neurotoxicity: >540 ppm
Results: The test compound was administered in the diet to rats (30/sex/dose) for two generations. Thirty pups/sex/dose were selected for developmental landmarks and behavioural testing, neuropathology and brain weight measurements. Designated F0 and F1 parents and F2 pups were examined for neuropathology and brain weight measurements. The systemic NOEL was 72 ppm, based on decreased body weight and body weight gain in both F0 and F1 males and females at the 540 ppm dose level. F0 food consumption was decreased in females, but F1 food consumption was decreased in both sexes at 540 ppm (\geq 207 ppm in F1 females during gestation and lactation). F0 females had decreased absolute brain weight and F0 males had increased relative liver weights at 540 ppm. F1 males had absolute brain weight decrease, relative brain rate increase and absolute liver weight increase at 540 ppm. Relative epididymal and testes weights were increased at 540 ppm. Female absolute kidney weights were decreased at \geq 207 ppm. Female relative brain weights were increased at 540 ppm. Reproductive NOEL was 207 ppm based on a significantly decreased live litter size in the F0 generation at 540 ppm. F1 generation mean pup weights were significantly decreased at 540 ppm. Pup NOEL was 207 ppm, based on a significant decrease in both F1 and F2 mean pup weights on Day 14 post partum at 540 ppm. The neurotoxicity NOEL was >540 ppm, as there were no significant neurotoxic effects observed at any dose level in either sex.
Method: FIFRA Guideline Study
GLP: Yes
Test substance: Other: Structurally similar compound Zinc Dimethyldithiocarbamate (ZDMC, Ziram), purity: 97.8%
Remarks: This study has been reviewed by FIFRA and judged to be acceptable for the reproduction endpoint. (05/21/96).
Additional study information is confidential and compensatable under FIFRA.
Reference: R.T. Vanderbilt, WIL-223003, WIL Research Laboratories, 1996
Reliability: (2) Valid with restrictions – data from a structurally similar compound

Type: Three-generation reproduction study

Species/strain: Rats, Sprague-Dawley
Sex: Male/Female
of animals: 30 (10 males and 20 females/dose)
Route of Administration: Dietary/Oral feed
Frequency of treatment: Daily
Doses: 0, 280, 1260 and 2800 ppm for 119 days
0, 140, 770 and 1400 ppm (dosed reduced due to toxicity)
Control group: Yes
NOEL Parental: 140 ppm
NOEL Reproduction: 140 ppm
NOEL F1 Offspring: 140 ppm
NOEL F2 Offspring: 140 ppm
Results: The test compound was administered in the diet to rats for three generations. The parental NOEL was established as 140 ppm due to decreased body weight gain at 770 ppm in males and decreased body weight gain in females during pregnancy at 770 ppm. The reproductive NOEL was 140 ppm due to decreased fertility index, decreased lactation index, decreased pup body weights and decreased pup survival at 770 ppm. There was a decrease in litter size at 2800 ppm.
Method: FIFRA Guideline Study
GLP: Yes
Test substance: Other: Structurally similar compound Zinc Dimethyldithiocarbamate (ZDMC, Ziram), purity: 98%
Remarks: This study has been reviewed by FIFRA and judged to be acceptable for the reproduction endpoint. (07/27/88). The conclusion reached by the reviewers was that ZDMC does not cause adverse reproductive effects in the rat when administered at or below the minimum toxic dose. Additional study information is confidential and compensatable under FIFRA.
Reference: R.T. Vanderbilt, Cannon Labs, Inc., 1979
Reliability: (2) Valid with restrictions – data from a structurally similar compound

*5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Species/strain: Mice, B6C3F1, BL6 and B6AKF1
Sex: Female
Route of Administration: Subcutaneous
Duration of the test: 18 days
Exposure period: Day 6-14 of gestation
Frequency of treatment: Daily
Doses: 46.4 and 100 mg/kg/b.w.
Control group: Yes, other: positive control
NOEL Maternal Toxicity: >100 mg/kg
NOEL teratogenicity: >100 mg/kg
Results: Groups of pregnant mice were treated with the test substance via subcutaneous injections into the nape of the neck to evaluate the effect on implantation, foetal mortality, weight and development, placental weight,

amniotic fluid volume, maternal weight, and maternal liver/body weight ratio. A Positive Control of 2,4,5-T was used. All treated mice were sacrificed on Day 18 of gestation. In the postnatal study, neonates were examined at birth, at 8 days, and then sacrificed. There were no embryotoxic or teratogenic effects observed that were attributed to the test substance in any strain of mice.

Maternal general toxicity: No toxic effects observed
Pregnancy/litter data: No toxic effects observed
Foetal data: No foetal anomalies observed
Litton Bionetics Research Labs Protocol

Method: No data
GLP: No data
Test substance: As prescribed by 1.1-1.4, purity: >97%

Remarks: The test substance was one of 48 compounds evaluated in this experiment. All compounds were selected due to use as insecticides, herbicides or fungicides.

Reference: NTIS PB223-160, August 1968
Reliability: (2) Valid with restrictions. Well documented and scientifically acceptable, but not all test parameters in compliance with current guidelines. No GLP data.

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

Type: Skin Sensitization / Human Skin Patch Test
Results: Patch testing on 20 human volunteers (14 men and 6 women ranging in age from 17 to 69) with the rubber accelerator ZDBC produced no positive reactions on initial application, no positive reactions during the course of 15 serial applications, and no positive reactions on a subsequent rechallenge. It was concluded that the test substance was not a cumulative irritant or a sensitising agent.

Remarks: No test method specified
Reference: Monsanto W-17, Barnard Free Skin & Cancer Hospital, 1947
Reliability: (2) Valid with restrictions – age of study, lack of detail in methodology

Type: Skin Sensitization / LLNA
Results: A modified Local Lymph Node Assay (LLNA) with ex vivo tritium thymidine (3H-TdR) labeling of the proliferating lymph node cells was used for determination of the allergic potential of chemicals used in the production of latex for medical gloves. 15 different chemicals with known or suspected capability to induce contact hypersensitivity reactions in humans were tested. 14 out of 15 chemicals tested as sensitizers. For ZDBC, no EC3 could be calculated due to low responses and lack of a dose-response relationship.

Remarks: The authors concluded that ZDBC would be the rubber accelerator of choice for use in exam gloves to minimize the potential for contact hypersensitivity reactions.

Reference: De Jong, *et al.*, Toxicological Sciences 66(2), 226-232, 2002

Reliability: (1) Valid without restriction

B. Toxicodynamics, toxicokinetics

*5.11 EXPERIENCE WITH HUMAN EXPOSURE

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