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

OVERVIEW

Cytec Industries Inc. agreed 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 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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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	Y	N
Partition Coefficient	Y	Y	Y	N
Water Solubility	Y	Y/N	Y	N
ENVIRONMENTAL FATE				
Photodegradation	Y	Y	Y	N
Stability in Water	Y	N	Y	N
Biodegradation	Y	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	Y	Y	N
ECOTOXICITY				
Acute Toxicity to Fish	Y	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	N	Y	N
Toxicity to Aquatic Plants	Y	N	Y	N
TOXICOLOGICAL DATA				
Acute Toxicity	Y	N	Y	N
Repeated Dose Toxicity (NR)	Y	N	Y	N
Genetic Toxicity-Mutation	Y	N	Y	N
Genetic Toxicity-Chromosomal Aberrations	Y	N	Y	N
Toxicity to Reproduction (NR)	Y	N	Y	N
Developmental Toxicity	Y	N	Y	N
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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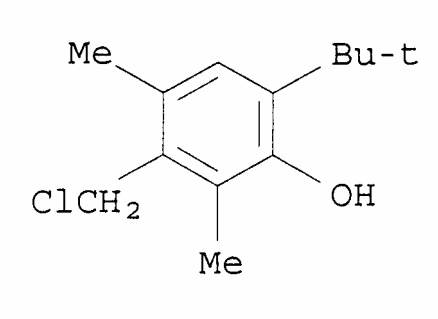
1. Introduction

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). The initial test plan and robust summaries were posted on the EPA website on June 4, 2003. A revised test plan and summaries were posted on January 13, 2004. That plan indicated that testing for the following endpoints would be conducted: vapor pressure, water solubility, hydrolysis as a function of pH, biodegradation, toxicity to fish, daphnia and algae and an in vitro chromosomal aberrations assay Although adequate data were present to show that the material was a closed system intermediate (and therefore was not subject to repeat dose or fertility testing) an OECD Test Guideline 422 study was recommended by the EPA to cover the developmental toxicity endpoint. 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.

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 (ºC)	45 [a,b,c] -32 [a,d,e]
Boiling point (ºC)	ca. 320 [b,f] 156 [a,d,e]
Relative density (g/cm^3)	1.044 [a,d,e]
Vapor pressure (hPa)	0.00042 at 25 ºC[a,b,c,g] 12 at 20 ºC[a,d]
Partition coefficient (Log Pow or Kow)	5.32 [b,f] 3.9 [a,d,e]
Water solubility (mg/l)	3.46 at 20 ºC[a,b,h] 10.19 at 25 ºC[b,f] 500 at 25 ºC [a,d,e]

[a] Measured value; [b]neat material; [c]Cytec Industries Inc. (2003); [d]industrial product liquefied with 11-13% methyl isobutyl ketone; [e]Cytec Industries Inc. (2000); [f]Estimated using EPIWIN; [g]SafePharm Laboratories (2004a); [h]SafePharm Laboratories (2004b).

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

4.1.3 Vapor Pressure

The vapor pressure of the neat substance has been determined by measurement (OECD Test Guideline 104 study) to be 0.00042 hPa at 25 ºC (SafePharm Laboratories, 2004a). The commercial 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).

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

The measured water solubility of the neat substance has been determined using an OECD Test Guideline 105 study (SafePharm Laboratories, 2004b). The solubility of 3.46 mg/l at 20 ºC thus obtained is probably understated, because the substance has been found to hydrolyze rapidly in water. EPWIN Wskow (v1.40) estimates a water solubility of 10.19 mg/l at 25 ºC for the neat material. A water solubility of 500 mg/l has been determined for commercial grade A-1846 dissolved in 11-13% methyl isobutyl ketone.

4.1.6 Summary/Test Plan for Physical Properties

Testing has been conducted to obtain measured values for vapor pressure and water solubility of the neat material. Sufficient screening level data are now available for physical properties of A-1846.

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

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 at 25 ºC[b] (Hydrolysis $T_{1/2}$)	< 9.8 minutes at pH 4 < 6.4 minutes at pH 7 instantaneously at pH 9
Henry's Law Constant[a]	6.85E-7 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 = 0.283 Water = 10.4 Soil = 52.6 Sediment = 36.7
Biodegradation [c]	7% after 28 days (OECD 301B)

[a] Estimated using EPIWIN; [b]SafePharm Laboratories (2004b); [c]SafePharm Laboratories (2004c)

using the program algorithm. A half-life of 8.9 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, an OECD Test Guideline 111 study was conducted (SafePharm Laboratories, 2004b). The results of this study indicate that neat A-1846 has a half-life in water at 25 ºC of <9.8 minutes at pH 4 and <6.4 minutes at pH 7. The rate of hydrolysis is too fast to measure at pH 9, where high concentrations of hydroxyl anion rapidly attack the chloride group, forming hydrochloric acid.

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, a melting point of 45 ºC and a vapor pressure of 31.5 mm Hg (42 hPa). Emission rates inputted into the program were air: 1000 kg/hr, water: 1000 kg/hr and soil: 1000 kg/h. 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

An OECD Test Guideline 301 B study (Ready Biodegradability, Modified Sturm Test) has been conducted on A-1846, which contained > 98% 6-tert-Butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0) and < 2% of unidentified impurities (SafePharm Laboratories, 2004c). In this study, the test material attained 7% degradation after 28 days. Therefore, it is not readily biodegradable. Results of the majority of the models used in the EPWIN suite also indicate that the material biodegrades slowly; however, one model (linear) indicates that the material biodegrades fast. The linear model is not considered to be valid for A-1846, since it is not in agreement with experimental results. Even though the substance does not itself biodegrade readily, it does hydrolyze rapidly under ambient conditions (See Sect. 4.2.2).

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. An OECD Test Guideline 111 stability in water (hydrolysis) study has been conducted, which indicates that hydrolysis takes place rapidly at neutral or acidic pHs at room temperature. Results of an OECD Test Guideline 301 B study indicate that the material is not readily biodegradable. No further testing is planned for any of these endpoints.

4.3 Ecotoxicity

4.3.1 Acute Toxicity to Fish

A static OECD Test Guideline 203 study has been performed in Oncorhynchus mykiss (rainbow trout) with A-1846 containing > 98% 6-tert-Butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0) and < 2% of unidentified impurities (Safepharm Laboratories, 2004d). Since the test material was not stable in the medium, the material actually used was the degradation product. The no observable effect concentration (NOEC) and 96-hr LC_{50} value (with respective 95% confidence limits) were 8.2 and 11 (10-12) mg degradation product/l, respectively. The 96-hr LC_{50} values for CAS No. 23500-79-0 in fish estimated by the EPA's ECOSAR model for the phenol and benzyl halide classes are 0.300 and 0.118 mg/l (respectively), indicating that this model does not accurately predict toxicity of this material towards fish (and is therefore invalid).

4.3.2 Acute Toxicity to Aquatic Invertebrates

A static OECD Test Guideline 202 study has been performed in Daphnia magna with A-1846 containing > 98% 6-tert-Butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0) and < 2% of unidentified impurities (Safepharm Laboratories, 2004e). Since the test material was not stable in the medium, the material actually used was the degradation product. The NOEC and 48-hr EC_{50} value (with respective 95% confidence limits) were 3.2 and 19 (14-25) mg degradation product/l, respectively. The EPA's ECOSAR models for phenols or benzyl halides predict 48-

hour EC_{50} values of 0.535 and 0.118 mg/l for Daphnia (respectively), which overestimate the toxicity of this material towards Daphnia (and therefore are invalid).

4.3.3 Acute Toxicity to Aquatic Plants

The same material that was used in the fish and daphnid toxicity tests was tested in an OECD Test Guideline 201 study in Pseudokirchneriella subcapitata algae (Safepharm Laboratories, 2004f). The no effect concentration (NOEC) was 5.1 mg degradation product/l and the 72 hour EC_{50} value determined for area under the growth curve was 6.6 mg degradation product /l. The EC_{50} value for growth rate (0-96 hr) with 95% confidence limits was 17 (15-20) mg degradation product/l. The EC_{50} values calculated for green algae by the ECOSAR models for phenols or benzyl halides (0.130 and 0.118 mg/l) are invalid, since they overestimate the toxicity of the material.

4.3.4 Summary/Test Plan for Ecotoxicity

LC_{50} and EC_{50} toxicity values for A-1846 towards fish, Daphnia and green algae have been determined in OECD Test Guideline studies. The LC_{50}/EC_{50} values in all three species are similar, and range from 6.6 -19 mg degradation product/l. ECOSAR modeling is invalid for this chemical since it does not accurately predict its toxicity towards aquatic species. No additional testing is necessary.

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 Test Guideline 423 study indicate that the oral LD_{50} 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 LC_{50} 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

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 and reproductive toxicity testing under the established guidelines of the HPV chemical program. However, to fill the developmental toxicity endpoint, an OECD Test Guideline 422 study was conducted (Mylchreest, 2004). This study qualifies as a guideline repeated dose toxicity study, since it was of sufficient duration and included clinical chemistries, hematologies and histopathologies commonly conducted in guideline studies.

In the OECD Test Guideline 422 study, Sprague-Dawley rats (10/sex/dose) were administered 0, 15, 50 or 200 mg/kg/day A-1846 in PEG 400 by gavage for a period of 34 days (males) or 43-57 days (females). Males were exposed for 14 days prior to mating and during mating, and females were exposed for 14 days prior to mating, and during mating, gestation and four days of lactation. The no observable effect limit (NOAEL) for systemic toxicity was < 15 mg/kg/day. Effects observed at 15 mg/kg/day were reduced body weight of females during gestation, mortality (N = 1) and clinical observations associated with dystocia (see Section 4.4.4) in pregnant females, and increased cholesterol in males and females. Additional findings at 50 mg/kg/day were increased liver weight in males and females, hepatocellular hypertrophy in males and a reduction of food consumption in females during gestation. At 200 mg/kg/day, additional findings included clinical signs (lung noise, diarrhea, hunched over posture and stained fur) in males and females, reductions in body weight gain, food consumption and food efficiency in males and females prior to mating, decreased hindlimb grip strength in males, decreased motor activity in males and females, hypertrophy of thyroid follicular epithelium in both sexes, hepatocellular hypertrophy in females, and decreased platelet counts in males.

4.4.3 Genetic Toxicity

4.4.3.1 Mutagenicity

An OECD Test 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

[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.

A chromosomal aberration test was performed in human lymphocytes with concentrations of A-1846 ranging from 17.5 to 280 micrograms/ml without S9 and 35 to 420 micrograms/ml with S9 from rat liver induced with phenobarbitone and beta-naphthoflavone (Safepharm Laboratories, 2004g). A-1846 caused a significant increase in the frequency of cells with aberrations at 105 (6% in treated vs. 0.5% in control) and 140 micrograms/ml (4.5% in treated vs. 0.5% in control) in the absence of S9 and 140 micrograms/ml (10.0% in treated vs. 0% in control) in the presence of S9. In both treatment groups, the predominant aberrations (other than gaps) were chromatid breaks and exchanges.

A recent OECD Test Guideline 474 micronucleus study performed in CD-1 male mice treated orally with 250, 500 or 1000 mg/kg A-1846 was negative at all concentrations. The study was valid, since the positive control material caused an increase in micronucleated polychromatic erythrocytes (PCE) and the highest dose used produced clinical symptoms of toxicity and a decrease in the PCE/NCE (normochromatic erythrocyte) ratio.

In conlusion, although A-1846 was positive in the *in vitro* human lymphocyte assay, it was negative in the *in vivo* mouse micronucleus study. Since results of *in vivo* studies are considered to be more reliable than *in vitro* studies, A-1846 is not considered to be clastogenic.

4.4.4 Reproductive and Developmental Toxicity

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 evaluated repeated dose and reproductive toxicity along with developmental toxicity was performed (an OECD Test Guideline 422 study) in lieu of a standard developmental toxicity test (OECD Test Guideline 414), as recommended by the EPA.

In the OECD Test Guideline 422 study, Sprague Dawley rats (10/sex/dose) were given 0, 15, 50 or 200 mg/kg/day A-1846 in PEG 400 for 14 days prior to mating, up to 14 days during mating, during gestation (females only), and to day 4 of lactation (females only) (Mylchreest, 2004). The NOAEL for systemic toxicity was <15 mg/kg bw/day, due to the mortality and clinical signs associated with dystocia (difficult or prolonged labor) and reduced body weight gain in females at all dose levels during gestation. Systemic effects noted at 50 and 200 mg/kg bw/day are described in detail in Section 4.4.2.

The NOAEL for reproductive effects was <15 mg/kg/day due to the occurrence of dystocia at all dose levels. There were no adverse reproductive effects seen in the males. All mating and fertility indices at any dose level were within the normal range. Therefore, this material caused reproductive toxicity effects only in the female rats.

The NOAELs for teratogenicity and fetal toxicity were 200 mg/kg/day and 15 mg/kg/day, respectively. There was no embyrolethality or gross abnormalities of the pups noted in this study. Maternal toxicity was seen at all dose levels. The accompanying reduced pup weights at 50 and 200 mg/kg/day are therefore not considered to be clear evidence of an effect. Therefore, this material should not be classified as a developmental toxicant.

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 toxicity studies have been conducted for A-1846 with regard to all mammalian toxicity endpoints. 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. Results of a chromosome aberration test in human lymphocytes were positive, indicating that this material is clastogenic.

Since the material is used exclusively as an intermediate, any forms of repeat dose testing (including reproductive) are not required. However, since developmental toxicity testing could not be waived, an OECD Test Guideline 422 study (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) was conducted in accordance with HPV Challenge Program recommendations. The NOAELs for systemic, reproductive, and fetal toxicity, and teratogenicity were <15 mg/kg/day, < 15 mg/kg/day, 15 mg/kg/day and 200 mg/kg/day (respectively), based on the findings of dystocia and reduced maternal body weight at all dose levels, reduced pup weights at 50 and 200 mg/kg/day and no embyrolethality or gross abnormalities of the pups at 200 mg/kg/day (highest dose used).

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. New, GLP, OECD guideline studies for vapor pressure and water solubility were conducted on the neat material. No additional testing is necessary.

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 new, OECD guideline hydrolysis study has been conducted that provides information on the rates of hydrolysis (half-lives) in water at various pHs. The results

indicate that the material hydrolyzes rapidly. The EPIWIN program was rerun with the new measured value for vapor pressure, and the corresponding values for environmental transport (fugacity) appropriately reflect all newly obtained data. Biodegradation testing indicates that the material is not readily biodegraded. No additional environmental fate testing is necessary.

Aquatic toxicity

The LC/EC_{50} values for A-1846 in OECD Test Guideline studies conducted in fish, daphnia and algae are similar (6.6 -19 mg degradation product/l). Since the potential for environmental release of significant quantities of this closed system industrial intermediate is limited, such concentrations are not expected to be present in waterways.

Mammalian toxicity

Adequate mammalian toxicity and mutagenicity/chromosome aberration data are now available. Acute exposure to large amounts of A-1846 is required to cause systemic toxicity. The material is irritating to skin. Irreversible eye injury may occur if eyes are not washed after contact. A-1846 is not mutagenic or clastogenic. Results of the OECD Test Guideline 422 study indicate that repeated exposure to fairly large amounts of A-1846 is required to produce systemic toxicity in male or nonpregnant female rats. Repeated exposure to concentrations ≥ 15 mg/kg/day prior to and during gestation causes dystocia in rats. The material is not teratogenic in rats, but exposure to concentrations ≥ 50 mg/kg/day is associated with reductions in fetal weight that are likely manifested by reduced maternal weight. Therefore, this material should not be classified as a developmental toxicant. Since the material is a closed-system intermediate with limited potential for human exposure, the likelihood for exposure to pregnant females is low.

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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[2]

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 has stated that "for closed system intermediates, a reduced test plan package reflecting the information needed to evaluate the hazards in case of an accident is considered the appropriate level of testing for screening purposes. This is because exposures resulting from chemical accidents are likely to be of relatively short versus chronic duration. The reduced testing consists of the Screening Information Data Set (SIDS) minus the tests for repeated dose toxicity and reproductive toxicity, but including a developmental toxicity test" (EPA, 1998).

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

[2] Note: The test plan originally submitted for CAS No. 23500-79-0 called for reduced testing, based on the manufacture and use of this substance solely as a closed system industrial intermediate. Appendix I was included with the original test to support reduced testing. The EPA, however, recommended conducting a combined screening test (OECD Test Guideline 422). Although a Test Guideline 422 study has now been conducted and is robustly summarized in the dossier and presented in the revised test plan, Appendix I is retained in the revised test plan because of its historical place in the test plan and its importance in characterizing exposure to this substance. The original Appendix has been revised to contain additional information about exposure and the EPA's policy for testing closed system intermediates.

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.