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**BPD/BPA Coalition**

BPD/BPA Coalition

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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**

**Updated**

**August, 2004**

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# 1. Introduction

Although nominally reaching the production trigger for the HPV program, the chemicals 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 BPD or BPA (Avecia, Inc.; Ferro Corporation; and Akzo-Nobel Functional Chemicals LLC) were surveyed about customers, distribution, use, and TCSA 8(c) records for these chemicals by the BPD/BPA Coalition Executive Director who summarized the member's confidential responses.<sup>1</sup> 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). 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. □

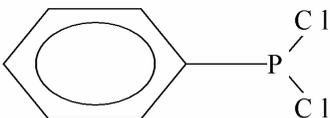
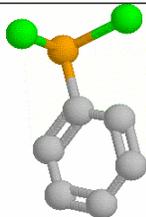
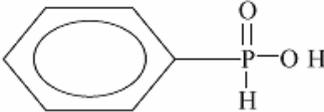
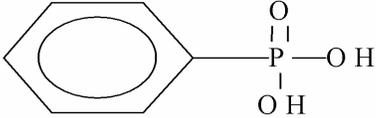
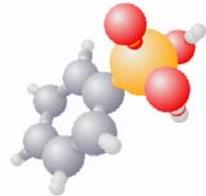
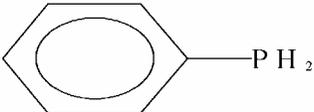
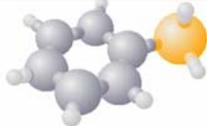
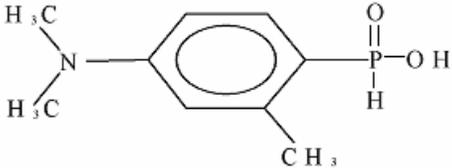
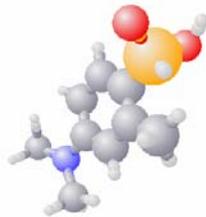
## 1.4. *Uses*

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. □

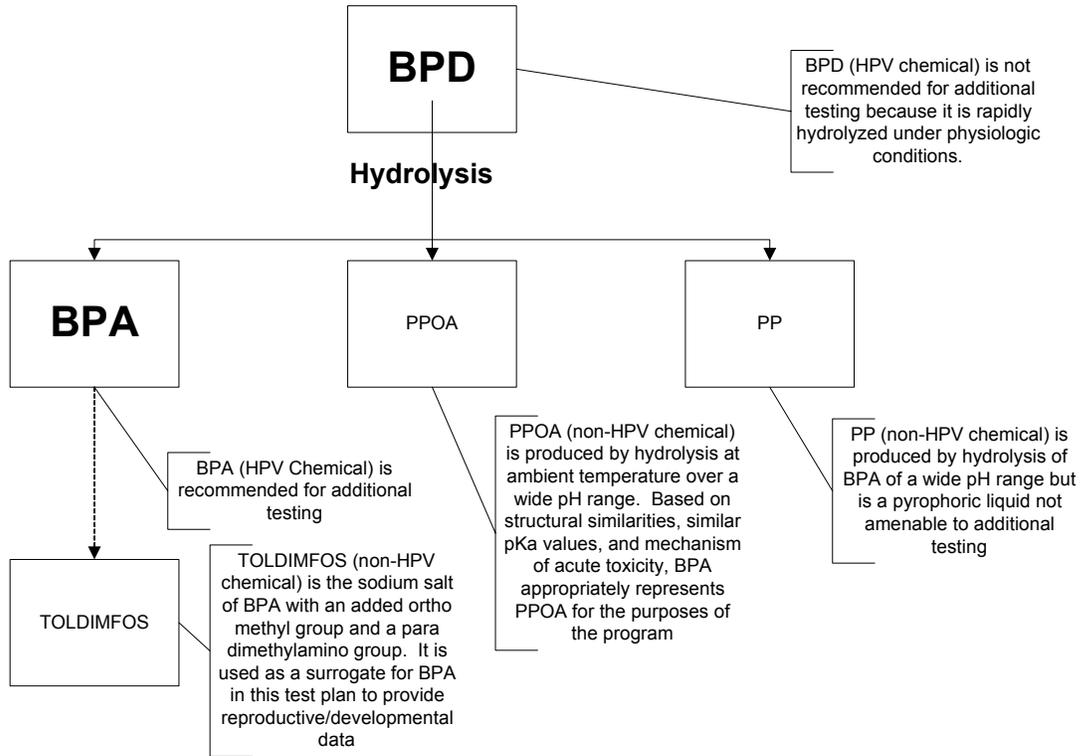
## 2. Chemical Names, Formulas, and Structures

CAS# (CAS Name) [Common Name] Acronym	Formula <sup>2</sup>	2-d Structure <sup>3</sup>	3-d Model <sup>4</sup>
<b>HPV Chemicals</b>			
<b>644-97-3</b> (Phosphonous dichloride, phenyl-) [Benzene phosphorus dichloride] <b>(BPD)</b>	C <sub>6</sub> H <sub>5</sub> Cl <sub>2</sub> P		
<b>1779-48-2</b> (Phosphinic acid, phenyl-) [Benzene phosphinic acid] <b>(BPA)</b>	C <sub>6</sub> H <sub>7</sub> O <sub>2</sub> P	Note: Most prevalent tautomeric form <sup>5</sup> 	
<b>BPD Hydrolysis Products in addition to BPA</b>			
<b>1571-33-1</b> (Phosphonic acid, phenyl-) [Phenyl phosphonic acid] <b>(PPOA)</b>	C <sub>6</sub> H <sub>7</sub> O <sub>3</sub> P		
<b>638-21-1</b> [Phenyl phosphine] <b>(PP)</b>	C <sub>6</sub> H <sub>7</sub> P		
<b>Substituted BPA salt with existing Reproductive/Developmental Data</b>			
<b>575-75-7</b> (phosphinic acid, [4-(dimethylamino)-2-methylphenyl]-, sodium salt) <b>[toldimfos]</b>	C <sub>9</sub> H <sub>13</sub> NO <sub>2</sub> PNa	Note: structure is for the acid 	

### 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 physicochemical 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%.

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 and ecotoxicity testing due to their chemical, structural, and toxicologic similarities and because phenylphosphine is impractical to test, the HPV chemical BPA is the material most appropriate for ecotoxicity testing in this program.

Because adequate information is available on mammalian toxicity endpoints for the purposes of the program, no additional mammalian testing is recommended.

Existing data and animal welfare considerations 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) adequate data for the screening purposes of the program for all mammalian endpoints are available when a substituted BPA, toldimfos, is used as a structurally-related surrogate to provide reproductive/developmental data, (2) existing animal data that shows that BPA by oral gavage causes gastrointestinal tract bleeding, necrosis, and occasionally perforation, and (3) the existing acute and repeated-dose study data are consistent with the view that the corrosive effects of BPA are the basis for its 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
<b>Physical/Chemical Characteristics</b>				
Melting Point	Yes	No	Yes	No
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
<b>Environmental Fate</b>				
Photodegradation	No	Calculate***	No	Calculate***
Stability in Water	Yes	No	Yes	No
Biodegradation	No	Calculate***	No	Yes
Transport (Fugacity)	No	Calculate***	No	Calculate***
<b>Ecotoxicity</b>				
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
<b>Mammalian Toxicity</b>				
Acute Toxicity	Yes	No	No (BPA) Yes (PPOA)	No**
Repeated Dose Toxicity	No	No*	Yes	No
Reproductive Toxicity	No	No*	Yes (toldimfos)	No
Developmental Toxicity	No	No*	Yes (toldimfos)	No
<b>Genetic Toxicity</b>				
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 oral gavage dosing with BPA is likely to cause serious animal distress and that other oral routes, i.e. dietary admixture, bypass the primary toxicity of BPA and do not represent realistic scenarios

\*\*\* 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 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 9<sup>6</sup> 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% 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. BPD hydrolysis data

The following BPD hydrolysis information is from an OECD 111 guideline study performed by Wildlife International, Easton, MD.<sup>6</sup>

The hydrolysis of BPD was monitored by recording the voltage output of a Cl<sup>-</sup> electrode on a strip chart recorder. Completion of the hydrolysis under the test conditions was determined by an asymptotic voltage output from the Cl<sup>-</sup> 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 <sup>-</sup>	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  $\pi$ -bonding. The P=O bond may be thought of as a coordinate bond with primarily  $\sigma$ -character.<sup>7</sup> 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 bond<sup>5</sup> 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.

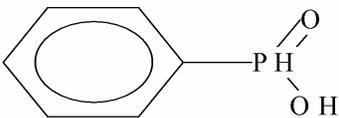
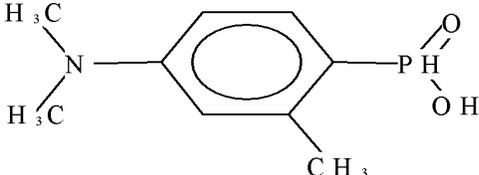
BPA will be used for new genetic and ecotoxicity testing under this test plan, and existing data on PPOA will provide information about acute toxicity and a substituted BPA (toldimfos) will provide information about reproductive/developmental toxicity.

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 and toldimfos are not HPV chemicals.

## **5.3. Toldimfos as an Existing Data Surrogate for BPA for Developmental/Reproductive Data**

Toldimfos is a compound with a long history of safe use in human medicine which is currently used only in veterinary medicine. A recent review of toldimfos by the European Agency for the Evaluation of Medicinal Products (EMA) group for the Evaluation of Medicines for Veterinary Use to support the setting of a tissue residue level for food products<sup>8</sup> is available. This source is important because of the animal welfare issues with testing BPA by a relevant route of exposure. The summary information in the EMA review is current (2000), reliable, and indicates a low level of concern for reproductive/developmental effects for toldimfos and BPA. The information from the EMA review provides an adequate alternative to new mammalian testing with BPA for the screening purposes of the program.

### 5.3.1. Structural similarity of BPA and Toldimfos

BPA	Toldimfos
phenylphosphinic acid	(phosphinic acid, [4 – (dimethylamino) -2-methylphenyl]-, sodium salt
	

Toldimfos sodium has the CAS# 575-75-7 and is phosphinic acid, [4-(dimethylamino)-2-methylphenyl]-, sodium salt.

An EMEA evaluation report<sup>8</sup> contains information about toldimfos which is relevant to its use as a surrogate for BPA for the reproductive/developmental endpoints. The information available is sufficient to have a low level of concern about reproductive/developmental issues with BPA. Toldimfos and BPA are both highly water soluble and, as expected, toldimfos is excreted rapidly in the urine, primarily as unmetabolized toldimfos. Therefore it is likely that BPA is also excreted as BPA and not significantly metabolized.

Although there are no directly comparable acute studies of BPA and toldimfos with same species and route of administration, the weight of the available information is that the LD<sub>50</sub> of toldimfos is on the order of grams/kg by parenteral routes<sup>8</sup>. The LD<sub>50</sub> of BPA by oral gavage<sup>58</sup> is 1710 mg/kg with death apparently secondary to gastrointestinal hemorrhage. Toldimfos may have somewhat greater repeated-dose toxicity than BPA because a 90-day feeding study with toldimfos<sup>8</sup> showed a variety of toxic signs while a 4-week feeding study with BPA at a dose that was ~80% of the toldimfos dose<sup>70</sup> did not show toxic signs. The weight of evidence is that toldimfos is an appropriate compound to use as a source of existing data on reproductive/developmental toxicity as a surrogate for BPA.

Toldimfos tissue distribution and residue studies were consistent with that for a highly water soluble compound with a short half-life which is eliminated via urine. This suggests that BPA would also have a short half-life and not accumulate in tissue.

## 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 acid<sup>9</sup> 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 1.92<sup>10</sup> 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 form<sup>11</sup>

### **6.2. PPOA Mechanism of Toxicity**

The acute toxicity of PPOA is similar to that of BPA with a similar LD50 (2000 mg/kg)<sup>12</sup> or between 500 and 2000 mg/kg in another study<sup>13</sup> and necropsy findings similar to those of BPA with gastrointestinal hemorrhage in the fatalities<sup>12</sup> and descriptions of multiple brown indistinct areas or multiple black eroded areas in the glandular mucosa of the stomach<sup>13</sup>.

The reported pKa value for PPOA is 1.85<sup>14</sup> 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 form<sup>11</sup>.

### **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 survived<sup>15</sup>, 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 BPA<sup>1</sup>, 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 gavage toxicity of BPA appears to be secondary to causing gastrointestinal bleeding and consequent animal distress.

No additional mammalian toxicology testing by the oral gavage 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 <sup>16</sup>	-51 <sup>17</sup>	225 <sup>18</sup>	10 @98°C <sup>19</sup>	Decomposes	Decomposes	Colorless liquid
1779-48-2 BPA	142.1 <sup>21</sup>	83 <sup>20</sup>	180 <sup>21</sup>	0.00014 <sup>22</sup>	77,000 @25° C <sup>23</sup>	0.04 <sup>24</sup>	White crystalline solid <sup>25</sup>

#### 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 <sup>26</sup>	162 <sup>27</sup>	Decomposes @ 271 C <sup>28</sup>	0.2 mmHg @ 25 C <sup>29</sup>	278,000 <sup>30</sup>	0.52 <sup>31</sup>	White crystalline solid <sup>32</sup>
638-21-1 Phenyl- phosphine	110.1 <sup>33</sup>	No Data	160.5 <sup>34</sup>	2.51 <sup>35</sup>	<1000 <sup>36</sup>	1.49 <sup>37</sup>	Colorless liquid PYROPHORIC <sup>38</sup>

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 <b>BPD</b> (179)	No Data	Rapidly decomposes to BPA, PPOA, phenylphosphine, and HCl <sup>6</sup>	See BPA	See BPA	See BPA	See BPA	See BPA
1779-48-2 <b>BPA</b> (142)	No Data	Half-life > 1 year at pH 1.2, 7, and 9. Half-life ~116 days at pH 4 <sup>39</sup>	Fast <sup>40</sup>	Primarily distributes to Water and Soil <sup>41</sup>	7328 <sup>42</sup>	6857 <sup>43</sup>	3830 <sup>44</sup>

### 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 <b>PPOA</b> (158.1)	57.6 <sup>45</sup>	No data	Fast <sup>46</sup>	Primarily distributes to Water and Soil <sup>47</sup>	28848 <sup>48</sup>	27907 <sup>49</sup>	16022 <sup>50</sup>
638-21-1 <b>Phenylphosphine</b> (110.1)	65.8 <sup>51</sup>	No data	Fast <sup>52</sup>	Primarily distributes to Water and Soil <sup>53</sup>	246 <sup>54</sup>	255 <sup>55</sup>	154 <sup>56</sup>

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

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 <sub>50</sub>	Repeated dose	Reproductive	Develop- mental.	Genetic toxicity	
					Mutagenicity	Chromosomal Aberrations.
644-97-3 <b>BPD</b> (179)	>500 mg/kg <sup>57</sup>	No Data	No Data	No Data	Mutagenic	No Data
1779-48-2 <b>BPA</b> (142)	1710 mg/kg (oral gavage) >4640 mg/kg (dermal) <sup>58</sup>	NOEL – 10,000 ppm in rat diet for 28 days (779 mg/kg for males and 859 mg/kg for females)	NOEL at 50 mg/kg s.c. (corresponds to > 1 g/kg by oral route) was not established primarily due to cannibalism of pups but no indication of compound-related toxicity. See text.	NOEL (toldimfos) 50 mg/kg s.c. (corresponds to > 1 g/kg by oral route). See text.	No Data	No Data

#### BPD Hydrolysis Products in addition to BPA

CAS # Chemical (Mol. Weight)	Acute LD <sub>50</sub>	Repeated dose	Reproductive	Develop- mental	Genetic toxicity	
					Mutagenicity	Chromosomal Aberrations.
1571-33-1 <b>PPOA</b> (158.1)	2000 mg/kg <sup>59</sup> 500-2000 mg/kg <sup>13</sup>	No Data	No Data	No Data	Not Mutagenic <sup>60</sup>	No Data
638-21-1 <b>Phenylphosphine</b> (110.1)	LC <sub>50</sub> 38 ppm/4 hours <sup>61</sup>	LOAEL 7.6 ppm in rats exposed for 10 days <sup>61</sup> LOAEL 2.2 ppm in rats and dogs exposed for 90 days <sup>62</sup>	Irreversible severe testicular degeneration in rats exposed to 2.2 ppm for 90 days. Reversible mild testicular degeneration in dogs exposed to 2.2 ppm for 90 days <sup>62</sup>	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 study<sup>63</sup> 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 of 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 gastritis<sup>64</sup>.

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.<sup>65</sup> 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 findings<sup>13</sup>.

No additional oral toxicity testing is proposed.

### **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 rabbits<sup>12</sup>. In this study, moderate erythema was observed which subsided within four days.

No mortality was observed in a single dose study with 24 hour exposure to neat PPOA at a dose 2000 mg/kg in rats<sup>66</sup>.

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.

No additional dermal toxicity testing is proposed.

#### **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 hours<sup>58</sup>, 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 tissues<sup>58</sup>.

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)<sup>67</sup>.

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.

No additional irritation/corrosion testing is proposed.

#### **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.<sup>68</sup>

No additional sensitization testing is proposed.

#### **7.6. Repeated Dose Toxicity**

##### **7.6.1. 14-day Repeated-dose Study**

Rats fed diet containing 0.0, 0.1 or 1% BPA 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 study<sup>69</sup>.

### **7.6.2. 28-day Repeated-dose Study**

A GLP-compliant four-week repeated-dose study<sup>70</sup> by dietary admixture of BPA at concentrations of 0, 100, 1000, and 10,000 ppm found no significant signs of adverse response in clinical signs, growth, neurobehavior, ophthalmology, and clinical and anatomical pathology at the highest dose tested of 10,000 ppm. The concentration of 10,000 ppm in the diet corresponded to 779 mg/kg for males and 859 mg/kg for females. The test article used in the study was from a Ferro Corporation production batch and reported have a purity of 99.3%. Test substance stability analyses were conducted at the beginning and end of the study. The CrI:CD (SD) IGS BR rats were approximately 6-8 weeks old at the start of the study and had 5 males and 5 females per dose group. Endpoints measured included weekly food consumption and body weights which were used to calculate the intake of BPA. The animals were observed twice daily for clinical signs of toxicity and detailed clinical observations were recorded weekly. Ophthalmologic examinations were conducted before the start of the study and prior to sacrifice. Neurobehavioral evaluations were conducted before the start of dosing and before sacrifice. A limited Functional Observation Battery including response to touch, auditory stimulus, tail-pinch, papillary response, and fore- and hindlimb grip strength. Motor activity was assessed in an automated infrared monitoring device which recorded both duration and number of movements.

Blood samples were collected at necropsy for hematology (14 parameters plus differential leukocyte count) and clinical chemistry (19 parameters) endpoints were measured or calculated using automated analyzers and/or microscopic examination. In addition to volume and appearance, 9 urine clinical endpoints were measured by an automated analyzer.

There were no BPA-related effects were occurred in hematology, coagulation, or clinical chemistry parameters.

There were no BPA-related gross pathology observations, or microscopic changes were detected in the comprehensive set of tissues examined including reproductive organs and the brain, spinal cord and sciatic nerve.

There were no BPA-related differences in mean body weight or mean body weight gain for either males or females.

There were no BPA-related effects on the neurobehavioral parameters measured.

This study adequately meets the SIDS data requirement for a repeated dose study of BPA.

### **7.6.3. Comparison with Acute Studies by Oral Gavage**

The results of the dietary admixture studies are 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 these studies 863 mg/kg in the diet for 14 days or 779 mg/kg (males) or 859 mg/kg (females) for 28 days did not show any signs of toxicity but in the ALD<sup>64</sup> study described in rats receiving a bolus dose of 450 mg/kg showed evidence of gastritis.

No additional repeated-dose testing is recommended.

### **7.7. Reproductive/Developmental Toxicity**

Toldimfos is a substituted BPA for which there is existing reproductive/developmental information available. Toldimfos is BPA with the addition of an ortho- methyl group and a para- dimethylamino group.

The route of administration used in most of the toldimfos studies reviewed by EMEA was subcutaneous or intramuscular injection<sup>8</sup>. Although these are not the routes of administration that would be used for new studies in the HPV program, these studies can provide valuable information to meet the screening needs of the program. Because of higher bioavailability, parenteral routes of administration of a given dose would be expected to have effects similar to significantly higher doses by an oral route. In other words, if a compound has a low degree of oral bioavailability, for example 5%, a 1 gram oral dose would be expected to roughly correspond in terms of toxic effects observed to a 50 mg/kg dose given by a parenteral route. Although factors such as chemical reactivity and metabolism can lead to differences in toxicity from one route to another, they are probably not important for toldimfos which is apparently neither very chemically reactive nor significantly metabolized.

Sufficient information is available<sup>8</sup> to show that the toxicity profile of 50 mg/kg per day of toldimfos in a 28 day repeated dose subcutaneous administration study is similar to the toxicity profile observed with 1 g/kg per day of toldimfos in a 90 day repeated-dose dietary admixture study. The bridging information across routes provided by these two repeated-dose studies with toldimfos provides an appropriate rationale for using an existing reproductive/developmental study with toldimfos by subcutaneous administration to meet the screening needs of the HPV program.

At the highest doses of toldimfos tested (50 mg/kg per day by subcutaneous administration and 1 g/kg day by dietary admixture), there were generally similar findings: clinical chemistry changes in liver enzymes and increased blood glucose, a lack of significant histopathology, and changes in absolute and relative organ weights. As a first approximation, the similar toxicologic profiles by the two routes suggest that the subcutaneous route is roughly 20-fold more bioavailable than the dietary admixture route. Put another way, the comparison of the subcutaneous administration study and the dietary admixture study of toldimfos suggests that a subcutaneous dose of 50 mg/kg of toldimfos corresponds approximately to the typical oral limit dose of 1 g/kg of toldimfos.

The approximate correspondence of the 50 mg/kg subcutaneous dose and a 1 g/kg dose by dietary admixture in repeated-dose studies means that, for the screening purposes of the HPV program, it is appropriate to use information from the two-generation reproductive/developmental study of toldimfos by the subcutaneous route to provide screening level information about the reproductive/developmental endpoint for the category represented by BPA as an alternative to conducting a dietary admixture study with BPA at 1 g/kg.

The GLP compliant reproductive/developmental study in Wistar rats<sup>8</sup> had reproductive endpoints unaffected by treatment except for a 10% loss of whole litters surviving in both the F<sub>1</sub> and F<sub>2</sub> generations. In this study, in all groups, including control, there was an unusually high level of cannibalism of pups which is discussed in Section 5.3 of the BPA robust summaries and was probably a result of the increased handling necessary for the use of the subcutaneous route of administration.

Histopathologic examination of the parent generations did not reveal abnormalities in the reproductive system or pituitary gland which could be treatment-related. The teratology component of the reproductive study found only sporadic abnormalities and no malformations in at the highest dosage level.

The lack of significant toxicologic findings in the subcutaneous route reproductive/developmental study with toldimfos up to at a dose level which corresponds roughly to an oral dose of 1 g/kg suggests that there is not a significant screening-level concern for reproductive/developmental toxicity with BPA.

A second set of information consistent with a low concern for reproductive/developmental toxicity with BPA was obtained by a computational toxicology approach. BPA, PPOA, and BPD were evaluated with the rule-based expert system DEREK (Version 7.0.0) for all alerts in bacteria and mammals. The only alert reported was for the endpoint irritation with BPD. An analysis with TOPKAT was considered but rejected because it does not appear to have adequate coverage of aryl phosphorous compounds.

No additional reproductive/developmental testing is recommended because: (1) toldimfos appears to be an appropriate structurally-related surrogate for BPA with acceptable existing data, (2) a computational toxicology assessment with DEREK did not generate alerts.

### **7.8. Mutagenicity**

BPD was tested in a GLP compliant bacterial mutation assay in *S. typhimurium* and *E. Coli*<sup>71</sup>. 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*<sup>60</sup>.

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 in an in-vitro chromosomal aberrations assay if there is an important difference in the profile of BPD and BPA in the bacterial mutagenesis assay.

## **8. Summary**

BPA will represent the category for new ecotoxicology and genetic toxicology studies. Data gaps in physiochemical properties will be filled by testing with BPA and BPD and calculation where appropriate. No additional mammalian testing is proposed because the endpoints are adequately met with information from BPA, PPOA, and toldimfos.

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