TEST PLAN FOR 6-TERT-BUTYL-3-(CHLOROMETHYL)-2,4-XYLENOL (CAS NO. 23500-79-0)

OVERVIEW

Cytec Industries Inc. agrees to sponsor 6-tert-butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0) in the U.S. EPA High Production Volume Chemical Program. The sponsor hereby submits a test plan for this substance. It is our intent to use existing data plus modeling data, and additional testing as proposed in the test plan to fulfill the Screening Information Set (SIDS) endpoints.

Table 1. Test Plan Matrix for 6-tert-butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0)

CAS No. 23500-79-0	Information	Estimation	Acceptable	New Testing Required
ENDPOINT	Y/N	Y/N	Y/N	Y/N
PHYS/CHEM PROPERTIES				
Melting Point	Y	N	Y	N
Boiling Point	Y	Y	Y	N
Density (NR)	Y	N	Y	N
Vapor Pressure	Y	N	N	Y
Partition Coefficient	Y	Y	Y	N
Water Solubility	Y	Y	N	Y
ENVIRONMENTAL FATE				
Photodegradation	Y	Y	Y	N
Stability in Water	N	N	N	Y
Biodegradation	N	N	N	Y
Transport between Environmental Compartments (Fugacity)	Y	Y	Y	N
ECOTOXICITY				
Acute Toxicity to Fish	Y	Y	N	Y
Acute Toxicity to Aquatic Invertebrates	Y	Y	N	Y
Toxicity to Aquatic Plants	Y	Y	N	Y
TOXICOLOGICAL DATA				
Acute Toxicity	Y	N	Y	N
Repeated Dose Toxicity (NR)	N	N	N	N
Genetic Toxicity-Mutation	Y	N	Y	N
Genetic Toxicity-Chromosomal Aberrations	N	N	N	Y
Toxicity to Reproduction (NR)	N	N	N	N
Developmental Toxicity	N	N	N	Y
OTHER TOXICITY DATA				
Skin Irritation (NR)	Y	N	Y	N
Eye Irritation (NR)	Y	N	Y	N

Y = yes; N = no; NR = not required

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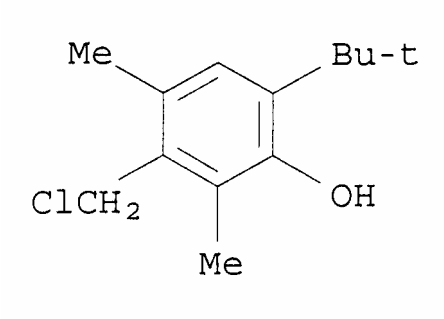
1. Introduction

Cytec Industries Inc. has agreed to supply hazard and exposure information under The U.S. EPA High Production Volume Chemical Program for 6-tert-butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0). This plan identifies existing data of adequate quality for this chemical, and outlines the intended testing to be conducted.

2. Designation of Test Substance

The test substance presented in this test plan is 6-tert-butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0). Its chemical structure is as follows:



This substance has the following synonyms:

2,4-dimethyl-3-(chloromethyl)-6-tert-butylphenol
3-(chloromethyl)-6-(1,1-dimethylethyl)-2,4-dimethylphenol
4-tert-butyl-3-hydroxy-2,6-dimethylbenzyl chloride

6-tert-butyl-2,4-dimethyl-3-chloromethyl phenol
6-tert-butyl-3-chloromethyl-2,4-dimethylphenol
phenol, 3-(chloromethyl)-6-(1,1-dimethylethyl)-2,4-dimethyl-
phenol, 6-tert-butyl-3-chloromethyl-2,4-xylenol

The trade name of 6-tert-butyl-3-(chloromethyl)-2,4-xylenol is A-1846. From this point forward, the material will be referred to by this acronym.

According to a MSDS sheet supplied by Cytec Industries Inc., A-1846 is usually stored with 11-13 wt. % methyl isobutyl ketone (CAS No. 108-10-1) added to liquefy the product. The product is also expected to contain 2-4 wt. % of 6-tert-butyl-2,4-xylenol.

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.

4. Discussion of Available Test Information

The A-1846 test plan matrix (as shown in Table 1 on page 2) was constructed after a careful evaluation of all existing data (see below). 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 sets of robust summaries.

4.1 Chemical and Physical Properties

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

Table 2. Chemical/physical properties of A-1846

Endpoint	A-1846 (CAS No. 23500-79-0)
Molecular weight grams/mol	226.75
Melting point	45 ºC [a,c] -32 ºC [a,d]
Boiling point	ca. 320 ºC [b,c] 156 ºC [a,d]
Relative density	1.044 g/cm^3 [a,d]
Vapor pressure (hPa at 20-25° C)	0.00018 [b,c] 12 [a,d]
Partition coefficient (Log Pow or Kow)	5.32 [b,c] 3.9 [a,d]
Water solubility (mg/l at 25 ° C)	10.19 [b,c] 500[d]

[a] Measured value; [b] Estimated using EPIWIN; [c] neat material; [d] industrial product liquefied with 11-13% methyl isobutyl ketone

4.1.1 Melting Point

A melting point of 45 ºC for the neat material is reported by the Cytec Industries Inc. (personal communication from internal documents). A melting point of -32 ºC is reported for the material in 11-13% methyl isobutyl ketone (Cytec Industries Inc. 2000).

4.1.2 Boiling Point

EPIWIN Mpbpwin was used to estimate a boiling point of about 320 ºC based on the structure of the molecule and a measured melting point of 45ºC. The substance is manufactured and stored as a liquid diluted with methyl isobutyl ketone. Therefore this material has a boiling point (156ºC) more reflective of that of methyl isobutyl ketone (115.8ºC). This boiling point information is deemed adequate for this substance, which in the pure state is not expected to boil below 250ºC and may, in fact, tend to decompose before boiling.

4.1.3 Vapor Pressure

The substance is isolated and used as a liquid with 11-13% methyl isobutyl ketone solvent present. The vapor pressure of this material is close to that of methyl isobutyl ketone (12 hPa at 20ºC). The vapor pressure estimated by EPIWIN Mpbpwin for the neat material is 0.00018 hPa. No measured vapor pressure data are available for the neat substance. Therefore, vapor pressure testing is proposed (OECD Test Guideline 104) for the neat material to assist in any determination of potential for release to the atmosphere.

4.1.4 Octanol/Water Partition Coefficient

EPIWIN Kowwin has been used to estimate a log Kow of 5.32. This highly positive value is consistent with the aromatic, non-polar molecular structure. The log Kow value reported for A-1846 in 11-13% methyl isobutyl ketone is 3.9

4.1.5 Water Solubility

EPWIN Wskow (v1.40) estimates a water solubility of 10.19 mg/l at 25 ºC, and the water solubility of 1846 in 11-13% methyl isobutyl ketone is 500 mg/l. Since there are no measured water solubility values for the neat substance, testing for water solubility is proposed (OECD Test Guideline 105).

4.1.6 Summary/Test Plan for Physical Properties

Testing is planned to obtained measured values for vapor pressure and water solubility of the neat material. The data obtained from these studies will be useful to better predict environmental fate for the substance.

4.2 Environmental Fate/Pathways

Results of environmental fate modeling and studies are summarized in Table 3.

4.2.1 Photodegradation

Photodegradation with hydroxyl radical sensitizer was estimated using EPIWIN/Aop (v1.90). An overall hydroxyl radical rate constant of 14.3539 E-12 cm^3/(molecule*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 8.942 hours was calculated assuming a constant concentration of OH radical and pseudo first order kinetics.

4.2.2 Stability in Water

EPIWIN Hydrowin cannot derive a water hydrolysis rate constant for this substance, since this model looks only at certain functional groups, such as esters, nitriles, amides, etc. Since the test substance contains a benzyl chloride functional group, and this group is known to potentially hydrolyze, a hydrolysis study will be conducted. It is likely that the rate of hydrolysis will be slowed because of the low solubility of this chemical.

Table 3. Environmental fate parameters for A-1846

Endpoint	Value
Indirect Photolysis (OH sensitizer) (Hydroxyl Radical Rate Constant)[a] (Atmospheric $T_{1/2}$) [a]	 14.3539 E-12 cm^3/molecule-sec 8.942 hours
Stability in Water [a]	Not expected to hydrolyze appreciably
Henry's Law Constant[a]	6.85E-007 atm-m^3/mol
Koc[a]	1.705E+4
Bioconcentration Factor (log BCF) [a]	2.945
Environmental transport (Fugacity Level III mass percentages)[a]	Air = 0.0002 Water = 11.6 Soil = 47.6 Sediment = 40.8
Biodegradation [a]	One linear Model – readily biodegradable Others- not readily biodegradable

[a] Estimated using EPIWIN

4.2.3 Fugacity

Level III fugacity modeling has been conducted on the test material using the EPIWIN model. Inputs to the program are CAS No. 23500-79-0 and a melting point of 45 ºC. Emission rates inputted into the program were air: 0 kg/hr, water: 1000 kg/hr, soil: 1000 kg/hr and sediment: 0 kg/hour. The following half-lives were calculated: T ½ air = 17.88 hrs, water = 1440 hr, soil = 1440 hr, and sediment = 5760 hr. The Biowin ultimate estimate is in the range of months. A Henry's Law Constant of 6.85E-7 atm-m^3/mol and a soil sediment partition constant (Koc) of 1.705E+4 were estimated using the EPIWIN/Henry and Pckoc Programs, respectively. The percent mass balances predicted for A-1846 in air, water, soil and sediment are shown in Table 3.

4.2.4 Biodegradation

A study that provides data on the rate and extent of biodegradation of A-1846 in the aqueous environment is not available. Results of the majority of the models used in the EPWIN suite indicate that the material biodegrades slowly; however, one model indicates that the material biodegrades fast. Since this modeling is not consistent, it is not sufficient to fill this endpoint. Biodegradation testing is therefore proposed (OECD Test Guideline 301 B or D).

4.2.5 Bioconcentration

A bioconcentration factor was calculated using the EPIWIN BCF Program (log BCF = 2.945). This value indicates that the material has some potential to bioaccumulate.

4.2.6 Summary/Test Plan for Environmental Fate Parameters

Estimated values are available for the hydroxyl radical induced photolysis rate constant and atmospheric half-life, Henry's Law Constant, soil sediment partition coefficient, Fugacity Level III environmental transport parameters and bioconcentration factor. No further testing is

planned for these endpoints. A stability in water (hydrolysis) study is planned. Biodegradation testing is also planned, since the results of EPIWIN modeling are not consistent.

4.3 Ecotoxicity

4.3.1 Acute Toxicity to Fish

The 96-hr LC50 value for fish estimated by the EPA's ECOSAR model for the phenol class is 0.300 mg/l, and for the benzyl halide class is 0.118 mg/l. No measured data are available, therefore testing is proposed.

4.3.2 Acute Toxicity to Aquatic Invertebrates

The EPA's ECOSAR models for phenols or benzyl halides predict 48-hour EC50 values of 0.535 and 0.118 mg/l for Daphnia, respectively. No measured data are available, therefore testing is proposed.

4.3.3 Acute Toxicity to Aquatic Plants

The 96-hr EC50 values calculated for green algae by the ECOSAR models for phenols or benzyl halides are 0.130 and 0.118 mg/l, respectively. No measured data are available, therefore testing is proposed.

4.3.4 Summary/Test Plan for Ecotoxicity

LC50 and EC50 toxicity values have been estimated by EPIWIN ECOSAR for fish, Daphnia and green algae. No aquatic toxicity studies are currently available that provide reliable measured data. Therefore the sponsors propose to conduct new aquatic acute studies in fish, daphnia and algae (OECD Test Guidelines 201, 202, and 203).

4.4 Human Health Data

4.4.1 Acute Mammalian Toxicity

This endpoint is filled by sufficient oral, inhalation and dermal toxicity studies in rodents. The LD_{50} value for the oral study in male rats conducted with A-1846 of 80.5 % purity is 7.71 ml/kg, or 8.04 g/kg (Brown, 1979). Results of an OECD Guideline 423 study indicate that the oral LD50 value for a more pure material in male and female rats is > 2000 mg/kg (Driscoll, 2000). According to a material safety data sheet, the 4-hour LC50 value for inhalation in the rat is > 2000 ppm (8.36 mg/l)(Cytec Industries Inc., 2000). The dermal LD_{50} value in rabbits was 9.98 ml/kg, or 10.4 g/kg (Brown, 1979).

Signs of toxicity in rats orally exposed to 2000 mg/kg purified test material were hunched posture, diarrhea, lethargy and pilo-erection (Driscoll, 2000). Animals recovered 2-4 days after dosing, and no abnormalities were found at necropsy. In a different study, all animals exposed to 5 or 10 ml/kg unpurified test material had a sluggish, unsteady gait after 1 hour of treatment (Brown, 1979). All animals treated with 5.0 ml/kg and 1/5 treated with 10.0 ml/kg recovered

within 2 days. Four out of five treated with 10.0 ml/kg died. Animals that died exhibited distended, gas-filled and injected stomachs, with glandular portions mottled pink and yellow; red kidney medullae; distended, liquid, blood-filled and injected intestines that were yellow and red in areas; and red adrenals. Survivors of this study exhibited stomachs adhered to abdominal walls and livers at necropsy.

In rabbits treated dermally with up to 10.0 ml/kg A-1846, no clinical signs of systemic toxicity were noted. However, erythema, edema, ecchymosis, areas of necrosis, and scabs were noted at the test site in several animals over the course of the study. One out of 4 rabbits treated with 3.2 ml/kg and 2/4 treated with 10.0 ml/kg died. These animals exhibited red kidneys at necropsy. Surviving animals in all groups treated with 3.2 to 10.0 ml/kg lost weight over the course of the study. Gross necropsies of these animals were normal.

4.4.2 Repeated Dose Mammalian Toxicity

No repeated dose toxicity experiments have been performed with A-1846. As documented in Appendix 1[1], A-1846 qualifies as a "type a" site limited, closed system, industrial intermediate. The potential for significant human exposure is strictly limited. Therefore, this material qualifies for exemption from repeated dose toxicity testing under the established guidelines of the HPV chemical program.

4.4.3 Genetic Toxicity

4.4.3.1 Mutagenicity

An OECD Guideline 471 test with 15 to 5000 micrograms/plate purified A-1846 has been performed on 4 strains of *S. typhimurium* (TA98, TA100, TA1535 and TA1537) and *E. coli* strain WP2uvrA- (Thompson, 2000). Results of this study and an additional screen performed with 1000 micrograms/plate in the same strains (Caterson, 1978) were negative. The OECD study is considered adequate to fill the endpoint. No additional testing is necessary.

4.4.3.2 Chromosomal aberration

No tests for this endpoint were located. In vitro testing is proposed for this endpoint (OECD Test Guideline 473).

4.4.4 Reproductive and Developmental Toxicity

Reproductive or developmental toxicity tests with A-1846 have not been conducted. Since material is a "type a" site limited, closed system, industrial intermediate, this material qualifies for exemption from reproductive, but not developmental toxicity testing. Even though repeated and reproductive tests are not required, a combined screening test that will evaluate repeated dose and reproductive toxicity along with developmental toxicity will be performed (an OECD Test Guideline 422 study) in lieu of a standard developmental toxicity test (OECD Test Guideline 414), as recommended by HPV Challenge Program guidelines.

[1] Detailed documentation of the information required to substantiate manufacture and use as an industrial intermediate with limited exposure is provided in Appendix I of this test plan.

4.4.5 Additional Data

4.4.5.1 Skin Irritation

The results of a dermal toxicity study in rabbits with material of 80.5% purity indicate that A-1846 is irritating to skin (Brown, 1979).

4.4.5.2 Eye Irritation

The commercially stored material that contains 11-13% methyl isobutyl ketone is severely irritating to rabbit eyes (Brown, 1979). Tissue destruction or an irreversible change in tissue occurred within 24 hours of instillation of 0.1 ml test material. The effect of washing was not assessed.

4.4.6 Summary/Test Plan for Mammalian Toxicity

Adequate acute toxicity studies have been conducted for A-1846. Results of these studies show that exposure to fairly large amounts of A-1846 is required to produce acute toxicity. The material is irritating to the skin and eyes, and is not mutagenic.

Since a chromosomal aberration test has not been performed, testing for this endpoint is proposed (OECD Test Guideline 473). Repeat dose and reproductive/developmental toxicity testing has not been performed. Since the material is used exclusively as an intermediate, any forms of repeat dose testing (including reproductive) are not required. However, developmental toxicity testing cannot be waived. An OECD Test Guideline 422 study (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) will be conducted to fill the developmental toxicity endpoint in accordance with HPV Challenge Program recommendations.

5. Summary

Physical properties

Adequate data are available for melting point and partition coefficient. A boiling point determination is not needed, because this material is not isolated as the neat substance, and because the EPIWIN Mpbpwin estimate of 320ºC is consistent with a very high boiling point that is consistent with the molecular structure of this substance. For the neat material, measured data are missing for vapor pressure and water solubility. Therefore, testing is planned for these endpoints.

Environmental fate properties

EPIWIN modeling provides adequate data for partition coefficient, hydroxyl radical-induced atmospheric photodegradation and environmental transport, as well as bioconcentration factor and Henry's Law Constant. A stability in water (hydrolysis) study is planned. Since no measured data are available regarding biodegradation and results of EPIWIN modeling are not consistent, testing for this endpoint is planned, even though the potential for environmental release of significant quantities of this closed system industrial intermediate is limited.

Aquatic toxicity

Testing in fish, Daphnia or algae has not been performed. The LC/EC_{50} values for A-1846 in these species estimated using EPIWIN are fairly low. Therefore, acute aquatic testing is proposed for fish, daphnia and algae.

Mammalian toxicity

Adequate acute mammalian toxicity and mutagenicity data are available, and no testing is proposed for these endpoints. An in vitro chromosome aberration test will be conducted to fill this endpoint. No repeat dose or reproductive toxicity data are available, but because A-1846 is manufactured and used exclusively as a site limited, closed system industrial intermediate (see Appendix 1 for further documentation), testing is not required for these endpoints. However, since developmental toxicity testing has not been conducted, a test that will incorporate repeat dose and reproductive/developmental toxicity testing (OECD Test Guideline 422) will be performed.

6. References

Brown DR. 1979. Antioxidant A-1846 Range Finding Toxicity Tests: Single Oral Dose, Single Dermal Dose, Skin Irritation, Eye Irritation. Carnegie-Mellon University Institute of Research, Report No 42-556, for American Cyanamid Company, dated July 26.

Caterson C. 1978. Mutagenicity test report (Ames Salmonella test) for A-1846. Report Number M78-170 from CRD Division, Plastics Additives Department, American Cyanamid.

Cytec Industries Inc. 2000. Material safety data sheet for A-1846, dated 10/30/200.

Driscoll R. 2000. Purified A-1846 (CT-684-00). Acute oral toxicity in the rat - acute toxic class method. SafePharm Laboratories Limited Project Number 971/115 for Cytec Industries, Inc., dated October 3.

EPIWIN AOP (v1.90).

EPIWIN BCF (v2.14).

EPIWIN ECOSAR (v0.99g).

EPIWIN HENRY (v3.10).

EPIWIN HYDROWIN (v1.67).

EPIWIN KOWWIN (v1.66).

EPIWIN Level III Fugacity modeling program.

EPIWIN MPBPWIN (v1.40).

EPIWIN PCKOC Program (v1.66).

EPIWIN WSKOW (v1.40).

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.

Thompson PW. 2000. Purified A-1846 (CT-684-00). Reverse mutation assay "Ames Test" using Salmonella Typhimurium and Escherichia Coli. SafePharm Laboratories Limited Project Number 971/116 for Cytec Industries Inc., dated October 30.

APPENDIX I

Documentation of manufacture and use of 6-tert-butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0) as a site-limited, closed system industrial intermediate

According to the EPA "Guidance for Testing Closed System Intermediates for the HPV Challenge Program, any chemical which is intended to undergo a further deliberate reaction to produce another industrial substance is considered an intermediate." It is believed that 6-tert-butyl-3-(chloromethyl)-2,4-xylenol fits the description of a type (a) closed system industrial intermediate. This description is as follows:

a) isolated intermediates which are stored in controlled on-site facilities

The EPA guidance also states that documentation is to be provided to support the claim for reduced testing. Such documentation includes information on number of sites, basis for closed process, and information on release, transportation or presence in distributed product. This information for 6-tert-butyl-3-(chloromethyl)-2,4-xylenol is provided below:

6-Tert-butyl-3-(chloromethyl)-2,4-xylenol is manufactured and converted at one plant site in the United States. This site is owned and operated by Cytec Industries Inc. Manufacture is carried out in a closed system (stainless steel reactor) by the chloromethylation of 6-tertiarybutyl-2,4-dimethylphenol using paraformaldehyde and hydrochloric acid (HCl). Some bis-chloromethyl ether (BCME) is formed as a byproduct from HCl and formaldehyde. BCME is a carcinogen regulated by the Occupational Safety and Health Administration (OSHA) (29 CFR 1910.1003), and these regulations apply to any area in which bis-chloromethylether may be processed or handled in concentrations greater than 0.1% by weight or volume in solid or liquid mixtures. These regulations require the use of a regulated area with access restricted to authorized employees only. Manufacture is carried out by remote control in a closed system operation within the required regulated area. If authorized employees must enter the regulated area for sampling when BCME may be present in the process at concentrations greater than 0.1% by weight or volume, they must wear a Saranek Tyvek suit, a self-contained breathing apparatus, impervious gloves, and boots. Then prior to each exit from the regulated area, the authorized employee must remove and leave protective clothing and equipment at the point of exit. At the last exit of the day, the authorized employee must decontaminate their personal protective equipment using water by standing under the Safety shower, then immediately upon exiting, the authorized employee must place their Saranek Tyvek suit and gloves into a properly labeled waste drum. While operated as a regulated area, the environment is kept under negative pressure with respect to non-regulated areas. Off-gases from the reactor are vented through a caustic scrubber to destroy residual BCME.

Following reaction, the aqueous layer is separated for recycle to the next batch. The organic layer containing the product 6-tert-butyl-3 (chloromethyl)-2,4-xylenol is washed with salt water to remove traces of residual HCl and formaldehyde from the product and to hydrolyze any traces

of residual BCME. The saltwater wash layers are sent to the plant waste water treatment system. The product is dehydrated under vacuum to remove residual water, and is then diluted with 11-13 % (wt. %) methyl isobutyl ketone (MIBK) and transferred through a closed line to a closed storage tank. The stringent controls applied to prevent exposure to BCME also prevent exposure to 6-tert-butyl-3-(chloromethyl)-2,4-xylenol during manufacture.

6-Tert-butyl-3-(chloromethyl)-2,4-xylenol in MIBK is transferred from its storage tank via a closed line to another closed reactor, where it is chemically converted on site to Cyanox R 1790 Antioxidant. This is the only use of 6-tert-butyl-3-(chloromethyl)-2,4-xylenol, with none of the 6-tert-butyl-3-(chloromethyl)-2,4-xylenol being sold, formulated into any other product or transported off site. The product (Cyanox R 1790 is analyzed for purity using gas chromatography. Analysis indicates no presence of A-1846 at the limit of detection (0.02 % by weight).

No workplace monitoring data are available for 6-tert-butyl-3-(chloromethyl)-2,4-xylenol. However, since this substance is always contained within a closed system, and because it has limited volatility, there is very limited potential for workplace exposure.