

201-15734A

TEST PLAN FOR m-DIISOPROPENYLBENZENE (CAS No. 3748-13-8)

OVERVIEW

Cytec Industries Inc. agreed to sponsor m-diisopropenylbenzene (CAS No. 3748-13-8) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The company hereby submits a revised, final test plan for this substance. All testing proposed in the previous test plan and/or recommended by the EPA has been completed. Existing plus modeled data now fulfill all Screening Information Set (SIDS) endpoints.

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1. Introduction

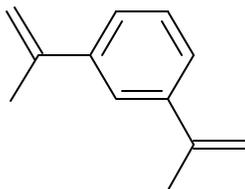
Cytec Industries Inc. agreed to supply hazard and exposure information under The U.S. EPA High Production Volume Chemical Program for m-diisopropenylbenzene (CAS No. 3748-13-8). The initial test plan and robust summaries were posted on the EPA website on January 16, 2003. A revised test plan and summaries were posted on July 25, 2003. That plan indicated that testing for the following endpoints would be conducted: chromosome aberrations (OECD Test Guideline 473) and reproductive/developmental toxicity (OECD Test Guideline 421). Testing for the aforementioned endpoints has been completed, and the current test plan (and accompanying robust summary document) communicates their results (in addition to data previously submitted). Testing that has been performed fulfills all requirements of the HPV program; therefore this test plan and robust summary document are considered final.

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2. Designation of Test Substance

The test substance presented in this test plan is 1,3-diisopropenylbenzene (CAS No. 3748-13-8). Its chemical structure is as follows:



This substance is known by the following synonyms:

m-diisopropenylbenzene; meta-diisopropenylbenzene; benzene, 1,3-bis(1-methylethenyl)-;
m-bis(1-methylvinyl)benzene; m-DIPEB (Cytec trade name)

The material will be referred to as m-diisopropenylbenzene in the test plan.

m-Diisopropenylbenzene is manufactured at one facility in the United States. It is shipped by tank car or tank truck to a Cytec Industries Inc. facility where it is used as an industrial intermediate converted to diisocyanate monomer. About 1% of this substance is drummed and shipped to another facility in the United States for use in optical products. An additional 5% (approximately) is exported. Manufacture takes place in closed systems, as does conversion to diisocyanate monomer. Based on manufacture at one facility and its predominate use as a closed system industrial intermediate, there is relatively limited opportunity for exposure to this

chemical.

3. Criteria for Determining Adequacy of Data

All available studies were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1997). Studies receiving a Klimisch rating of 1 or 2 were considered to be adequate. The m-diisopropenylbenzene test plan matrix (as shown in Table 1) was constructed after a careful evaluation of all existing data (see Sections 4.1- 4.46 below).

Table 1. Test Plan Matrix for m-diisopropenylbenzene

CAS No. 3748-13-8	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
ENDPOINT	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYS/CHEM PROPERTIES							
Melting Point	Y	N	Y	N	N	Y	N
Boiling Point	Y	N	Y	N	N	Y	N
Density	Y	N	Y	N	N	Y	N
Vapor Pressure	Y	N	Y	Y ¹ /N ²	N	Y	N
Partition Coefficient	Y	N	Y	Y	N	Y	N
Water Solubility	Y	N	Y	N	N	Y	N
ENVIRONMENTAL FATE							
Photodegradation	Y	N	Y	Y	N	Y	N
Stability in Water	Y	N	Y	N	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	N	Y	Y	N	Y	N
Biodegradation	Y	Y	N	N	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	Y	N	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	N	Y	N	Y	Y	N
Toxicity to Aquatic Plants	Y	Y	N	N	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	N	Y	N	Y ³ /N ⁴	Y	N
Repeated Dose Toxicity	Y	N	Y	N	Y	Y	N
Genetic Toxicity-Mutation	Y	Y	N	N	Y	Y	N
Genetic Toxicity-Chromosomal Aberrations	Y	Y	N	N	Y	Y	N
Toxicity to Reproduction	Y	Y	N	N	Y	Y	N
Developmental Toxicity	Y	Y	N	N	Y	Y	N
OTHER TOXICITY DATA							
Skin Irritation (NR)	Y	N	Y	N	N	Y	N
Eye Irritation (NR)	Y	N	Y	N	N	Y	N
Sensitization (NR)	Y	N	Y	N	Y	Y	N

Y = yes; N = no

¹ at 25 degrees C; ² at > = 69.3 degrees C; ³ oral study; ⁴inhalation and dermal studies

This matrix is arranged by study type (columns) and screening data endpoints (rows), and indicates if data are provided for each end point in the set of robust summaries.

4. Discussion of Available Test Information

4.1 Chemical and Physical Properties

The results of chemical/physical property testing are shown in Table 2.

Table 2. Chemical/physical properties of m-diisopropenylbenzene

Endpoint	Value
Melting point (° C)	-38 to -40 ^a
Boiling point (° C)	231 ^a
Vapor pressure (hPa)	0.1 (at 25° C) ^b 3.1 (at 69.3° C) ^a 990.6 (at 231° C) ^a
Partition coefficient (Log Pow or Kow)	4.89 ^b
Water solubility (mg/l at 25° C)	5.6 ^a 5.0 ^b

^ameasured; ^b estimated by EPIWIN

4.1.1 Melting Point

A measured melting point of -38 to -40°C was recently determined for m-diisopropenylbenzene (Rivera, C. 2002) following ASTM E-794 (standard test method for melting and crystallization temperatures by thermal analysis). The purity of the test substance was 98.9%. The EPIWIN/MPBPWIN model (v.1.40) estimates a value of -14°C.

4.1.2 Boiling Point

A measured boiling point of 231°C is listed on the Material Safety Data Sheet (Cytec Industries Inc., 2002). The purity of the m-diisopropenylbenzene was 100%.

4.1.2 Vapor Pressure

Vapor pressures have been measured for m-diisopropenylbenzene at several temperatures (Cytec Industries Inc., unpublished information). These values include a pressure of 3.1 hPa at 69.3° C and 990.6 hPa at 231° C. EPIWIN/MPBPWIN (v.1.40) estimates a vapor pressure of approximately 0.1 hPa at 25° C, which is generally consistent with the measured value of 3.1 hPa at 69.3°C.

4.1.4 Octanol/Water Partition Coefficient

A log Kow value of ca. 4.89 was estimated by EPIWIN KOWWIN (v1.66), with the values for the CAS No. and boiling point (231 degrees C) being inputted. The program calculates the log

Kow based on molecular structure and an algorithm that sums up individual contributions for the chemical fragments present in the molecule. This positive value is consistent with a non-polar aromatic substance with no water-soluble functional groups, which would be expected to have a high affinity for organic solvents, such as octanol.

4.1.5 Water Solubility

A measured water solubility value of 5.6 mg/l at room temperature has recently been determined for m-diisopropenylbenzene (Stanek, 2002). The purity of the test substance was 98.9%. The EPIWIN/WSKOW program (v.1.40) estimated a water solubility of 5 mg/l based on an inputted log Kow of 4.89.

4.1.6 Summary/Test Plan for Physical Properties

Measured values are available for melting point, boiling point, vapor pressure and water solubility. The log Kow (partition coefficient value) was obtained using EPIWIN and is consistent with the molecular structure of the test substance and with its measured low water solubility value. The available data are sufficient to characterize the physical properties of m-diisopropenylbenzene as an organic liquid with relatively high boiling point, low vapor pressure and low water solubility. No further testing for these endpoints is planned.

4.2 Environmental Fate/Pathways

The results of environmental fate modeling and studies are summarized in Table 3 below.

Table 3. Environmental fate parameters for m-diisopropenylbenzene

Endpoint	Value
Indirect Photolysis (OH sensitizer) (Hydroxyl Radical Rate Constant) ^a (Atmospheric T _{1/2}) ^a	ca 1.04 x 10 ⁻¹¹ cm ³ /(molecule*sec) 1.225 hours
Stability in Water	No reliable measured or estimated data ^b
Henry's Law Constant ^a	3.48 x 10 ⁻³ atm-m ³ /mol
Koc ^a	4036
Environmental transport (Fugacity Level III mass percentages) ^a	Air = 0.214 Water = 24.9 Soil = 63.9 Sediment = 11.0
Biodegradation ^c	Not readily biodegraded

^a Estimated using EPIWIN

^b The test substance does not possess functional groups generally recognized to be readily hydrolyzable in water under neutral ambient conditions.

^c Measured value

4.2.1 Photodegradation

Photodegradation with hydroxyl radical sensitizer was estimated using EPIWIN/AOP (v1.90).

An overall OH rate constant of ca $1.04 \times 10^{-11} \text{ cm}^3/(\text{molecule} \cdot \text{sec})$ was calculated based on the summation of individual rate constants for each bond fragment in the molecule using the program algorithm. A half-life of 1.225 hours was calculated assuming a constant concentration of OH radical and pseudo first order kinetics. No information was found with respect to direct photolysis of m-diisopropenyl benzene, but hydroxyl radical-induced photodegradation would be expected to remove the substance from the atmosphere quickly.

4.2.2 Stability in Water

An attempt was made to estimate the rate of hydrolysis for m-diisopropenylbenzene using the EPIWIN/HYDROWIN program (v1.67). This estimation method, however, is valid only for molecules containing certain functional groups, including esters, carbamates, amides, and halomethanes. Measured hydrolysis data are not available. The test substance contains no functional groups generally recognized to readily undergo hydrolysis under neutral ambient conditions. Therefore, hydrolysis of this material is not likely to take place readily, especially at neutral ambient, conditions. Carbon-carbon double (olefinic) bonds are not readily attacked by water, but olefinic bonds can react with cold concentrated sulfuric acid via addition of a proton (H^+) followed by addition of sulfate anion (HSO_3^-) to form the alkyl sulfuric acid, which can then undergo hydrolysis to form the corresponding alcohol (Fieser and Fieser, 1957). However, since this reaction is not likely to occur in natural waters, one may conclude that hydrolysis of m-diisopropenylbenzene is unlikely to be an important degradative process in the environment.

4.2.2 Fugacity

Level III fugacity modeling has been conducted on the test material using the EPIWIN model. Measured inputs to the program are melting point (-39°C), boiling point (231°C), vapor pressure (1 mm Hg), and water solubility (5 mg/l). The value inputted for vapor pressure is the measured value extrapolated down to 25 degrees C. The results indicate that the test substance will partition in increasing preference to air, sediment, water and soil. A calculated Henry's Law Constant (the ratio of volatility to water solubility) of $3.48 \times 10^{-3} \text{ atm} \cdot \text{m}^3/\text{mol}$ suggests that the test substance has some limited tendency to volatilize from water to the atmosphere. The value is consistent with the material having low volatility, but also having a limited affinity to water. A water soil partition constant (Koc) of 4036 has been estimated using EPIWIN PCKOC (v1.66). This value indicates that the test substance possesses slight soil mobility.

4.3.4 Biodegradation

An OECD Test Guideline 301D (Close Bottle Test) has been conducted with 2 mg/l of a test material containing 97.5-99.1% m-diisopropenylbenzene (Drozdowski, 1987a). Under the conditions of the study, the test material did not biodegrade. At the concentration tested, the test material was not soluble. To increase surface area and immersion and reduce partitioning, the test material was applied to a carrier. Because the ability of the carrier to promote degradation of insoluble substances was not demonstrated with a reference material, the study was given a reliability rating of 2 (valid with restrictions).

The results of this study are not inconsistent with what one might expect based on the molecular

structure of the test substance. m-Diisopropenylbenzene is an aromatic substance with non-polar olefinic side chains. A substance with this structure has limited solubility in water, and possesses no functional groups that are readily vulnerable to biodegradation.

4.3.5 Summary/Test Plan for Environmental Fate Parameters

The environmental fate parameters discussed above indicate that the test substance, when released to the air, will readily undergo photodegradation (atmospheric half life ca 1.2 hours). However, some atmospheric material may be washed into the hydrosphere. Material released to water has some tendency to volatilize (Henry's Law Constant 3.48×10^{-3} atm-m³/mol), but is expected to biodegrade slowly. As a result of limited solubility, material released to water in significant quantity is likely to be deposited in soil or sediment as well as air (due to some volatilization). The material is not likely to be strongly persistent in the environment, because it does have some soil mobility (estimated Koc = 4036) and can volatilize slowly to the atmosphere, where it readily undergoes photodegradation. Sufficient data exist to characterize the environmental fate parameters at the screening level and no testing for these endpoints is planned.

4.3 Ecotoxicity

The results of studies and ECOSAR modeling are summarized in Table 4 below.

Table 4. Ecotoxicity of m-diisopropenylbenzene

Endpoint	Value	
	Experimental (mg/l)	ECOSAR (mg/l)
Toxicity to fish (96-hr LC ₅₀)	6.2	0.225
Toxicity to Daphnia (48-hr LC ₅₀)	4	0.295
Toxicity to Algae (96-hr EC ₅₀)	4.92	0.218

4.3.1 Acute Toxicity to Fish

A static GLP study in fathead minnows was performed with a material containing 99.13% m-diisopropenylbenzene (Bowman, 1986). The no observable effect concentration (NOEC) and lethal concentration in 50% of the organisms (LC₅₀) in this 96-hour study were 1.2 and 6.2 mg/l, respectively. None of the fish exposed to ≤ 2.5 mg/l and all fish exposed to 20 mg/l died by 96 hours. This study was given a reliability rating of 2 (valid with restrictions) since concentrations of test material were not analytically confirmed and the results may have been influenced by insolubility of the test material at 10 and 20 mg/l. The 96-hour LC₅₀ value for fish estimated by the EPA's ECOSAR model (v0.99) is 0.225 mg/l, which is approximately an order of magnitude less than the measured value.

4.3.2 Acute Toxicity to Aquatic Invertebrates

A static, GLP study in *Daphnia magna* was performed with a test material containing 99.13% m-diisopropenylbenzene (Forbis et al., 1986). The NOEC and LC₅₀ values in this 48-hour study were 1 and 4 mg/l, respectively. None of the *Daphnia* exposed to ≤ 1.8 mg/l and all organisms exposed to 5.6 and 10 mg/l died by 48 and 24 hours, respectively. An oily film was present on the surface of water containing 5.6 and 10 mg/l, suggesting that the material might not be completely soluble at these concentrations. The study was given a reliability rating of 2 (valid with restrictions) since concentrations of test material were not analytically confirmed. The EPA's ECOSAR model (v0.99) predicts a 48-hour EC₅₀ value of 0.295 mg/l for *Daphnia*, which is approximately an order of magnitude less than the measured value.

4.3.3 Acute Toxicity to Aquatic Plants

The toxicity of m-diisopropenylbenzene (98.3% pure) to *Selenastrum capricornutum* was tested according to OECD Test Guideline 201 (Drozdowski, 1987b). For this test, the index of toxicity is inhibition of growth rate. The NOEC, and effective concentration in 50% of the organisms (EC₅₀) at 96 hours were 1.77 and 4.92 mg/l, respectively. No growth occurred in cells exposed to 18 mg/l for 96 hours. In this study, there was no mention of the higher concentrations (10 and 18 mg/l) being insoluble. Based on results of the other aquatic toxicity tests, it is likely that the material was not completely soluble at these concentrations. Since concentrations of test material were not analytically confirmed, the study was given a reliability rating of 2 (valid with restrictions). The 96-hour EC₅₀ value calculated for green algae by the ECOSAR model (v0.99) is 0.218 mg/l, which is approximately an order of magnitude less than the measured value.

4.3.4. Summary/Test Plan for Ecotoxicity

Results of adequate studies in fathead minnows, *Daphnia magna* and *Selenastrum capricornutum* show that m-diisopropenylbenzene is of moderate toxicity to these species. For all the species tested, the average no effect concentrations and EC/LC₅₀ values were approximately 1 and 5 mg/l. In all the studies, the LC₅₀ values are likely to have been influenced by slight insolubility at the highest concentrations used (10 to 20 mg/l). As shown by Rivera (2002), the solubility limit of the material is 14 mg/l. Since the higher concentrations used in the aquatic toxicity studies did not appear to be completely soluble, the amount of test material available to the organisms at these concentrations was probably less than the nominal concentrations. Therefore, the actual EC/LC₅₀ values are likely to be slightly lower than those determined in the experimental studies.

Results of ECOSAR modeling suggest that the EC/LC₅₀ values for fish, *Daphnia* and algae are approximately an order of magnitude less than measured values. These values are considered to be conservative estimates of the toxicity of the material to aquatic organisms. No additional testing is necessary.

4.4 Human Health Data

4.4.1 Acute Mammalian Toxicity

This endpoint is filled by two sufficient oral toxicity studies in rats (Calkins, 1981a; Chow,

1981a), two inhalation studies in rats (Myers, 1986; Nachreiner, 1986), and one dermal toxicity study in rabbits (Chow, 1981b). The oral and dermal LD₅₀ values (lethal doses in 50% of the animals) were 13.2 ml/kg (approximately 12,200 mg/kg) and > 2000 mg/kg (the highest concentration tested), respectively. The LC₅₀ value for aerosol inhalation was between 0.545 mg/l (the LC₀) and 5.576 mg/l (the LC₁₀₀). The purity of the test material used in all the acute studies was at least 97.5%. The oral study conducted by Calkins and the inhalation study conducted by Nachreiner are considered to be the critical studies for the endpoint, and were given reliability ratings of 1 (valid without restriction).

Clinical signs observed in rats treated orally with 5.0 to 20 ml/kg m-diisopropenylbenzene included diarrhea, lacrimation, lethargy, urine-soaked fur, nasal discharge, alopecia, crusty nose and eyes, and cold body temperature (Calkins, 1981a; Chow, 1981a). Four out of five males treated with 20 ml/kg exhibited alopecia/edema around the anus. Most of the signs were present only for the first days of the study (with the exception of alopecia, which generally appeared a week after treatment). The frequency or variety of signs did not appear to increase with increasing doses of test material, and did not exhibit any sex-related trends (with the exception of alopecia/edema around the anus of high dose males). The only effect noted in rabbits treated dermally with 2000 mg/kg m-diisopropenylbenzene after abrading the skin was slight dermal irritation (Chow, 1981b).

In rats exposed to 5.576 mg/l (5,576 mg/m³) m-diisopropenylbenzene aerosol for 6 hours by inhalation, signs of toxicity such as wet fur, red perinasal wetness, lacrimation, whole body tremors, dermal irritation, hyperactivity, ataxia, and mouth breathing were observed during the first 90 minutes of exposure (Nachreiner, 1986). A complete loss of motor activity was observed in these animals for the remainder of the exposure period. After exposure, all animals exhibited absent toe, tail pinch, and surface righting reflexes, hypothermia, respiratory difficulties, wet fur, and dermal irritation. All of the animals appeared to be moribund before death (which occurred within 24 hours of exposure). In rats inhaling the nonlethal concentration (0.545 mg/l or 545 mg/m³), ocular irritation occurred during exposure. By contrast, no signs of toxicity were observed in rats exposed to a saturated atmosphere of m-diisopropenylbenzene vapor for 6 hours (Myers, 1986).

4.4.2 Repeated Dose Mammalian Toxicity

A 28-day inhalation toxicity test (5 days per week for 4 weeks) with 107, 510, and 970 mg/m³ m-diisopropenylbenzene (98.3% pure) has been performed in rats. Rats were predominantly exposed to vapor at 107 mg/m³ and approximately 50% vapor at 970 mg/m³. The estimated percentage of respirable particles at 510 and 970 mg/m³ was 86% and 89%, respectively. Exposure to 970 mg/m³ m-diisopropenylbenzene was associated with decreased weight and weight gain in males, increased numbers of segmented neutrophils in the blood of both males in females, increased urine volume in males, increased liver weight, and increased concentrations of serum enzymes that are markers for liver toxicity. Effects observed at 510 mg/m³ included reduced weight gain in males early on in the study, and increased urine volume and relative liver weight in males (without any changes in clinical chemistry parameters or pathology). Symptoms of eye irritation were observed in 1/10 animals exposed to 107 mg/m³ and 6/10 animals exposed to 510 or 970 mg/m³. Since study personnel did not consider the effects observed at 510 mg/m³

to be indicative of systemic toxicity, they assigned a no observable adverse effect level (NOAEL) of 510 mg/m³. However, since the effects observed at this concentration were also observed at 970 mg/m³, they appear to be related to treatment. Since no systemic effects were observed at 107 mg/m³, this concentration appears to be a more accurate estimation of the NOAEL.

Results of the OECD Test Guideline 421 study that was recently conducted (see Section 4.4.4) indicate that repeated, oral exposure of up to 1000 mg/kg/day m-diisopropenylbenzene for 15-27 days or 40-53 days is well-tolerated in male and female rats (respectively). In this experiment, there was no effect of treatment on body weight, food consumption, weights of epididymides and testes, gross pathology, or histopathology of selected organs (coagulating glands, epididymides, prostate, seminal vesicles, testes, pituitary, ovaries, uterus/cervix, vagina or stomach).

4.4.3 Genetic Toxicity

4.4.3.1 Mutagenicity

m-Diisopropenylbenzene (98.36% pure) has been tested for mutagenicity in an OECD Test Guideline 471 study conducted with *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2uvra- (Thompson and Bowles, 1999). In these tests, the highest concentrations of m-diisopropenylbenzene that did not cause excessive toxicity were not mutagenic in the absence or presence of a metabolic activation system.

4.4.3.2 Chromosomal Aberration

An OECD Test Guideline 473 chromosomal aberration test was performed in Chinese Hamster Ovary (CHO) cells with concentrations of m-diisopropenylbenzene ranging from 0 - 49.38 micrograms/ml without S9 and 0 - 197.5 micrograms/ml micrograms/ml with S9 from rat liver induced with phenobarbitone and beta-naphthoflavone (Safeparm Laboratories Limited, 2004a). Two experiments were conducted with either a 4 hour treatment period (followed by a 20 hour recovery period) or a 24 hour treatment period. In both experiments, there was no effect of test material on the frequency of cells with aberrations at any dose level, in either the presence or absence of S9 mix.

4.4.4 Reproductive and Developmental Toxicity

According to established guidelines of the HPV chemical program, chemicals that are used solely as intermediates are exempt from reproductive toxicity testing. Since there is minor use of the test substance (about 1% of total use) that disqualified the material as being used solely as a closed system intermediate (see Section 2), an oral OECD Test Guideline 421 Study (Reproduction/Developmental Screening Test) was conducted (Safeparm Laboratories Limited, 2004b).

In the OECD Test Guideline 421 study, Sprague Dawley rats (10/sex/dose) were given 0, 100, 300 or 1000 mg/kg/day m-diisopropenylbenzene in arachis oil for 14 days prior to mating (males and females), up to 13 days during mating (males and females), during gestation (females only),

and to day 5 of lactation (females only). The NOAELs for systemic, reproductive and developmental toxicity were 1000 mg/kg/day. There was no effect of test material on maternal or paternal body weight or food consumption, weights of the testes or epididymis, histopathology of reproductive organs, or any index of fertility measured. The mating and parturition indices were 100% in all groups. There was no significant effect of treatment on any index of toxicity measured in pups (live birth or viability index, litter size, litter weight, pinna unfolding, surface righting reflex, sex ratio or gross pathology).

Results of the 28-day repeated dose inhalation study indicate that inhalation of up to 970 mg/m³ m-diisopropenylbenzene has no effect on the histopathology of the ovaries and testes. This also suggests that the material has no effect on reproduction at this dose.

4.4.5 Additional Data

4.4.5.1 Skin and Eye Irritation

Adequate studies in rabbits show that 100% pure m-diisopropenylbenzene is slightly irritating to skin and eyes (Chow, 1981b,c). Effects observed in eye irritation study consisted of conjunctival redness, chemosis and/or discharge, which abated within 10 days of exposure. Nasal discharge was observed in 3/9 animals a few days after exposure. No irritation to the cornea or iris was observed.

4.4.5.2 Sensitization

Results of a well-conducted GLP study in guinea pigs indicate that 100% pure m-diisopropenylbenzene is a sensitizer (Calkins, 1981b). Animals receiving induction applications of undiluted test material exhibited a dose-dependent dermal contact sensitization response when challenged with 100% test material and rechallenged with 12.5, 25, 50 and 100% test material.

4.4.6 Summary/Test plan for Mammalian Toxicity

Adequate studies with m-diisopropenylbenzene have been conducted for all endpoints. Acute oral, inhalation and dermal studies show that acute exposure to fairly large amounts of m-diisopropenylbenzene is required to cause lethality. Signs of nervous system toxicity are observed prior to death in rats exposed to 5,576 mg/m³ m-diisopropenylbenzene by inhalation. Symptoms of toxicity observed in animals exposed to nonlethal concentrations of m-diisopropenylbenzene (by any route) are consistent with its ability to cause slight irritation to the skin and eyes. A well-conducted study in guinea pigs shows that m-diisopropenylbenzene is sensitizing. Results of the 28-day repeated dose inhalation study in rats show that exposure to 510 mg/m³ m-diisopropenylbenzene produces adaptive changes in the liver (i.e. increased liver weight), and exposure to 970 mg/m³ causes increased release of enzymes from the liver (but no pathologic changes). An OECD Test Guideline 421 study in rats indicated that oral exposure of up to 1000 mg/kg/day m-diisopropenylbenzene prior to mating and during gestation and lactation did not cause systemic, reproductive or developmental toxicity. Adequate studies show that m-diisopropenylbenzene is not mutagenic or clastogenic.

5. Summary

In summary, valid data are present to satisfy all physical/chemistry, environmental and mammalian toxicity endpoints. Existing and new studies on acute, repeated dose, genetic (mutations and chromosomal aberrations) and reproductive/developmental toxicity are sufficient to satisfy these endpoints. Data for eye and skin irritation and sensitization are adequate (although not required).

6. References

- Bowman J. 1986. Static Acute Toxicity Report #34332. Acute toxicity of m-DIPEB to fathead minnows (*pimephales promelas*). Analytical Biochemistry Laboratories Inc. study for American Cyanamid Company, dated May 23, 1986.
- Calkins JE. 1981a. Determination of the oral LD50 in rats of #11583B14. BRC Project Number 81-160 and American Cyanamid Project Number CT-012-80, dated December 10, 1981.
- Calkins JE. 1981b. Contact sensitization study in guinea pigs of #11583B14. BRC Project Number 81-150. American Cyanamid Project No. CT-012-80 dated Dec 8, 1981.
- Chow CP. 1981a. Acute pilot oral toxicity of CL 116,755 in rats. American Cyanamid Company Project Number 18750, dated 6/29/81.
- Chow CP. 1981b. Acute pilot dermal toxicity study of CL 116,755 in rabbits. American Cyanamid Company Project number 18754, dated 6-29-81.
- Chow CP. 1981c. Primary eye irritation study of CL 116,755 to rabbits. American Cyanamid Company Project number 18754, dated 6-29-81.
- Cytec Industries Inc. 2000. Material Safety Data Sheet, dated March 27.
- Cytec Industries Inc. 2002. Unpublished information.
- Dodd DE and Kintigh WJ. 1988. CT-256-86 Four-week aerosol inhalation study on rats. Union Carbide Bushy Run Research Center Project Report 49-573, dated December 21, 1988.
- Drozdowski D. 1987a. Ready biodegradability: The OECD closed bottle test. Test sample: CT-256-86. Report Number 07154-2 for American Cyanamid, dated 11/24/87.
- Drozdowski D. 1987b. Algal growth inhibition test (OECD Method) of CT-256-86. United States Testing Company, Inc. Report 06498-3 for American Cyanamid Company, dated Jan 22, 1987.

EPIWIN AOP Program (v1.90).

EPIWIN ECOSAR Program (v0.99).

EPIWIN HYDROWIN Program (v1.67).

EPIWIN KOWWIN Program (v1.66).

EPIWIN PCKOC Program (v1.66).

EPIWIN Level III fugacity modeling.

EPIWIN MPBPWIN program (v.1.40).

EPIWIN WSKOW Program (v1.40).

Fieser, LF and Fieser M. 1957. Introduction to Organic Chemistry. D. C. Heath and Company, Boston, pp. 52-3.

Forbis AD, Schoen LT and Frazier S. 1986. Static Acute Toxicity Report #34333. Acute toxicity of m-DIPEB to *Daphnia magna*. Analytical Biochemistry Laboratories Inc. study for American Cyanamid Company, dated April 25, 1986.

Klimisch HJ, Andreae M and Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Reg Tox Pharm* 25:1-5.

Myers RC. 1986. CT-256-86 Single saturated vapor inhalation study with rats. Union Carbide, Bushy Run Research Center Project Report 49-526, dated June 27, 1986.

Nachreiner DJ. 1986. CT-256-86 Pilot project for 5-day inhalation study. Union Carbide, Bushy Run Research Center Project Report 49-902, dated July 24, 1986.

Rivera, C. 2002a. Thermal analysis of m-DIPEB. Stamford Research Laboratories, Analytical Services Department, Notebook Ref. S19606-190, dated November 1, 2002.

Safepharma Laboratories Limited. 2004a. Chromosome aberration testing CHO cells in vitro: OECD 473. SPL Project Number 971/187, dated May 22, 2003.

Safepharma Laboratories Limited. 2004b. M-DIPEB (CT-760-02): Oral gavage reproduction and developmental toxicity screening study in the rat. SPL Project Number 971/234, dated October 27, 2004.

Stanek, E. 2002. PPM meta-Diisopropenylbenzene in Water, Stamford Research Laboratories, Analytical Services Department, Notebook Ref. S19556, dated November 21, 2002.

Thompson PW, Bowles AJ. 1999. m-DIPEB (CT-664-99) Reverse mutation assay "Ames Test" using Salmonella typhimurium and Escherichia coli. Safepharma Laboratories Limited (SPL) Project number 971/073 for Cytex Industries, Inc., dated Oct. 13, 1999.