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**Final HPV Data Summary
For
Benzoyl Chloride
CAS No. 98-88-4**

August 15, 2005

Benzoates Panel
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

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Appendix: IUCLID Data Set for Benzoyl Chloride

1. Introduction

Arkema Inc. (fka ATOFINA Chemicals, Inc.), Lanxess Corp. (fka Bayer Chemicals LLC), and Velsicol Chemical Corporation formed a consortium under the American Chemistry Council (ACC) Benzoates Panel (Panel) to participate in the High Production Volume (HPV) Challenge Program for benzoyl chloride, (CAS 98-88-4). This substance is classified as a high production volume (HPV) chemical according to criteria established by the U.S. EPA.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted a thorough literature search for available data, published and unpublished, on benzoyl chloride (CAS 98-88-4). It has also performed an analysis of the adequacy of the existing data and with this revised submittal package is providing the IUCLID containing (robust) summaries and test plan.

Also in consideration of animal welfare concerns, the Panel has submitted surrogate data for the hydrolysis products of benzoyl chloride in lieu of recommending testing in the algae, repeated dose and reproductive/developmental categories because of the rapid hydrolysis of benzoyl chloride to benzoic acid and hydrochloric acid. In its review of the Panel's original submission on December 24, 2003, EPA had recommended this approach to the use of surrogate data, a suggestion welcomed by PETA in their comments on the original test plan.

2. Evaluation of SIDS endpoints

In this section, an evaluation of all located data available on SIDS endpoints is given.

The substance under consideration is an organic liquid. Because it is an acyl chloride, benzoyl chloride is very reactive towards water, alcohols and amines. In aqueous systems it is almost instantly converted to benzoic acid and hydrogen chloride; even at low pH, the half-life is less than 10 minutes.

2.1. Physico-chemical endpoints

Adequate data on melting point, boiling point, density and vapor pressure are available. Since the substance is a liquid, melting point is not a required endpoint. The partition coefficient and water solubility could not be measured because the substance reacts with water. The log K_{ow} was calculated with EPISuite, but the program indicated that the estimate was questionable due to the fact that acyl halides hydrolyse.

Conclusion: Physico-chemical endpoints have been fulfilled.

Benzoyl chloride CAS 98-88-4				
	Value	Comment	Klimisch Score#	Reference (See Appendix)
Melting point (°C)	-1		2	2-5
Boiling point (°C)	197.2		2	2,3,5
Density (g/cm ³)	1.21	at 20°C	2	2,6
Vapor pressure (hPa)	.5	at 20 °C	2	5-6
Partition coefficient (log K_{ow})	1.1	1,2-dichlorobenzene/water	2	7
Water solubility (mg/L)	N.A.	decomposition	2	4-5

N.A. = Not applicable

- Klimisch score 1 = Reliable without restriction, Klimisch score 2 = Reliable with restriction

2.2. Environmental fate

The half-life for reaction of benzoyl chloride with hydroxyl radicals in the atmosphere was estimated to be 2.1 days by EPA's Graphical Exposure Modelling System. Hydrolysis is very fast. Therefore, distribution of this substance over the different compartments is not applicable. The substance is expected to be partitioned to the water compartment and is expected to be hydrolysed before it can reach other compartments. The substance was degraded by 90% within 10 days as measured by biological oxygen demand. Therefore, the substance can be considered readily biodegradable.

Conclusion: Environmental fate endpoints have been fulfilled.

Benzoyl chloride CAS 98-88-4				
	Value	Comment	Klimisch Score#	Reference (See Appendix)
Photodegradation (t1/2)	2.1 days		2	10
Hydrolysis (t1/2)	16 sec	pH not mentioned	2	12-14
Distribution in water/air/soil/sediment	N.A.	see hydrolysis		
Ready biodegradability	90% in 10 d		2	15

N.A. = Not applicable

- Klimisch score 1 = Reliable without restriction, Klimisch score 2 = Reliable with restriction

2.3. Ecotoxicity

In a static 96-hour acute fish study with *Pimephales promelas* – predominantly performed according to OECD 203 - an LC50 of 34.1 mg/L was determined. The pH of the test solution at the end of the exposure period had dropped to 5.2 in fresh water, due to decomposition of benzoyl chloride to hydrogen chloride. The dissolved oxygen had decreased below the 60% level. A second static test with *Pimephales promelas* resulted in an LC50 of 34.7 mg/L. Two other static tests with *Brachydanio rerio* and *Leuciscus idus* resulted in an LC50 of 7.5 and 200 mg/L, respectively, but analytical monitoring of the system was not done. The overall weight of evidence results in an LC50 of ca. 34 mg/L.

For invertebrates, a static 96-h test with *Palaemonetes pugio* resulted in an LC50 of 180 mg/L. No algal inhibition data is available on benzoyl chloride. Due to the very quick hydrolysis in water of benzoyl chloride, algal inhibition data has been provided in the IUCLID for both primary hydrolysis products, hydrochloric acid (HCl) and benzoic acid (BenzA).

Conclusion: All ecotoxicity endpoints have been fulfilled. Surrogate data has been provided in lieu of the algal inhibition endpoint. No testing is recommended.

Benzoyl chloride CAS 98-88-4					
	Value	Species	Time of exposure (hr)	Klimisch Score#	Reference (See Appendix)
Acute fish (LC50, mg/L)	34.1	<i>Pimephales promelas</i>	96	2	16
Acute invertebrates (EC50, mg/L)	180	<i>Palaemonetes pugio</i>	96	2	16
Algal inhibition (EC50, mg/L)	*HCl=6	<i>Selenastrum</i>	96	2	33
	BenzA=75	<i>capricornutum</i>	3	2	43

* - Surrogate data on the primary hydrolysis products have been provided for this endpoint

- Klimisch score 2 = Reliable with restriction

2.4. Mammalian toxicity

2.4.1. Acute toxicity

In an acute oral study, 6 different doses from 1.0-5.0 ml/kg were administered to male Wistar rats (10 animals/dose). An LD50 of ca. 2,500 mg/kg bw was determined. All animals showed symptoms including sedation, extension spasm and reduced general condition. Macroscopic examination was not performed. Other non-guideline studies with similar values for the LD50 (1,900-2,618 mg/kg bw) are available.

Acute inhalation toxicity was evaluated in male and female Wistar rats exposed to concentrations of 0.19, 0.50, 0.71, 1.45 and 1.98 mg benzoyl chloride/L for 4 hours. At 1.45 and 1.98 mg/L, 5/10 and 6/10 males as well as 1/10 and 3/10 females died, respectively. Clinical signs included inactivity, piloerection, unkempt fur, and difficulties in breathing up to 19 days post exposure in all rats. Pathological examination of rats that died showed dark red colored lungs with emphysema; some rats showed lung edema. Surviving rats at the two highest exposure levels exhibited lung emphysema with mottled appearance; some showed enlarged adrenals. From the information available, it is concluded that the test is comparable to a guideline study (OECD 403). The LC50 for males and females is ca. 1.45 and >1.98 mg/L, respectively. Two more studies using shorter exposure periods confirmed that the LC50 >2 mg/L.

The LD50 for acute dermal toxicity was determined to be above the limit test value of 2000 mg/kg bw. In 2 male and 2 female rabbits were exposed to neat benzoyl chloride. All rabbits exhibited fissuring on the site of application. Benzoyl chloride is expected to react/hydrolyse directly on the site of application; therefore, only systemic effects of benzoic acid would be expected.

Conclusion: Acute toxicity endpoints have been fulfilled.

2.4.2. Genetic toxicity

The test substance was not mutagenic in the Bacterial Reverse Mutation Assay (Ames test) with *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 strains. Four other reverse mutation tests with *S. typhimurium* strains are available, one of which reported an ambiguous result and one a positive result. Three of four reverse mutation tests with *E. coli* strains were negative. A *Bacillus subtilis* recombination assay was also reported to be negative.

Benzoyl chloride was negative in an *in vivo* micronucleus assay in which 0 or 1750 mg/kg bw of benzoyl chloride was administered to mice by gavage. The study was performed under GLP following guideline OECD 474.

Conclusion: Genetic Toxicity endpoints have been fulfilled.

2.4.3. Repeated dose toxicity

Adequate data for repeated dose toxicity could not be located for benzoyl chloride. However, due to the rapid hydrolysis of benzoyl chloride, data for the hydrolysis products, benzoic acid and hydrogen chloride, was used to address this endpoint.

In a 28 day inhalation study on benzoic acid, Sprague Dawley rats were exposed 6hrs/day, 5 days/week to concentrations of 0, 25, 250 and 1200 mg/m³. The no observed adverse effect level (NOAEL) was determined to be 25 mg/m³ and the lowest observed adverse effect level (LOAEL) was 250mg/m³.

Ninety day inhalation studies of hydrogen chloride have been conducted on both rats and mice at concentrations of 10, 20 and 50 ppm for 6hrs/day, 5 days/week. In mice, microscopic inflammatory changes were observed in the lowest dose and therefore a NOAEL could not be determined. The LOAEL was 10 ppm. The systemic NOAEL was 10 ppm. Similar results were obtained from two separate strains of rats in which the LOAEL was determined to be 50 ppm.

Conclusion: The repeated dose toxicity endpoint has been satisfied through the use of surrogate data for the hydrolysis products.

2.4.4. Reproductive/developmental toxicity

Adequate data on reproductive and developmental toxicity could not be located for benzoyl chloride. Due to the rapid hydrolysis of benzoyl chloride, data have been submitted for the hydrolysis products, benzoic acid and hydrogen chloride.

In 90 day inhalation studies in mice and rats exposed to hydrogen chloride at 10, 20 and 50 ppm 6hours/day, 5days/week, there were no exposure related changes observed in the reproductive organs when examined histologically. As presented at OECD SIAM 13 in 2001, no reliable studies have indicated toxicity to reproduction and the development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. Orally administered hydrochloric acid did not cause developmental toxicity to laboratory animals; thus hydrogen chloride is not expected to have developmental toxicity.

A four generation feeding study conducted on benzoic acid in rats fed a diet including 0.5 or 1% of the test substance demonstrated no effects on the dams or on the growth and development of the offspring. For maternal toxicity, the NOAEL was greater than 750 mg/kg bw and the NOAEL for teratogenicity was 750 mg/kg bw. There was no influence on growth or organ weights, no effects on fertility and no remarkable histopathological findings.

Conclusion: The reproductive/developmental toxicity endpoint has been satisfied through the use

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of surrogate data for the hydrolysis products, hydrochloric acid and benzoic acid, of benzoyl chloride.

Conclusion (mammalian toxicity): Acute toxicity and genetic toxicity endpoints have been fulfilled. The repeated dose, reproductive and developmental toxicity endpoints have been adequately addressed through data on the hydrolysis products.

Benzoyl chloride CAS 98-88-4				
	Value	Species	Klimisch Score#	Reference (See Appendix)
<i>Acute toxicity</i>				
Acute oral (LD50, mg/kg)	ca. 2500	Wistar rat	2	4, 20, 21
Acute dermal (LD50, mg/kg)	>2000	New Zealand white rabbit	2	22
Acute inhalation (LC50, mg/m ³)	ca. 1.45	Wistar rat	2	25
<i>Genetic toxicity</i>				
<i>in vitro</i> gene mutation (Ames test)	negative	S. typhimurium TA98, TA100, TA1535 and TA1537	1	30
<i>in vivo</i> (micronucleus)	negative	mouse	1	37
Repeated Dose NOAL, ppm	*HCl 50	Rat and mouse	2	14,28
Repro/developmental toxicity, NOAEL, mg/kg	*Benz Acid 750	Rats	2	27

* - Surrogate data provided for hydrolysis products (HCl = hydrochloric acid, Benz Acid = benzoic acid).

- Klimisch score 1 = Reliable without restriction, Klimisch score 2 = Reliable with restriction

2.5. Data matrix

A table with all data available on SIDS endpoints is presented below.

Benzoyl chloride CAS 98-88-4				
	Value	Comment/Species	Klimisch Score#	Reference (See Appendix)
Physicochemical properties				
Melting point (°C)	-1		2	2-5
Boiling point (°C)	197.2		2	2,3,5
Density (g/cm ³)	1.21	at 20°C	2	2,6
Vapor pressure (hPa)	.5	at 20 °C	2	5-6
Partition coefficient (log K _{ow})	1.1	1,2-dichlorobenzene/water	2	7
Water solubility (mg/L)	N.A.	decomposition	2	4-5
Environmental fate				
Photodegradation (t1/2)	2.1 days		2	10
Hydrolysis (t1/2)	16 sec	pH not mentioned	2	12-14
Distribution in water/air/soil/sediment	N.A.	see hydrolysis		
Ready biodegradability	90% in 10 d		2	15
Ecotoxicity				
Acute fish (96-h LC50, mg/L)	34.1	<i>Pimephales promelas</i>	2	16
Acute invertebrates (96-h EC50, mg/L)	180	<i>Palaemonetes pugio</i>	2	16
Algal inhibition (EC50, mg/L)	*HCl 6, BenzAcid 75	<i>Selenastrum capricornutum</i>	2	33,43
Mammalian toxicity				
Acute toxicity				
Acute oral (LD50, mg/kg)	ca. 2500	Wistar rat	2	4, 20, 21
Acute dermal (LD50, mg/kg)	>2000	New Zealand white rabbit	2	22
Acute inhalation (LC50, mg/m ³)	ca. 1.45	Wistar rat	2	25
Genetic toxicity				
<i>in vitro</i> gene mutation (Ames test)	negative	<i>S. typhimurium</i> TA98, TA100, TA1535 and TA1537	1	30
Chromosomal aberration				
<i>in vivo</i> (micronucleus)	negative	mouse	1	37
Repeated Dose (NOAL, ppm)	*HCl 50	Rat and mouse	2	14,28
Repro/developmental toxicity (NOAEL, mg/kg)	*Benzoic Acid 750	Rat	2	27

N.A. = Not applicable

* - Surrogate data provided for hydrolysis products

- Klimisch score 1 = Reliable without restriction, Klimisch score 2 = Reliable with restriction

3. Data availability –Complete, no testing proposed

The availability of data is depicted in the following table.

	Benzoyl chloride CAS 98-88-4
Physico-chemical	
Melting point	+
Boiling point	+
Density	+
Vapor Pressure	+
Partition Coefficient	N.A.
Water Solubility	N.A.
Environmental Fate	
Photodegradation	+
Hydrolysis	+
Distribution in compartments	N.A.
Ready Biodegradability	+
Ecotoxicity	
96-h LC50 Fish	+
48-h EC50 Daphnia	+
72-h EC50 Algal Inhibition	++
Mammalian toxicity	
Acute toxicity	+
Repeated Dose Toxicity	+
Genetic Toxicity	+
Reproductive/Developmental Toxicity	++

+ = data available

++ Data for hydrolysis products provided in lieu of additional testing

N.A. = not applicable

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APPENDIX

IUCLID Data Set for Benzoyl Chloride