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**BPD (Benzene Phosphorous Dichloride)
and
BPA (Benzene Phosphinic Acid)**

HPV TEST PLAN

Submitted to the U.S. Environmental Protection Agency

by the

BPD/BPA Coalition

November, 2003

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1. Introduction

Although nominally reaching the production trigger for the HPV program, the materials in this test plan Benzene Phosphorus Dichloride (BPD) and its hydrolysis product, Benzene Phosphinic Acid (BPA) are cases where a high production volume does not correlate with a high exposure potential.

1.1. Manufacturers

In July, 2003, the three known manufacturers of phenyl phosphonous dichloride (BPD – CAS # 644-97-3) or phenyl phosphinic acid (BPA – CAS # 1779-48-2) (Avecia, Inc.; Ferro Corporation; and Akzo-Nobel Functional Chemicals LLC) were surveyed about customers, distribution, use, and TCSA 8(c) records for these products by the BPD/BPA Coalition Executive Director who summarized the member's confidential responses.¹ These summary survey results are the basis for the information in items 1.2 through 1.5.

1.2. Customers

Two of the manufacturers produce BPD, all three handle BPD and two produce BPA. The number of BPD/BPA customers is less than 10, with usage at a very limited number of sites.

1.3. Distribution

The manufacturers of BPD and BPA sell directly to customers except for laboratory chemical distributors. The quantity of either material distributed to chemical distributors is very small (fewer than 3 distributors) and generally in small quantities (20 – 30 pounds per sale) with total annual sales to laboratory distributors are less than \$1,000. Almost all of BPD sales are to major customers who use the material as an intermediate to convert into BPA as a photoinitiator and reactive polymer additive. In the few cases where a manufacturer sells to an agent, the end customer is known to the manufacturer. All three manufacturers have the understanding that BPA customers react/consume the material at the time of usage.

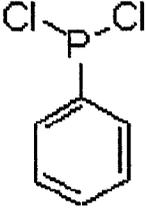
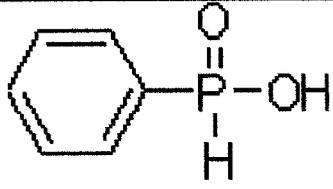
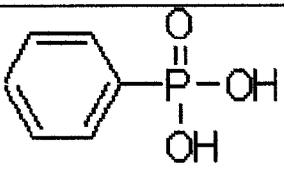
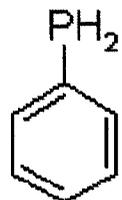
1.4. Uses

Almost all of the BPD is converted to BPA. BPA is used primarily in nylon applications. A small amount of BPD is consumed at customer sites for applications in flame retardants which are reacted into polymers. Some BPD is used for research purposes in very small quantities. Less than 1000 pounds per year of BPD is used in pharmaceutical manufacturing. Even smaller quantities of BPD are used as an intermediate in other processes.

1.5. TSCA 8 (c) Reports

None of the manufacturers of BPD and/or BPA had any allegations of significant adverse reactions (TSCA 8(c) reports) on file. The production of BPD and BPA began in the early 1960's.

2. Chemical Names, Formulas, and Structures

CAS# (CAS Name) [Common Name] Acronym	Formula ²	2-d Structure ³	3-d Model ⁴
HPV Chemicals			
644-97-3 (Phosphonous dichloride, phenyl-) [Benzene phosphorus dichloride] (BPD)	$C_6H_5Cl_2P$		
1779-48-2 (Phosphinic acid, phenyl-) [Benzene phosphinic acid] (BPA)	$C_6H_7O_2P$		
BPD Hydrolysis Products in addition to BPA			
1571-33-1 (Phosphonic acid, phenyl-) [Phenyl phosphonic acid] (PPOA)	$C_6H_7O_3P$		
638-21-1 [Phenyl phosphine] (PP)	C_6H_7P		

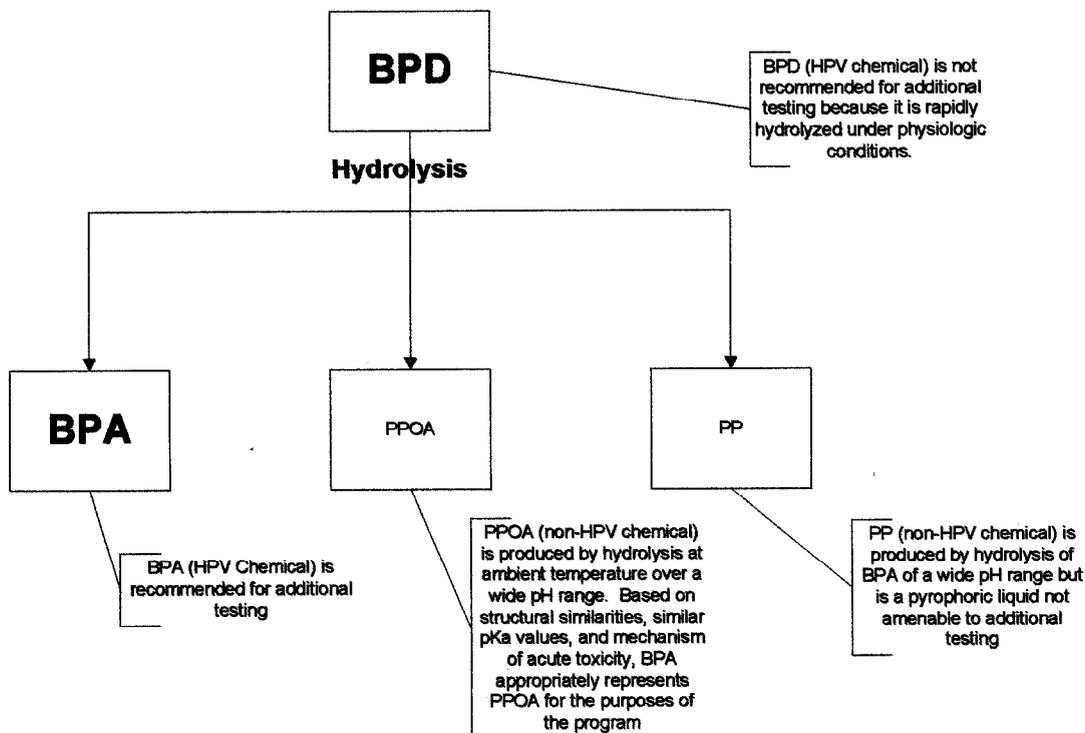
Note: The form shown is the most prevalent tautomeric form of the free acid.⁵

3. BPD/BPA Test Plan Summary

Although reaching the production trigger for the HPV program, the materials in this test plan Benzene Phosphorus Dichloride (BPD) and its hydrolysis product, Benzene

Phosphinic Acid (BPA) are a case where a high production volume does not correlate with a high exposure potential.

Relationship of Chemicals Discussed in Test Plan



BPD and BPA are both recommended for determination of selected physiochemical properties and BPA is recommended for the genetic toxicology testing needed to fill data gaps.

Under industrial conditions with control of temperature, addition rate, and pH, BPD is typically hydrolyzed to BPA with yields greater than 99.9%.

Under the test conditions of the OECD 111 guidelines, BPD is very rapidly hydrolyzed to BPA, PPOA and the pyrophoric liquid phenylphosphine.

Because BPA adequately represents PPOA for toxicity testing due to their chemical, structural, and toxicologic similarities and because phenylphosphine is impractical to test, BPA is the material most appropriate for ecotoxicology testing. BPA was considered for mammalian toxicology testing but was rejected based on the considerations described below.

Three main considerations (animal welfare, absorption, and existing data) lead to the conclusion that BPA should not be recommended for any mammalian toxicology testing by any route of administration. The considerations leading to this conclusion are: (1)

existing animal data that shows that BPA by oral gavage causes gastrointestinal tract bleeding, necrosis, and occasionally perforation, (2) the reported pKa values for BPA and PPOA are less than 2 and therefore BPA is mainly in the ionized form upon ingestion and absorption in the stomach will be low and even lower in the intestines, and (3) the existing acute and subacute study data are consistent with the view that the corrosive effects of BPA are the basis for its toxicity. Even dilute solutions of BPA would not be appropriate for mammalian testing, especially in a repeated-dose study design. It is not appropriate to test even dilute solutions of BPA in animals because: (1) no NOEL has been reported for gastrointestinal hemorrhage induced by BPA, (2) it is likely that even dilute solutions would cause gastrointestinal irritation and its consequent distress, (3) dilute solutions are not relevant to the industrial use of BPA, and (4) the primary toxicity of BPA is explained by its acidic properties, thus testing dilute solutions would not be relevant to the materials as used in industrial applications and would ignore their primary mechanism of toxicity.

4. Table of Available and Sufficient Data for BPD and BPA and Proposed Testing

Endpoint	BPD		BPA	
	Data Available & Sufficient	Testing Proposed	Data Available & Sufficient	Testing Proposed
Physical/Chemical Characteristics				
Melting Point	Yes	No	No	Yes
Boiling Point	Yes	No	No	Yes
Vapor Pressure	No	Yes	No	Yes
Partition Coefficient	No	No (decomposes)	No	Yes
Water Solubility	No	No (decomposes)	No	Yes
Environmental Fate				
Photodegradation	No	Calculate***	No	Calculate***
Stability in Water	No	Ongoing	No	Ongoing
Biodegradation	No	Calculate***	No	Yes
Transport (Fugacity)	No	Calculate***	No	Calculate***
Ecotoxicity				
Acute Toxicity to Fish	No	No*	No	Yes
Acute Toxicity to Invertebrates	No	No*	No	Yes
Acute Toxicity to Aquatic Plants	No	No*	No	Yes
Mammalian Toxicity				
Acute Toxicity	Yes	No	No (BPA) Yes (PPOA)	No**
Repeated Dose Toxicity	No	No*	No	No**
Reproductive Toxicity	No	No*	No	No**
Developmental Toxicity	No	No*	No	No**
Genetic Toxicity				
Bacterial Gene Mutations	Yes	No	No (BPA) Yes (PPOA)	Yes
Chromosomal Aberrations (in vitro)	No	No****	No	Yes

* No testing proposed as BPD rapidly hydrolyzes to BPA and related compounds

** No testing proposed based on animal welfare concern that repeated dosing is likely to cause serious animal distress

*** Calculated data to be updated after obtaining adequate values for physiochemical properties

**** BPD will be tested if there is an important difference in the profile of BPD and BPA in the bacterial mutagenesis assay

5. Category Justification

The basis for treating the high production volume (HPV) chemicals BPD and BPA as members of a category for the purposes of the HPV program is that, across a wide pH range, BPD rapidly hydrolyzes converting primarily to BPA and the structurally similar PPOA (which is not an HPV chemical) with the remainder converting to phenylphosphine (a pyrophoric liquid which is impractical to test).

Based on draft data from an OECD 111 guideline study, BPD hydrolyzes to BPA, PPOA, and phenylphosphine in about 1.5 minutes at the pH values tested ranging from 1.2 to 9⁶ in an exothermic reaction producing HCl. The OECD 111 guideline conditions do not represent commercial production. In commercial production, the hydrolysis of BPD to BPA is controlled to give a yield of 99.9% or greater.

Because it is practical to make stock aqueous solutions of BPA up to about 7% concentration for use in testing, BPA will be used as the test material for the ecotoxicology and genetic toxicology studies recommended in this test plan. Depending upon the relative profiles of BPD and BPA in the bacterial mutagenesis assay, BPD may be tested in an in-vitro chromosomal aberrations assay

5.1. Preliminary BPD hydrolysis data

The following BPD hydrolysis information is from the draft report of an OECD 111 guideline study being performed by Wildlife International, Easton, MD.⁶

The hydrolysis of BPD was monitored by recording the voltage output of a Cl⁻ electrode on a strip chart recorder. Completion of the hydrolysis under the test conditions was determined by an asymptotic voltage output from the Cl⁻ electrode which was reached in less than two minutes under all test conditions. Aliquots were taken for HPLC analysis at approximately 5 minutes following the addition of BPD in acetonitrile to the appropriate buffer.

pH	Mass Balance for the Percentage of Nominal Mass of BPD in pH-Adjusted Reagent Water			
	Cl ⁻	PPOA	BPA	PP
1.2	39.6	35.8	20.5	12.4
4	39.6	29.3	25.5	5.59
7	39.6	32.1	22.1	6.44
9	39.6	29.5	27.4	5.81

Although the proportions of the hydrolysis products vary with pH, PPOA and BPA are the predominant hydrolysis products.

5.2. BPA as Representative of the Hydrolysis Products

PPOA and BPA are structurally similar, they have similar pKa values which are less than 2, and they have similar acute toxicities, therefore BPA, the HPV material, is the practical and appropriate test material to represent the BPD/BPA category and the hydrolysis products of BPD.

BPA and PPOA are more structurally similar than is often appreciated. Although PPOA is traditionally shown with a P=O bond, this does not imply π -bonding. The P=O bond may be thought of as a coordinate bond with primarily σ -character.⁷ Similarly, although BPA is typically shown with two -OH groups, this structure represents the less prevalent tautomeric form. The more prevalent of free BPA form has a P=O bond⁵ as does PPOA.

Use of BPA to represent the BPD/BPA category is supported by the data that, although not directly comparable because of the difference in experimental designs (fixed-doses versus acute toxic class), shows that the existing lethality data for acute oral gavage dosing of BPD, BPA, and PPOA are similar. The other product of the hydrolysis of BPD, phenylphosphine, is not amenable to testing because it is a pyrophoric liquid.

BPA is the appropriate material to use for the testing recommended in this test plan because: (1) of the rapid hydrolysis of BPD primarily to BPA and PPOA, (2) BPA is the HPV chemical in this program, and (3) PPOA is not an HPV chemical.

6. Test Plan Considerations

6.1. BPA Mechanism of Toxicity:

The acute toxicity of BPA is similar to that of mineral acids, for example sulfuric acid⁸ and appears to be the manifestation of gastrointestinal hemorrhage and sequelae. This is not surprising given that BPA is a relatively strong organic acid with literature reported pKa values of 1.35 and 1.92⁹ in aqueous media. Because the reported pKa values are less than both the typical pH of the stomach (pH =2) and intestine (pH=6), neither area would favor absorption of the nonionized form¹⁰

6.2. PPOA Mechanism of Toxicity

The acute toxicity of PPOA is similar to that of BPA with a similar LD50 (2000 mg/kg)¹¹ or between 500 and 2000 mg/kg in another study¹² and necropsy findings similar to those of BPA with gastrointestinal hemorrhage in the fatalities¹¹ and descriptions of multiple brown indistinct areas or multiple black eroded areas in the glandular mucosa of the stomach¹².

The reported pKa value for PPOA is 1.85¹³ which is similar to that reported for BPA. Because the pKa value is less than both the typical pH of the stomach (pH =2) and intestine (pH=6), neither area would favor absorption of the nonionized form¹⁰.

6.3. BPD Mechanism of Toxicity

The acute toxicity of BPD appears similar to that of BPA and PPOA. Because the single animal tested in the rangefinding study at 2000 mg/kg died and 5 animals dosed in the main study at 500 mg/kg survived¹⁴, the acute toxicity is comparable to that of BPA and PPOA despite the differences in experimental design. The female animal dosed with 2000 mg/kg was found dead on the day after dosing. The necropsy notation was, "Stomach and intestine contents dark (black)", which is consistent with death by gastrointestinal hemorrhage.

6.4. Consideration of Human Experience

In a BPD/BPA Coalition survey of the manufacturers of BPD and BPA¹, there were no TSCA 8(c) allegations of adverse effect reports on file. There is no indication that there are unknown hazards associated with BPD and BPA.

6.5. Consideration of Animal Welfare

The acute oral toxicity of BPA appears to be secondary to causing gastrointestinal bleeding and consequent animal distress.

No additional mammalian toxicology testing by the oral route is recommended because of the likelihood of gastrointestinal bleeding and animal distress even with dilute solutions which would be exacerbated with repeated dosing.

Similarly, no additional mammalian toxicology testing is recommended by the dermal route because the most relevant study, a combined repeated dose/reproductive study with the OECD 422 design by the most relevant route (dermal) would be expected to cause severe skin irritation with repeated dosing and produce serious animal distress which would interfere with the purpose of the study.

7. Evaluation of Existing Data and Proposed Testing

7.1. Physical/Chemical Properties

Few of the physical/chemical properties data are available from reliable sources and testing will be required to meet the objectives of the program.

HPV Chemicals

CAS # Chemical	MW	MP °C	BP °C	Vapor pressure (mmHg)	Water Solubility (mg/L)	Log Kow	Physical Appearance.
644-97-3 BPD	178.98 ¹⁵	-51 ¹⁶	225 ¹⁷	10 @98°C ¹⁸	Decomposes	Decomposes	Colorless liquid
1779-48-2 BPA	142.1 ²⁰	83 ¹⁹	180 ²⁰	0.00014 ²¹	77,000 @25° C ²²	0.04 ²³	White crystalline solid ²⁴

BPD Hydrolysis Products in addition to BPA

CAS # Chemical	MW	MP °C	BP °C	Vapor pressure (mmHg)	Water Solubility (mg/L)	Log Kow	Physical Appearance
1571-33-1 PPOA	158.1 ²⁵	162 ²⁶	Decomposes @ 271 C ²⁷	0.2 mmHg @ 25 C ²⁸	278,000 ²⁹	0.52 ³⁰	White crystalline solid ³¹
638-21-1 Phenyl- phosphine	110.1 ³²	No Data	160.5 ³³	2.51 ³⁴	<1000 ³⁵	1.49 ³⁶	Colorless liquid PYROPHORIC ³⁷

Except where the properties of the material preclude meaningful testing, i.e. decomposition of BPD in water, BPD and BPA physical chemical properties other than physical appearance and handbook values will be determined by current OECD guideline methods.

7.2. Environmental Fate and Ecotoxicology

There is little existing experimental data on the environmental fate and ecotoxicity of the BPD, BPA or PPOA. The values in the tables are model calculations and testing will be required to meet the objectives of the program

HPV Chemicals

CAS # Chemical (Mol. Weight)	Environmental Fate				Ecotoxicity LC50 or EC50 (mg/L)		
	Photo-degradation (hr.)	Stability in water (25°C)	Bio-degradation	Transport/ Distribution	Fish (96 hr)	Aquatic Invertebrates (48 hr)	Aquatic Plants
644-97-3 BPD (179)	No Data	Decomposes to BPA, PPOA, phenylphosphine, and HCl,	See BPA	See BPA	See BPA	See BPA	See BPA
1779-48-2 BPA (142)	No Data	No data	Fast ³⁸	Primarily distributes to Water and Soil ³⁹	7328 ⁴⁰	6857 ⁴¹	3830 ⁴²

BPD Hydrolysis Products in addition to BPA

CAS # Chemical (Mol. Weight)	Environmental Fate				Ecotoxicity LC50/EC50 (mg/L)		
	Photo-degradation (hr.)	Stability in water (25°C)	Bio-degradation	Transport/ Distribution	Fish (96 hr)	Aquatic Invertebrates (48 hr)	Aquatic Plants
1571-33-1 PPOA (158.1)	57.6 ⁴³	No data	Fast ⁴⁴	Primarily distributes to Water and Soil ⁴⁵	28848 ⁴⁶	27907 ⁴⁷	16022 ⁴⁸
638-21-1 Phenylphosphine (110.1)	65.8 ⁴⁹	No data	Fast ⁵⁰	Primarily distributes to Water and Soil ⁵¹	246 ⁵²	255 ⁵³	154 ⁵⁴

Photodegradation and Transport/Distribution will be recalculated following determination of physical/chemical properties. Biodegradation, and ecotoxicity to fish, aquatic invertebrates, and aquatic plants will be evaluated for BPA using OECD guideline methods.

7.3. Acute Toxicity

Some useful acute toxicity information is available for the HPV chemicals and BPD hydrolysis products. Because of the considerations described in detail below, only genetic toxicity endpoints are recommended for additional testing.

HPV Chemicals

CAS# Chemical (Mol. Weight)	Acute LD ₅₀	Repeated dose	Reproductive	Develop- mental.	Genetic toxicity	
					Mutagenicity	Chromosomal Aberrations.
644-97-3 BPD (179)	>500 mg/kg ⁵⁵	No Data	No Data	No Data	Mutagenic	No Data
1779-48-2 BPA (142)	1710 mg/kg (oral gavage) >4640 mg/kg (dermal) ⁵⁶	NOAEL – 863 mg/kg/day for 10 days in rat diet	No Data	No Data	No Data	No Data

BPD Hydrolysis Products in addition to BPA

CAS # Chemical (Mol. Weight)	Acute LD ₅₀	Repeated dose	Reproductive	Develop- mental	Genetic toxicity	
					Mutagenicity	Chromosomal Aberrations.
1571-33-1 PPOA (158.1)	2000 mg/kg ⁵⁷ 500-2000 mg/kg ¹²	No Data	No Data	No Data	Not Mutagenic ⁵⁸	No Data
638-21-1 Phenylphosphine (110.1)	LC ₅₀ 38 ppm/4 hours ⁵⁹	LOAEL 7.6 ppm in rats exposed for 10 days ⁶⁰ LOAEL 2.2 ppm in dogs exposed for 90 days	Irreversible testicular degeneration in rats exposed to 2.2 ppm for 90 days. Reversible testicular degeneration in dogs exposed to 2.2 ppm for 90 days ⁶¹	No Data	No Data	No Data

7.3.1. Oral

The toxicity profile of BPA shares the characteristic of tissue destruction with mineral acids such as sulfuric or hydrochloric acids. In an acute study⁶² where BPA was administered to male rats by gavage and the calculated LD₅₀ was 1710 mg/kg, the survivors at 1000 mg/kg had areas of necrotic tissue in their gastrointestinal tracts and the rats that died at 2150 mg/kg had extensive areas of gastrointestinal hemorrhage. At 2150 mg/kg death occurred in 10-14 hours, while with 4640 mg/kg, death occurred in 2-5 hours. The clinical signs noted at 1000 mg/kg of depression subsiding at 48-96 hours are consistent with acidosis and shock following gastrointestinal hemorrhage. Similarly, the

clinical signs noted at higher levels or depression with periods of excitation and soft dark stool are consistent with serious gastrointestinal bleeding and consequent distress.

An approximate lethal dose (ALD) for BPA was 2250 mg/kg in a study where rats dosed with BPA where lethal doses produced acute gastric distress, distended abdomen, and signs of shock. At necropsy there was evidence of gastric necrosis and spillage of the gastric contents into the abdominal cavity. Four animals that received less than the ALD (as low as 450 mg/kg) showed evidence of gastritis⁶³.

The structurally similar material, PPOA had a similar acute toxicity profile in Sprague Dawley male rats with an LD50 of 2000 mg/kg, clinical observations of depression, gastrointestinal hemorrhage in fatalities, and no significant pathology (indicating healing and recovery) in the survivors.⁶⁴ A current acute oral toxicity study using two doses indicated the LD50 for PPOA was between 500 and 2000 mg/kg and reported similar clinical observations and necropsy findings¹².

No additional oral toxicity testing is proposed because doses sufficient to cause toxicity appears to be indirectly toxic by causing gastrointestinal bleeding and distress. It is expected that even dilute solutions would cause gastrointestinal irritation and consequent animal distress. The gastrointestinal irritation and consequent animal distress would be expected to be exacerbated by repeated dosing.

7.3.2. Dermal

No mortality was observed in a single dose study with 24 hour exposure to neat BPA at 4640 mg/kg in rabbits¹¹. In this study, moderate erythema was observed which subsided within four days.

No mortality was observed in a single dose study of with 24 hour exposure to neat PPOA at a dose 2000 mg/kg in rats⁶⁵.

At least slight dermal irritation was noted in all animals. Slight to moderate erythema was noted in all animals on Study Days 1 and 3 with the exception of one female which had a score of 3 and necrotic appearing areas on Study Day 3. Two on 5 females had erythema scores of 2 and edema scores on 1 on Study Day 7 and erythema scores of 1 on Study Day 10. Slight to moderate desquamation was noted at the administration site for 9 of 10 animals on Study Day 3 (males and females combined).

The dermal irritation observed in these studies with a single application would be expected to increase in a study with repeated dosing and cause severe animal distress.

7.4. Irritation/Corrosion

When 0.5 gram of neat (without a solvent) BPA was applied under occluded conditions to the flanks of rabbits for 24 hours⁵⁷, no erythema or edema was observed at the 24 and 72 hour time points. However, when 0.5 g of BPA was applied to abraded skin for 24 hours (and therefore water was present) all six rabbits had erythema scores of 4 (severe)

at the 24 and 72 hour time points. The edema scores was 4 for all six rabbits at the 24 hour time point and lower at the 72 hour time point. The difference in scores between the intact and abraded skin is probably due to the presence of water released from the abrasion and producing, essentially, a saturated solution of BPA in contact with the abraded skin. Based on the observations with PPOA described below where the PPOA was moistened, severe skin lesions were produced. The need for water for BPA to manifest its irritant properties is consistent with the observation that administration of BPA in the eye lead to gross destruction of the cornea and all surrounding tissues⁵⁷.

In rabbits, application of neat PPOA under semi-occluded conditions for 4 hours produced severe erythema and slight to moderate edema. Necrotic appearing areas and skin ulcerations were observed at all test sites. The study was terminated prematurely on Study Day 7 because of ulceration of the skin at the test site of all three animals. The primary dermal irritation index was determined to be 6.5 (considered to be severely irritating)⁶⁶.

These studies show that BPA and PPOA can be irritating with dermal exposure and because they show acute irritation, repeated dermal dosing would be very likely to cause cumulative dermal injury and animal distress.

7.5. Sensitization

PPOA was not considered to be a skin sensitizer in a recent Magnusson and Kligman maximization test in guinea pigs because none of the animals showed a dermal reaction to the challenge application of the 10% w/w mixture of PPOA in petrolatum.⁶⁷

7.6. Repeated Dose Toxicity

Rats fed diet containing 0.0, 0.1 or 1% corresponding to approximately 0, 85, and 863 mg/kg of BPA in corn oil in the diet for 14 days did not show toxic signs. Weight gain, feed intake, and clinical signs were normal in both dosed groups. Clinical chemistry (aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase, alkaline phosphatase, urea nitrogen, glucose and creatinine), hematology (red and white blood cell counts, red cell indices, platelet count hemoglobin concentration, and hematocrit) and relative and absolute liver kidney weights were normal in both dosed groups. No compound-related lesions were found in the gross and histopathologic examinations. No site of toxic action was identified in this repeated dose study⁶⁸. This result is consistent with the preceding acute gavage studies because rats eat over an extended period of time per day and this study clearly shows that repeated doses which are not concentrated in composition or time and do not cause acute gastrointestinal injury do not show signs of toxicity. In this study 863 mg/kg in the diet for 14 days did not show any signs of toxicity but in the ALD study cited above rats receiving a bolus dose of 450 mg/kg showed evidence of gastritis.

No additional mammalian toxicology testing is recommended because the most relevant study, a combined repeated dose/reproductive study with the OECD 422 design, by the most relevant route (dermal) would be expected to cause severe skin

irritation with repeated dosing and serious animal distress which would interfere with the purpose of the study.

No additional oral toxicity testing is proposed because doses sufficient to cause toxicity appears to be indirectly toxic by causing gastrointestinal bleeding and distress. It is expected that even dilute solutions would cause gastrointestinal irritation and consequent animal distress. The gastrointestinal irritation and consequent animal distress would be expected to be exacerbated by repeated dosing.

7.7. Reproductive/Developmental Toxicity

No information on reproductive/developmental toxicity was located on BPD and BPA and testing is not appropriate given the acute effects of these materials and the apparent lack of significant potential for exposure.

No additional mammalian toxicology testing is recommended because the most relevant study, a combined repeated dose/reproductive study with the OECD 422 design, by the most relevant route (dermal) would be expected to cause severe skin irritation with repeated dosing and serious animal distress which would interfere with the purpose of the study.

No additional oral toxicity testing is proposed because doses sufficient to cause toxicity appear to be indirectly toxic by causing gastrointestinal bleeding and distress. It is expected that even dilute solutions would cause gastrointestinal irritation and consequent animal distress. The gastrointestinal irritation and consequent animal distress would be expected to be exacerbated by repeated dosing.

7.8. Mutagenicity

BPD was tested in a GLP compliant bacterial mutation assay in *S. typhimurium* and *E. Coli*⁶⁹ In this assay, BPD was mutagenic in *S. typhimurium* strain TA98 in the presence of S9-mix and in *E. coli* strain WP2P in both the presence and absence of S9-mix. PPOA was not mutagenic when tested in a GLP compliant bacterial mutation assay in *S. typhimurium* and *E. Coli*⁵⁸

As described above, BPD would be expected to rapidly hydrolyze to BPA, PPOA, and phenylphosphine in the aqueous cell culture media, therefore, to meet the needs of the program, BPA is proposed for a bacterial mutation assay in *S. typhimurium* and *E. coli* and an in-vitro chromosomal aberrations assay. Because BPD was mutagenic in the bacterial mutation assay and PPOA was not, BPD is proposed for testing an in-vitro chromosomal aberrations assay if there is an important difference in the profile of BPD and BPA in the bacterial mutagenesis assay.

References:

- ¹ Smock, W. (2003) Survey of BPA/BPD Manufacturers with Responses. BPA/BPD Coalition.
- ² Chemical Abstracts Service.(2002 National Chemical Inventory 2002 Issue 2. American Chemical Society. ISSN 1089-6279.
- ³ Division of Specialized Information Systems, National Library of Medicine, National Institutes of Health (2003) ChemIDplus. <http://chem.sis.nlm.nih.gov/chemidplus/>. Visualization with Chime from MDL Informations Systems, Inc., San Leandro, CA. and Corina from Molecular Networks GmbH, Erlangen, Germany. Note: BPA structure modified to represent the more prevalent tautomeric form of the free acid.
- ⁴ Division of Specialized Information Systems, National Library of Medicine, National Institutes of Health (2003) ChemIDplus. <http://chem.sis.nlm.nih.gov/chemidplus/>. Visualization with Chime from MDL Informations Systems, Inc., San Leandro, CA. and Corina from Molecular Networks GmbH, Erlangen, Germany. Note: BPA structure modified to represent the more prevalent tautomeric form of the free acid.
- ⁵ Chapman and Hall's Dictionary of Organic Compounds, Fifth Ed., Phenylphosphinic acid, p. 4658.
- ⁶ Van Hoven, R. L., and Nixon, W.B. (2003) (Draft) Hydrolytic Stability of Benzene Phosphonous Dichloride. Project Number 534C-123. Wildlife International, Ltd., Easton, MD.
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