BASF Corporation

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201-15012

December 30, 2003

Michael Leavitt
Administrator
U. S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Subject: Chemical Right-to-Know Program: Electronic Submission of Documents (CAS No. 68915-38-8) to oppt.ncic@epa.gov and chem.rtk@epa.gov

Dear Administrator Leavitt:

BASF Corporation is submitting the attached test plan and robust summaries for cyclohexane, oxidized, aq. ext. (68915-38-8) under the U.S. Environmental Protection Agency High Production Volume (HPV) Challenge Program. These documents are being submitted in electronic format (Adobe Acrobat pdf files). If you require additional information or have problems with the electronic format, please contact me via the information below

Sincerely,

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Attachments : Test Plan (68915-38-8_TP.pdf)
Robust Summaries (68915-38-8_RS.pdf)

cc: H. Perryman, BASF Corporation
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C. Priester, BASF AG

Cyclohexane, Oxidized, Aq. Ext.

CAS Number 68915-38-8

201-15012B

A Mixture Also Know as:

- EP-306 Acid Water
- COP Acid Water
- Dicarboxylic Acid Solution
- Dicarbonsaeure Loesung A Ber. Trocken
- Dicarbonsaeure Loesung L Ber. Trocken
- Abstreifsaeure

U.S. EPA HPV Challenge Program Submission

December 30, 2003

Prepared by:

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Executive Summary

EP-306 is an aqueous mixture of monocarboxylic acids (C1 – C6), dicarboxylic acids (C4-C6), 6-hydroxycaproic acid, esters of alcoholic and acidic components, and trace amounts of oxidized cyclohexane, which is produced as a site-limited intermediate in the purification of cyclohexanone. During the purification process, the oxidized cyclohexane stream is washed with water to remove the soluble components described above. The water wash is then concentrated to form EP-306. EP-306 is stored on-site and, due to its high content of adipic acid and 6-hydroxycaproic acid, used as a feed stock for the on-site manufacture of 1,6-hexanediol. Any material not used is disposed of on-site via deep well injection. Annual production ranges between 50 and 75 million pounds. Due to its use only on-site, potential human exposures are limited to site personnel who may contact the product during manufacturing upsets and routine diagnostic checks.

The physical-chemical properties of EP-306 encompass those of its components. At 20 °C, EP-306 is a liquid / solid slurry with a low vapor pressure. Its components are expected to partition to water in the environment, where they are both soluble and stable with little potential for bioaccumulation due to their relatively low log $K_{o/w}$ values (-0.6 to 2). EP-306 is biodegradable in a wastewater treatment facility. The photochemical half-lives of the major EP-306 components, adipic acid and 6-hydroxycaproic acid, in air are 1 – 2 days, although several minor components have half-lives of about 20 days. Fish, *daphnids*, and algae are acutely affected by EP-306 with LC_{50} / EC_{50} values of 220 – 460 mg/l, > 100 mg/l and 27 -35 mg/l, respectively. Data in fish indicate that these effects may be due to changes in pH, rather than the intrinsic toxicity of EP-306 components themselves.

EP-306 or major components exhibit low acute toxicity by all three routes of potential exposure with LD_{50} / LC_{50} values of: > 5000 mg/kg (oral, EP-306), > 7940 mg/kg (dermal, adipic acid), and > 7.7 mg/l (inhalation, adipic acid). *In vitro* data for EP-306 and *in vivo* data on major components indicate that EP-306 is neither mutagenic nor clastogenic. Chronic toxicity data are not available for EP-306 itself. However, data sufficient to meet these needs are available for adipic acid, the major component of EP-306. Adipic acid data can also be used as a surrogate for 6-hydroxycaproic acid, the second most prevalent component in EP-306, as 6-hydroxycaproic acid will be metabolically converted to adipic acid once absorbed into the body. As these two chemicals are the most prevalent components in EP-306, it is likely that they also constitute a major fraction of the unidentified esters in EP-306. In the body, the EP-306 esters would be hydrolyzed by carboxyesterases to their alcoholic and acidic components. Thus, the total fraction of these two chemicals in EP-306 constitutes approximately 90 % of the organic components in EP-306. In a two-year rat feeding study, adipic acid exhibited a NOAEL of ~ 500 mg/kg; 4-fold greater doses affected only food consumption and body weight gain. Male and female reproductive organs were not affected at any dose. In a developmental study, rats were gavaged with adipic acid. No effects were observed on maternal or fetal survival, reproductive outcomes, embryotoxicity, or teratogenicity at the highest dose tested (288 mg/kg). These data are sufficient to assess the repeated-dose, reproductive and developmental hazards posed by EP-306, particularly given its use as a site-limited intermediate.

Based on the available information, no further testing is recommended for EP-306.

Testing Plan and Rationale

CAS # 68915-38-8 EP-306	Information Available?	OECD Study ?	GLP Study?	Supporting Information?	Estimation Method?	Acceptable?	Testing Recommended?	
HPV Endpoint								
Physical Chemical								
Melting Point	Y	N	N	N	N	Y	N	
Boiling Point	Y	N	N	N	N	Y	N	
Vapor Pressure	Y	N	N	Y	Y	Y	N	
Partition Coefficient	Y	N	N	Y	Y	Y	N	
Water Solubility	Y	N	N	Y	Y	Y	N	
Environmental & Fate								
Photo-Degradation	Y	N	N	Y	Y	Y	N	
Water Stability	Y	N	N	Y	N	Y	N	
Transport	Y	N	N	Y	Y	Y	N	
Biodegradation	Y	Y	Y	Y	Y	Y	N	
Ecotoxicity								
96-Hour Fish	Y	N	N	Y	N	Y	N	
48-Hour Invertebrate	Y	Y	Y	Y	N	Y	N	
96-Hour Algae	Y	N	N	Y	N	Y	N	
Toxicity								
Acute	Y	N	N	Y	N	Y	N	
Genetic Toxicology *in vitro*	Y	Y	Y	Y	N	Y	N	
Genetic Toxicology *in vivo*	Y	N	N	Y	N	Y	N	
Repeated Dose	Y	N	N	Y	N	Y	N	
Reproductive	Y	N	N	Y	N	Y	N	
Developmental	Y	N	N	Y	N	Y	N	

1.0 Introduction

The aqueous extract of oxidized cyclohexane (designated EP-306 by BASF Corporation)(CAS No. 68915-38-8) is a yellow-colored intermediate produced during the production and purification of cyclohexanone. Cyclohexanone is produced via the cyclohexane oxidation route for the manufacture of caprolactam. By-products formed during this oxidation process must be removed as part of the overall purification of cyclohexanone. Purification is accomplished in part via a water wash to remove most of the soluble mono and dicarboxylic acids from the oxidized cyclohexane stream. The water wash is then concentrated to form EP-306. As indicated in Table 1, the primary components of EP-306 are water (~ 50 %), adipic acid (~ 18 %) and 6-hydroxy caproic acid (~ 12 %). EP-306 is transported via pipeline to large on-site storage tanks. From here, it is transported via pipeline as a raw material feed stock for the on-site manufacture of 1,6-hexanediol. The two primary organic components are separated from EP-306 during this process. Seventy percent of EP-306 is used for the manufacture of 1,6-hexanediuol; the remainder is sent to an on-site deep well facility for disposal. The annual production of EP-306 ranges between 50 and 75 million pounds. Since EP-306 is an intermediate that is made, stored and consumed on-site, potential human exposures are limited to operational personnel who may contact EP-306 during either manufacturing upsets or system sampling for quality and routine diagnostic checks.

Table 1. Typical Composition of EP-306

EP-306 Component	Weight %
Formic Acid	1 – 3
Acetic Acid	0.05 - 0.3
Propionic Acid	0.05 – 0.3
Butyric Acid	0.2 – 0.6
Valeric Acid	0.2 – 0.6
Caproic Acid	0.05 - 0.1
Succinic Acid	0.3 – 1
Glutaric Acid	1 – 2
Adipic Acid	**12 – 24**
6-Hydroxycaproic Acid	**10 – 14**
Cyclohexanol	0.1 – 0.4
Cyclohexanone	0.05 – 0.2
Cyclohexyl Hydroperoxide	0.1 – 0.2
Other*	5 – 10
Water	**40 – 60**

* Primarily esters of 6-hydroxycaproic acid and acidic components

Information and study results on EP-306 as well as surrogate chemicals (adipic acid and a dicarboxylic acid mixture) are briefly reviewed in this rationale document to indicate how they meet the Screening Information Data Set (SIDS) endpoints of the United States Environmental Protection Agency (USEPA) High Production Volume (HPV) Challenge program. Robust summaries of studies on EP-306 are attached to this document; robust summaries and/or information for EP-306 surrogates are referenced at the end of this document.

2.0 Physical-chemical Data

Physical-chemical data for EP-306 are available from the manufacturer and are summarized in Table 2.

Table 2. Physical-chemical Properties of EP-306

Melting Point	-6 to 45 ˚C (1,2)
Boiling Point	101 °C @ 1013 hPa (2)*
Vapor Pressure	77 hPa @ 40 ˚C (2)*
Partition Coefficient	Log $K_{o/w}$ = -0.59 to 1.92 (3,4)
Water Solubility	Miscible (2, 4)

* Initial Value

The data indicate that EP-306 is a liquid/solid mixture at room temperature. The mixture begins to boil at a temperature slightly higher than that of water. The upper end of the boiling point range is anticipated to be ~ 338 ˚C, the boiling point for adipic acid, the known EP-306 component with the highest boiling point (3). The initial vapor pressure for EP-306 is slightly higher than that of water, likely due to the presence of formic acid, the only EP-306 component with a vapor pressure greater than that of water (3). As the mixture evaporates and loses the more volatile components, the vapor pressure will decrease and eventually approach ~ 4×10^{-7} hPa, the vapor pressure of adipic acid, the least volatile known component of EP-306 (3).

Table 3. Log $K_{o/w}$ and Water Solubility of Known EP-306 Components

EP-306 Component	Log Ko/w (4,5)	Water Solubility (5) (mg/l)
Formic Acid	-0.54 (exp)	955,000 (cal)
Acetic Acid	-0.17 (exp)	476,000 (cal)
Propionic Acid	0.33 (exp)	174,000 (cal)
Butyric Acid	0.79 (exp)	66,100 (cal)
Valeric Acid	1.39 (exp)	18,600 (cal)
Caproic Acid	1.92 (exp)	5,900 (cal)
Succinic Acid	-0.59 (exp)	808,000 (cal)
Glutaric Acid	-0.29 (exp)	396,000 (cal)
Adipic Acid	**0.08 (exp)**	**167,000 (cal)**
6-Hydroxycaproic Acid	**0.59 (cal)**	**229,000 (cal)**
Cyclohexanol	1.23 (exp)	33,700 (cal)
Cyclohexanone	0.81 (exp)	24,100 (cal)
Cyclohexyl Hydroperoxide	1.85 (cal)	2,750 (cal)

(exp), experimental value; (cal), calculated value

A single octanol-water partition coefficient is inappropriate for a mixture with components of varying hydrophilicities. To understand the potential distribution and bioaccumulative properties of EP-306, individual components must be taken into consideration. Table 3 contains the experimental and calculated log Ko/w values listed in EPI Suite (4,5). The range of Log Ko/w values suggests that EP-306 has little potential for bioaccumulation. All EP-306 components are soluble in water, with solubilities at 25 ˚C ranging from 2,700 mg/l (cyclohexyl hydroperoxide) to 955,000 mg/l (formic acid)(5).

Recommendation: No additional physical-chemical studies are recommended. The available data fill the HPV required data elements with sufficient precision to define potential hazards of this mixture.

3.0 Environmental Fate and Pathways

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program (AOP) Program that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals (6). The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The approach used was to take the components of EP-306 and individually determine their reactivity with hydroxyl radical assuming each component will be unaffected by the others after vaporization into the troposphere. Using the default atmospheric hydroxyl radical concentration in AOP program and the range of estimated rate constants of major components of EP-306 for reaction with hydroxyl radical, the estimated half-life of EP-306 components in air is approximately 1 to 20 days. Table 4 below provides a summary of the results.

Table 4. Half-Life of Known EP-306 Components

EP-306 Component	Half-Life (6) (Days)
Formic Acid	20.6
Acetic Acid	17.2
Propionic Acid	7.71
Butyric Acid	3.96
Valeric Acid	2.60
Caproic Acid	1.94
Succinic Acid	3.87
Glutaric Acid	2.56
Adipic Acid	**1.91**
6-Hydroxycaproic Acid	**1.09**
Cyclohexanol	0.61
Cyclohexanone	0.88
Cyclohexyl Hydroperoxide	0.76

Theoretical Distribution (Fugacity) of EP-306 in the environment was estimated using the MacKay EQC level III model with standard defaults in EPI Suite (v 3.10) using 100% release to water as the means of entry into the environment (7). The approach used was to estimate the fugacity of each EP-306 component assuming that one component will not greatly affect the distribution of the other. It is apparent that the major components distribute almost exclusively to water. Although the hydrolytic stability of EP-306 in water has not been tested, carboxylic acids, alcohols and ketones are organic functional groups that are known to be generally resistant to hydrolysis and therefore are considered to have an estimated half-life in water of more than 1 year (8). The only component that may be lost to the hydrolytic process in water is cyclohexyl hydroperoxide. Although organic hydroperoxides are typically stable in pure water, they can be reduced to the alcohol in the presence of oxidizable substrates and metal ions.

The biodegradability of EP-306 was measured under GLP conditions in a carbon dioxide evolution test (OECD 301 B). Results indicated that EP-306 is biodegradable as 70 % to 80 % of the theoretical carbon dioxide production occurred after 28 days (9). These results are consistent with the ready biodegradability measured for adipic acid (10), the major component of EP-306. In addition, BIOWIN (v4.00) modeled results for each component of EP-306 indicates that all are rapidly degradable (11).

Table 5. Theoretical Distribution (Fugacity) of EP-306 Components in the Environment

EP-306 Component	Percent Distribution (7)			
	Air	**Water**	**Soil**	**Sediment**
Formic Acid	0.006	99.8	0.021	0.15
Acetic Acid	0.003	99.8	0.015	0.15
Propionic Acid	0.023	99.8	0.029	0.15
Butyric Acid	0.025	99.8	0.027	0.16
Valeric Acid	0.018	99.8	0.023	0.18
Caproic Acid	0.027	99.7	0.024	0.23
Succinic Acid	<0.001	99.9	<0.001	0.15
Glutaric Acid	<0.001	99.9	<0.001	0.15
Adipic Acid	<0.001	99.8	<0.001	0.15
6-Hydroxycaproic Acid	<0.001	99.8	<0.001	0.15
Cyclohexanol	0.076	99.7	0.016	0.19
Cyclohexanone	0.315	99.5	0.032	0.18
Cyclohexyl Hydroperoxide	0.248	99.5	0.023	0.26

Recommendation: No additional fate and pathway studies are recommended. The available data fill the HPV required data elements.

4.0 Ecotoxicity

4.1 Toxicity to Fish

Overall, the measured results with EP-306, adipic acid (the major component of EP-306), as well as a mixture of C4 to C6 dicarboxylic acids indicate that EP-306 has a low acute ecotoxicity (Table 6). At 96 hours, the LC_0 and the no observed effect concentration (NOEC) for EP-306 were 215 mg/l; the next two higher concentrations (464 mg/l and 1000 mg/l) caused 100% mortality within 48 hours and 4 hours, respectively (12). In a parallel portion of this study, no mortality was observed at 96 hours when the pH of the EP-306 test solution (1,000 mg/l) was adjusted to 7.3. This study closely followed the OECD 203 guideline with the exception of the recommended fish species. These results are supported by LC_{50} studies with EP-306 surrogates: undiluted adipic acid in the fathead minnow (97 mg/l)(13) and a dilute dicarboxylic acid mixture in the Rainbow trout (240 mg/l)(14) and Bluegill sunfish (340 mg/l)(15).

Table 6. Measured Aquatic Toxicity of EP-306 and Surrogate Chemicals

Endpoint	EP-306	Adipic Acid	C4 to C6 Dicarboxylic Acid Mixture
Fish, 96-hr LC_{50}	220-460 mg/l (12)	97 mg/l (13)	240 - 340 mg/l (14, 15)*
Daphnia, 48-hr EC_{50}	> 100 mg/l (16)	85.7 mg/L (17)	> 1,000 mg/L (18)*
Algae, 96-hr EC_{50}	No Data	26.6 mg/l (19)	35 mg/l (20)

*Containing: glutaric acid (16.43%), succinic acid (4.77%), adipic acid (3.9%), nitric acid (3.9%), and water (71%)

4.2 Toxicity to Aquatic Invertebrates

Aquatic invertebrate toxicity was examined in studies with *Daphnia magna*. In a GLP study by BASF following the OECD 202 protocol, the 48-hr EC_0 and EC_{50} were > 100 mg/l (16). As with fish, these results are consistent with 48-hr EC_{50} values obtained with EP-306 surrogates: undiluted adipic acid (85.7 mg/l)(17) and a dilute dicarboxylic acid solution (> 1,000 mg/l)(18). In the BASF study, analytical measurements of the test solutions were performed at the start (0 hr) and end (48 hr) of the test by quantification the 6-hydroxycaproic acid peak. At 0 hr, the analytical concentrations closely approximated the nominal concentrations. However, at 48 hr, the analytical concentrations were about 20% to 45% higher than expected, perhaps reflecting hydrolytic cleavage of the unspecified esters in EP-306 to 6-hydroxycaproic acid and one of the component acids.

4.3 Toxicity to Aquatic Plants

The toxicity of EP-306 to aquatic plants has not been evaluated. Data, however, are available on EP-306 components and surrogates. Adipic acid (purity unspecified)(19) and a mixture of C4 to C6 dicarboxylic acids (purity unspecified) were tested for their ability to inhibit the growth *of Scenedesmus subspicatus*; the 96-hr EC_{50} values were 26.6 mg/l (19) and 35 mg/l (20), respectively. Other support for the low level of toxicity comes from modeling. The EPI Suites ECOSAR model estimates the 96-hr EC_{50} values for adipic acid and 6-hydroxycaproic acid to be > 26,000 mg/l and > 11,000 mg/l, respectively (21). The difference in EC_{50} values between experimental and modeled data may be due in part to an effect of pH.

Recommendation: No additional ecotoxicity studies are recommended. The available information fills the HPV required data elements.

5.0 Acute Mammalian Toxicity

5.1 Oral Toxicity

The oral LD_{50} of EP-306 was determined to be greater than 5,000 mg/kg in Wistar rats (22). Rats (five males and 5 females) were gavaged with one of four doses ranging from 681 mg/kg to 5,000 mg/kg. The NOEC was 681 mg/kg. Symptoms of exposure included: apathy, dyspnea, staggered and spastic gait, piloerection, and a poor general state. Three of 10 rats died at 5,000 mg/kg; animals dying on study exhibited general congestion, emaciation, empty and distended gastrointestinal tract, and mucosal inflammation of the glandular stomach. No pathologic findings were observed in the survivors. These results are supported by oral LD_{50} studies of EP-306 components and surrogates: dosed as a 20% adipic acid solution in corn oil (5,050 mg/kg)(23) and a C4 to C6 dicarboxylic acid mixture (composition and purity not specified)(6,629 mg/kg)(24).

Table 7. Acute Toxicity of EP-306 and Surrogate Chemicals

Endpoint	EP-306	Adipic Acid	C4 to C6 Dicarboxylic Acid Mixture
Oral LD_{50} (rat)	> 5,000 mg/kg (22)	5,050 mg/kg (23)	6,829 mg/kg (24)*
Dermal LD_{50} (rabbit)	No Data	> 7,940 mg/kg (25)	> 7,940 mg/kg (26)
Inhalation LC_{50} (rat)	No Data	> 7.7 mg/l (27)	No Data

*Containing: glutaric acid (60%), succinic acid (25%), and adipic acid (15%)

5.2 Dermal Toxicity

Although no acute dermal studies with EP-306 have been performed, studies exist for component and surrogate chemicals. The dermal LD_{50} of adipic acid and a C4 to C6 dicarboxylic acid mixture in rabbits were both determined to be greater than 7,940 mg/kg (25, 26). In both studies, the test material was administered for 24 hr under occluded conditions to groups of one (low dose) or two (high dose) male/female rabbits. During the 14-day post-dosing observation period, symptoms of exposure included loss of appetite and inactivity. The viscera were not affected, and no deaths occurred. Although group sizes are less than optimal, the relatively high doses administered as well as the relatively low dermal bioavailability anticipated for dilute EP-306 components suggest that the available data adequately address the acute dermal hazard posed by EP-306.

5.3 Inhalation Toxicity

A four-hour LC_{50} for adipic acid (99.8% purity) was measured in Sprague-Dawley rats (27). In this study, groups of 10 male and 10 female rats received nose-only exposures to adipic acid dust (MMAD 50% of 3.5 μm) at analytically measured concentrations of 5.4 mg/l and 7.7 mg/l for 4 hours and were observed for 14 days post-exposure. No clinical findings or mortalities were observed at either exposure concentration. As the recommended (OECD 403) limit–dose for respirable materials is 5 mg/l, this study of adipic acid is considered an adequate test for the acute inhalation toxicity of EP-306.

Recommendation: No additional acute toxicity studies are recommended. The available data fill the HPV required endpoints for acute toxicity. The weight of evidence shows that EP-306 exhibits low acute toxicity by all routes of exposure, particularly dermal exposure, the route most likely to be involved in human exposures under current use / manufacturing conditions.

6.0 Mammalian Genotoxicity

The SIDS/HPV requirement for genetic toxicity screening includes two end-points, one sensitive to point mutations and one sensitive to chromosomal aberrations. For EP-306, these requirements are fulfilled by multiple studies on either EP-306 itself or surrogate chemicals (Table 8).

6.1 Genotoxicity *in vitro*

The mutagenic potential of EP-306 was evaluated under GLP conditions in a *Salmonella typhimurium* (OECD 471) and *Escherichia coli* (OECD 472) reverse mutation assay using the standard plate and preincubation tests (28). Four strains of *S. typhimurium* (TA 98, TA 100, TA 1535, TA 1537) and *E. coli* WP2 uvrA were exposed with and without S-9 activation to five doses of EP-306 ranging from 40 μg/plate to 10,000 μg/plate. No mutagenic response was observed. In both the standard plate and preincubation tests, a bacteriotoxic effect was observed in some strains at doses ≥ 5,000 μg/plate. These results are supported by two standard plate incorporation assays with EP-306 surrogates. In the first, five strains of *S. typhimurium* (TA 98, TA 100, TA 1535, TA 1537, TA 1538) and *E. coli* WP2 uvrA were exposed with and without S-9 activation to five doses of adipic acid (purity unspecified) ranging from 33 μg/plate to 10,000 μg/plate (29). In the second, five strains of *S. typhimurium* (TA 98, TA 100, TA 1535, TA 1537, TA 1538) were exposed under GLP conditions with and without S-9 activation to five doses of C4 to C6 dicarboxylic acid mixture ranging from 30 μg/plate to 3,000 μg/plate (30). No mutagenic response was observed in either study. In a pretest, cytotoxicity was observed with the dicarboxylic acid mixture at a dose of 5,000 μg/plate.

Table 8. Genetic Toxicity of EP-306 and Surrogate Chemicals

Endpoint	EP-306	Adipic Acid	C4 to C6 Dicarboxylic Acid Mixture
Mutagenic?	No Ames Assay (28)	No Ames Assay (29)	No Ames Assay (30)*
Clastogenic?	No Data	No *In vivo* Cytogenetic Assay (31) Dominant Lethal Assay (32)	No *In vivo* Cytogenetic Assay (33)**

*Containing: glutaric acid (30-35%), succinic acid (9-11%), adipic acid (6-9%), nitric acid (0.5-3%), and water (42-54.5%)
**Containing: glutaric acid (28.8%), succinic acid (12.7%), adipic acid (7.9%), nitric acid (1.8%), and water (48.8%)

6.2 Genotoxicity *in vivo*

The clastogenic potential of EP-306 was evaluated using results of studies performed with surrogate chemicals. In the acute portion of an *in vivo* cytogenetic assay in rats, male rats (15/group) received a single dose of adipic acid at one of four doses ranging from 3.75 mg/kg to 5000 mg/kg and were killed at 6 hours, 24 hours and 48 hours post-exposure (31). In the subacute portion of the study, male rats (5/group) were exposed once daily for five days to four doses of adipic acid ranging from 3.75 mg/kg to 2,500 mg/kg; rats were killed 6 hours after the last dose. Fifty metaphase bone marrow cells/animal were evaluated for chromosomal aberrations. Results of both procedures were negative, although a few aberrations within the historical control range were noted in the middle two doses of the subacute study. In a dominant lethal assay (32), rats were exposed to adipic acid using the same acute / subacute procedure and doses previously described. Males were then mated with two virgin females each week for either 8 (acute study) or 7 (subacute study) consecutive weeks. Females were killed and examined for evidence of implantations fourteen days after separation from the males. Although significant differences (decreased implantations, decreased corpora lutea, increased preimplantaion loss) were occasionally observed between the control and experimental groups at the lower two doses, adipic acid was judged not to produce dominant lethal changes as the observed effects revealed no dose-response or time-trend response.

The results with adipic acid are supported by a GLP *in vivo* cytogenetic assay of a C4 to C6 carboxylic acid mixture in rats (33). Male (2750 mg/kg) and female (1375 mg/kg) rats received a single dose of a C4 to C6 carboxylic acid mixture and were killed 6 hours (8 males/5 females), 18 hours (5 of each sex) and 30 hours (5 of each sex) post-exposure. Fifty metaphase bone marrow cells/animal were evaluated for chromosomal aberrations. Results were negative despite achieving / exceeding of the maximum tolerated dose as evidenced by toxic signs in both sexes (e.g., inactivity, decreased body tone, piloerection, vocalization at touch) and the death of 3 of 18 males.

Recommendation: No additional testing is recommended as the SIDS requirements are met by the battery of *in vitro* and *in vivo* studies on EP-306 and surrogate chemicals that are sensitive to both mutagenic and clastogenic events. The data indicate EP-306 has a low genotoxic potential.

7.0 Long-Term Mammalian Toxicity

As indicated in the Introduction, EP-306 is a site limited intermediate with limited potential for exposure. As such, testing for repeated dose toxicity and reproductive toxicity are not required under the US HPV Challenge program (34). However, sufficient chronic toxicity data are available on adipic acid, the major component of EP-306 to meet the requirements for a non site limited material. These data can also be used as a surrogate for 6-hydroxycaproic acid, the second most prevalent component in EP-306, as 6-hydroxycaproic acid will be metabolically converted to adipic acid once absorbed into the body. As these two chemicals are the most prevalent components in EP-306, it is likely that they also constitute a major fraction of the unidentified esters in EP-306. In the body, the EP-306 esters would be hydrolyzed by carboxyesterases to their alcoholic and acidic components. Thus, the total fraction of these two chemicals in EP-306 is thought to comprise approximately 90% of all organic components in EP-306. On this basis, toxicity data on adipic acid can serve as an appropriate reference for the chronic hazard posed by EP-306. Data on adipic acid are presented below.

7.1 Repeated Dose and Reproductive Toxicity

In a two-year chronic feeding study (35), male and female rats were exposed to adipic acid in the diet at concentrations of: 0%, 0.1%, 1%, 3%, and 5% (males) and 0% and 1% (females). The average daily consumption of adipic acid over the study period was: 16.9 mg, 175 mg, 506 mg, and 814 mg per rat for the four dose groups. Assuming an average rat body weight of 0.35 kg, these consumption values correspond to adipic acid doses of 48 mg/kg-day, 500 mg/kg-day, 1450 mg/kg-day, and 2330 mg/kg-day. In males, the percent survival of each test group was greater than that of the control group. Body weights and food consumption in the two highest dose groups were significantly less than the control group. No differences were observed in tumor incidence, clinical signs, weights of ten unspecified organs, or in gross and microscopic histopathology of 15 unspecified organs. Clinical chemistry and hematology data were not reported. The same endpoints were evaluated in females, except that tissue weights were limited to four unspecified organs. No significant differences were observed between the experimental and control groups. These data indicate that the No Observed Adverse Effect Level (NOAEL) for adipic acid is approximately 500 mg/kg-day with 4-fold greater doses associated with effects on only food consumption and body weight gain.

There are no guideline studies on the reproductive toxicity of adipic acid. However, the SIDS Manual (36) indicates that the reproductive endpoint can be addressed when a 90-day repeated dose study demonstrates no effect on the reproductive organs and data from a developmental toxicity study are available. The study discussed above did not detect toxicity to the reproductive tissues evaluated: testes (weights and histpathology), ovaries (histopathology), and uterus (histopathology). This information, combined with the developmental toxicity data described below, indicate that adipic acid / EP-306 does not pose a significant reproductive hazard.

Recommendation: No additional testing is recommended, as the available data are sufficient to assess the repeated dose toxicity and reproductive organ pathology of EP-306.

7.2 Developmental Toxicity

Pregnant rats (24-25 per group) were exposed to adipic acid by gavage on days 6-15 of gestation at one of four doses ranging from 2.9 mg/kg to 288 mg/kg (38). On day 20, the dams were killed and the number of implantation and resorption sites as well as live and dead fetuses were recorded. All fetuses were examined for external congenital abnormalities; lives fetuses were weighed. Visceral and skeletal examinations of the fetuses were also performed. No effects were observed on: maternal or fetal survival, reproductive outcomes, embryotoxicity, or teratogenicity. The maternal and developmental NOAELs in the rat were determined to be > 288 mg/kg. In another developmental toxicity study (39), pregnant rabbits (13-20 per group) were exposed to adipic acid by gavage on days 6-18 of gestation at one of four doses ranging from 2.5 mg/kg to 250 mg/kg. The maternal and fetal endpoints examined were comparable to those discussed above in the rat. No effects were observed on: maternal or fetal survival, reproductive outcomes, embryotoxicity, or teratogenicity. The maternal and developmental NOAELs in the rabbit were determined to be > 250 mg/kg. Although maternal toxicity was not demonstrated in these developmental toxicity studies, it should be taken into consideration that adipic acid is regulated by the FDA as GRAS (generally recognized as safe) and is a permitted direct food additive (at levels as high as 1.3% for some food items) considered suitable for all segments of the population, including pregnant females (39).

Recommendation: No additional developmental toxicity testing is required as the available data are sufficient to assess the developmental hazard posed by EP-306.

8.0 Conclusions

It is concluded that the available information on EP-306 fills the data requirements for all endpoints specified in the EPA HPV Challenge program: physical-chemical parameters, environmental fate, aquatic toxicity and mammalian toxicity. Although the available studies do not meet all the requirements of the current OECD guidelines, taken together the information provided a reliable hazard assessment, particularly given the use of EP-306 as a site-limited intermediate. On this basis, further testing is not recommended.

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10.0 ROBUST SUMMARIES

[SEE IUCLID DATA SET: EP-306]

201-15012B

I U C L I D
Data Set

EP-306

Existing Chemical	:	ID: 68915-38-8
CAS No.	:	68915-38-8
TSCA Name	:	Cyclohexane, oxidized, aq. ext.

Producer related part

Company	:	BASF Corporation
Creation date	:	12.12.2003

Substance related part

Company	:	BASF Corporation
Creation date	:	12.12.2003
Memo	:	
Printing date	:	30.12.2003
Revision date	:	
Date of last update	:	30.12.2003
Number of pages	:	18
Chapter (profile)	:	
Reliability (profile)	:	
Flags (profile)	:	

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	BASF Corporation
Contact person	:	
Date	:	
Street	:	3000 Continental Drive
Town	:	Mt. Olive, NJ 07828-1234
Country	:	
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

16.12.2003

1.2 SYNONYMS AND TRADENAMES

EP-306 Acid Water
COP Acid Water
Dicarboxylic Acid Solution
Dicarbonsaeure Loesung A. Ber. Trocken
Dicarbonsaeure Loesung L. Ber. Trocken
Abstreifsaeure

2.1 MELTING POINT

Value	:	35 – 45 °C
Method	:	Determined via unknown method by BASF Corporation on product
Year	:	
GLP	:	
Test substance	:	EP-306 Acid Water
Remark	:	
Reliability	:	(2) valid with restrictions

26.12.2003 (1)

Value	:	-6 °C
Method	:	Determined via unknown method by BASF AG on product
Year	:	
GLP	:	
Test substance	:	Dicarbonsaeure Loesung A. Ber. Trocken
Remark	:	Solidification temperature
Reliability	:	(2) valid with restrictions

26.12.2003 (2)

2.2 BOILING POINT

Value	:	ca. 101 °C at 1013 hPa
Decomposition	:	
Method	:	Determined via unknown method by BASF AG on product
Year	:	
GLP	:	
Test substance	:	Dicarbonsaeure Loesung A. Ber. Trocken
Remark	:	Initial value
Reliability	:	(2) valid with restrictions

26.12.2003 (2)

2.3 DENSITY

Type	:	Density
Value	:	= 1.04 g/cm³ at 50 °C
Remark	:	Measured value for typical product
Test substance	:	EP-306 Acid Water
Reliability	:	(2) valid with restrictions

26.12.2003 (1)

Type	:	Density
Value	:	= 1.06 g/cm³ at 45 °C
Test substance	:	Dicarbonsaeure Loesung A. Ber. Trocken
Remark	:	Measured value for typical product
Reliability	:	(2) valid with restrictions

26.12.2003 (2)

2.4 VAPOUR PRESSURE

Value	:	77 hPa at 40 °C
Decomposition	:	
Method	:	Determined via unknown method by BASF AG on product
Year	:	
GLP	:	
Test substance	:	Dicarbonsaeure Loesung A. Ber. Trocken
Remark	:	Initial value
Reliability	:	(2) valid with restrictions

26.12.2003 (2)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	-0.59 to 1.92
pH value	:	-
Method	:	other (calculated): EPI Suite (v3.10)
Year	:	
GLP	:	
Test substance	:	

Method : The Ko/w of each component was calculated with EPI Suite based on its CAS No. The table below provides a summary of the Ko/w values for each component and indicates whether the value was an experimental value listed in EPI Suite (exp) or a value calculated by EPI Suite (cal).

Result :

EP-306 Component	Log Ko/w
Formic Acid	-0.54 (exp)
Acetic Acid	-0.17 (exp)
Propionic Acid	0.33 (exp)
Butyric Acid	0.79 (exp)
Valeric Acid	1.39 (exp)
Caproic Acid	1.92 (exp)
Succinic Acid	-0.59 (exp)
Glutaric Acid	-0.29 (exp)
Adipic Acid	0.08 (exp)
6-Hydroxycaproic Acid	0.59 (cal)
Cyclohexanol	1.23 (exp)
Cyclohexanone	0.81 (exp)
Cyclohexyl Hydroperoxide	1.85 (cal)

Test substance	:	EP-306 Components
Conclusion	:	Components have a Log Ko/w between about –0.6 and 2
Reliability	:	(2) valid with restrictions EPIWIN estimates are assigned a reliability of 2
Flag	:	Critical study for SIDS endpoint

26.12.2003 (3,4)

2.6.1 WATER SOLUBILITY

Value :
pH Value : 2.4
concentration : 50 g/l at 20 °C
PKa :
Description : Miscible
Method : Determined via unknown method by BASF AG on product
Year :
GLP :
Test substance : Dicarbonsaeure Loesung A. Ber. Trocken
Reliability
26.12.2003 (2)

Value : 2,750 to 955,000 mg/l at 25 °C
pH Value :
concentration :
PKa :
Description :
Method : other (calculated): EPI Suite (v3.10)
Year :
GLP :
Test substance :

Method : EPI Suite (v3.10) was used to determine the water solubility of EP-306 components at 25 °C to gain an understanding of the components range of water solubilities. Calculations were based in CAS Nos.

Result :

Component	Water Sol (mg/L)
Formic Acid	955,000
Acetic Acid	476,000
Propionic Acid	174,000
Butyric Acid	66,100
Valeric Acid	18,600
Caproic Acid	5,900
Succinic Acid	808,000
Glutaric Acid	396,000
Adipic Acid	167,000
6-Hydroxycaproic Acid	229,000
Cyclohexanol	33,700
Cyclohexanone	24,100
Cyclohexyl Hydroperoxide	2,750

Test substance : EP-306 Components
Conclusion : The mixture can be considered soluble in water
Reliability : (2) valid with restrictions
EPIWIN estimates are assigned a reliability of 2
Flag : Critical study for SIDS endpoint
27.12.2003 (4)

3.1.1 PHOTODEGRADATION

Type	:	Air
Light Source	:	Sun light
Sensitizer	:	OH
Conc. of Sensitizer	:	1.5E6 OH/cm^3
Rate Constant	:	
Degradation	:	
Method	:	other (calculated): EPI Suite (v3.10)
Year	:	
GLP	:	
Test substance	:	

Method : The overall OH rate constant (cm3/molecule*sec) and half-life (days) for each EP-306 component was calculated with EPI Suite based on its CAS No. The table below provides a summary of these values..

Result :

EP-306 Component	OH Rate Constant (cm3/mol.*s)	Half-life (days)
Formic Acid	0.520×10^{-12}	20.6
Acetic Acid	0.622×10^{-12}	17.2
Propionic Acid	1.39×10^{-12}	7.71
Butyric Acid	2.70×10^{-12}	3.96
Valeric Acid	4.11×10^{-12}	2.60
Caproic Acid	5.52×10^{-12}	1.94
Succinic Acid	2.76×10^{-12}	3.87
Glutaric Acid	4.18×10^{-12}	2.56
Adipic Acid	5.59×10^{-12}	1.91
6-Hydroxycaproic Acid	9.78×10^{-12}	1.09
Cyclohexanol	17.5×10^{-12}	0.61
Cyclohexanone	12.1×10^{-12}	0.88
Cyclohexyl Hydroperoxide	14.0×10^{-12}	0.76

Test substance : EP-306 Components

Conclusion : Components have half-lives between about 0.6 and 20 days, with major components exhibiting half-lives of about 1 to 2 days.

Reliability : (2) valid with restrictions
EPIWIN estimates are assigned a reliability of 2

Flag : Critical study for SIDS endpoint

26.12.2003 (5)

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other: water
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	
Year	:	

Method : EP-306 components, when well mixed into the environment, will distribute according to their individual physical-chemical properties. To understand the relative distribution of components, it is necessary to look at the individual components. It was assumed that materials originated in water as this is considered the most likely manner in which EP-306 will enter the environment.

Result :

SMILES : O=CO
CHEM : Formic acid
CAS NUM: 000064-18-6
MOL FOR: C1 H2 O2
MOL WT : 46.03
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.00633	570	0
Water	99.8	208	1000
Soil	0.021	208	0
Sediment	0.149	832	0

Persistence Time: 231 hr

****
SMILES : O=C(O)C
CHEM : Acetic acid
CAS NUM: 000064-19-7
MOL FOR: C2 H4 O2
MOL WT : 60.05
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0027	347	0
Water	99.8	208	1000
Soil	0.0149	208	0
Sediment	0.15	832	0

Persistence Time: 231 hr

****
SMILES : O=C(O)CC
CHEM : Propanoic acid
CAS NUM: 000079-09-4
MOL FOR: C3 H6 O2
MOL WT : 74.08
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0232	210	0
Water	99.8	208	1000
Soil	0.0294	208	0
Sediment	0.151	832	0

Persistence Time: 231 hr

****
SMILES : O=C(O)CCC
CHEM : Butanoic acid

CAS NUM: 000107-92-6
MOL FOR: C4 H8 O2
MOL WT : 88.11
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.025	107	0
Water	99.8	208	1000
Soil	0.0271	208	0
Sediment	0.156	832	0
Persistence Time:	231 hr		

****
SMILES : O=C(O)CCCC
CHEM : Pentanoic acid
CAS NUM: 000109-52-4
MOL FOR: C5 H10 O2
MOL WT : 102.13
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0178	62.4	0
Water	99.8	208	1000
Soil	0.0233	208	0
Sediment	0.176	832	0
Persistence Time:	231 hr		

****
SMILES : O=C(O)CCCCC
CHEM : Hexanoic acid
CAS NUM: 000142-62-1
MOL FOR: C6 H12 O2
MOL WT : 116.16
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0267	46.5	0
Water	99.7	208	1000
Soil	0.0237	208	0
Sediment	0.234	832	0
Persistence Time:	231 hr		

****
SMILES : O=C(O)CCC(=O)O
CHEM : Butanedioic acid
CAS NUM: 000110-15-6
MOL FOR: C4 H6 O4
MOL WT : 118.09
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	5.34e-014	92.9	0
Water	99.9	208	1000

Soil	7.9e-008	208	0
Sediment	0.149	832	0
Persistence Time:	231 hr		

****
SMILES : O=C(O)CCCC(=O)O
CHEM : Pentanedioic acid
CAS NUM: 000110-94-1
MOL FOR: C5 H8 O4
MOL WT : 132.12
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.37e-013	61.5	0
Water	99.9	208	1000
Soil	1.27e-007	208	0
Sediment	0.15	832	0
Persistence Time:	231 hr		

****
SMILES : O=C(O)CCCCC(=O)O
CHEM : Hexanedioic acid
CAS NUM: 000124-04-9
MOL FOR: C6 H10 O4
MOL WT : 146.14
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	9.39e-012	45.9	0
Water	99.8	208	1000
Soil	1.05e-006	208	0
Sediment	0.15	832	0
Persistence Time:	231 hr		

****
SMILES : O=C(O)CCCCCO
CHEM : 6-HYDROXYCAPROIC ACID
CAS NUM: 001191-25-9
MOL FOR: C6 H12 O3
MOL WT : 132.16
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	7.52e-011	26.2	0
Water	99.8	208	1000
Soil	3.03e-006	208	0
Sediment	0.153	832	0
Persistence Time:	231 hr		

****
SMILES : OC(CCCC1)C1
CHEM : Cyclohexanol
CAS NUM: 000108-93-0
MOL FOR: C6 H12 O1

MOL WT : 100.16
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0757	14.7	0
Water	99.7	360	1000
Soil	0.0165	360	0
Sediment	0.19	1.44e+003	0

Persistence Time: 338 hr

****
SMILES : O=C(CCCC1)C1
CHEM : Cyclohexanone
CAS NUM: 000108-94-1
MOL FOR: C6 H10 O1
MOL WT : 98.15
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.315	40.2	0
Water	99.5	360	1000
Soil	0.0317	360	0
Sediment	0.175	1.44e+03	0

Persistence Time: 334 hr

****
SMILES : C1(OO)CCCCC1
CHEM :
CAS NUM: 000766-07-4
MOL FOR: C6 H12 O2
MOL WT : 116.16
---------- EPI SUMMARY (v3.10) ----------
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.248	18.3	0
Water	99.5	360	1000
Soil	0.0232	360	0
Sediment	0.262	1.44e+03	0

Persistence Time: 330 hr

Test substance : EP-306 Components
Conclusion : EP-306 compounds if released into water, will distribute primarily to water.
Reliability : (2) valid with restrictions
Calculated values are assigned a reliability of 2.
Flag : Critical study for SIDS endpoint
26.10.2003 (6)

3.5 BIODEGRADATION

Type : Aerobic
Inoculum : activated sludge, domestic
Concentration : 65 mg/l

Contact time	:	
Degradation	:	= 70 - 80 % after 28 days
GLP	:	Yes
Year	:	1992
Result	:	Biodegradable
Method	:	CO_2 Evolution Test preformed according to the OECD-301B test guideline
Result	:	Evolution of CO_2 from the test material reached 52% of the theoretical CO_2 content ($ThCO_2$) at 14 days and 78% at 28 days. The CO_2 / $ThCO_2$ value for the reference substance (aniline) was 60% - 70% at 14 days.
Test condition	:	The test substance concentration and total organic carbon concentration were 65 mg/l and 20 mg/l, respectively. Inoculum consisted of activated sludge from laboratory waste treatment plants which were fed with municipal and synthetic sewage. Sludge was washed for 24 hours and then added to test vessels at a concentration of 30 mg/l dry solids.
Test substance	:	Dicarboxylic acid solution: water (42.9%), free carboxylic acids (27.8%), and alcohols (13.3%)
Reliability	:	(1) valid without restrictions GLP guideline study.

26.12.2003 (7)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : Static
Species : *Leuciscus idus L.,* golden variety (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : 215 nominal
LC0 : 215 nominal
LC50 : 215 - 464 nominal
Limit test : No
Analytical monitoring : No
Method : DIN 38 412
Year :
GLP : No
Test substance :

Method : After preliminary tests, 10 fish (golden orfe, mean wt 2.8 g) were exposed to test material at one of four concentrations. Glass test containers (16 l) contained 10 liters of demineralized tap water resalted with: 294.0 mg/l $CaCl_2 \bullet 2\ H_20$, 123.3 mg/l $MgSO_4 \bullet 7\ H_20$, 64.8 mg/l NaHCO3, and 5.8 mg/l KCl. Test material was added directly to the vessels without pretreatment. Ten fish were added to each container after the test material had been mixed with the test water.

Conditions were:

Temperature	20 °C
Acid Capacity	0.8 mmol/l
Total Hardness	2.5 mmol/l
Ratio Ca/Mg Ions	4
Ratio Na/K Ions	10
pH	~7.9 (control)
DOC	(see table)

Remark :
Result : In the definitive test, the following results were recorded

Nom. Conc		No. Dead Fish at					
(mg/L)	# fish	1 hr	4 hr	24 hr	48 hr	72 hr	96 hr
100	10	0	0	0	0	0	0
215	10	0	0	0	0	0	0
464	10	0	1*	9*	10	10	10
1000	10	0*	1	10	10	10	10
0	10	0	0	0	0	0	0
1000**	10	0	0	0	0	0	0

* Symptoms: Narcotic-like state
** Test solution after pH-adjustment

Nom. Conc		pH at			
(mg/L)	Start	24 hr	48 hr	72 hr	96 hr
100	7.2	7.7	7.6	7.7	7.7
215	5.8	6.4	6.9	7.2	7.3
464	4.7	4.9	4.9		
1000	4.2				

0	8.0	7.9	7.8	7.9	7.9
1000**	7.3	7.7	7.7	7.7	7.7

** Test solution after pH-adjustment

Nom. Conc	Oxygen Content (mg/l) at				
(mg/L)	Start	24 hr	48 hr	72 hr	96 hr
100	8.2	8.2	8.2	8.3	8.4
215	8.3	7.8	7.7	7.8	7.9
464	8.4	8.8	7.7		
1000	8.7				
0	8.0	8.3	8.2	8.1	8.2
1000**	8.3	8.5	8.3	8.2	8.1

** Test solution after pH-adjustment

Test substance : Dicarbonsaeureloesung L. Ber. Trocken
Conclusion : The LC50 for the golden orfe under these conditions is 215 - 464 mg/L.
Reliability : (1) valid without restriction
Well-documented guideline study conducted under GLP-like conditions. Comparable to OECD 203 study except for test species.
Flag : Critical study for SIDS endpoint
30.12.2003 (8)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : Static
Species : *Daphnia magna* (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : > 100 (nominal)
EC50 : > 100 (nominal)
24 hour EC50 : > 100 (nominal)
Limit Test : no
Analytical monitoring : Yes
Method : Acute toxicity for Daphnia. EEC Directive 79/831/EEC, Annex V, Part C2.
Year : 1989
GLP : Yes

Method : A static toxicity test was conducted in 20 mL test tubes containing 10 mL test solution. The dilution water used in this study was an ultrapure, deionized water (conductivity < 0.05 µS/cm) containing the following macronutrients (mg/l): Ca (80.1), Mg (12.2), Na (19.8), K (3.2), Si (1.0), Cl (144.9), NO_3 (0.2), PO_4 (0.2), SO_4 (48.4), HCO_3 (47.1) and vitamins (µg/l): thiamine (75.0), B_{12} (1.0), biotin (0.75). The medium had the following properties:

Temperature	20 ± 2 °C
Alkalinity up to pH 4.3	0.80 – 1.00 mmol/l
Total Hardness	2.20 – 3.20 mmol/l
Ratio Ca/Mg Ions	~4
pH	7.5 – 8.5
Conductivity	550 – 650 µS/cm

Test solutions were made by the combining the dilution water with the test material to yield concentrations (mg/l) of: 0, 12.5, 25, 50, 100. Twenty *daphnids* (5 per test tube; 4 test tubes per concentration) were exposed to each test solution. *Daphnid* swimming ability was evaluated at 0, 3, 24, and 48 hr after gentle agitation of the test tube

Temperature was measured at 0, 24, and 48 hr in a extra test tube close to the experimental test tubes; temperatures ranged from 20.3 °C – 21.5 °C. Oxygen content and pH were measured at 0 and 48 hr in one replicate of each test concentration; results are provided below.

Nom. Conc	pH		Oxygen Content (mg/l)	
(mg/L)	0 hr	48 hr	0 hr	48 hr
0	8.0	7.9	8.4	8.3
12.5	7.8	7.8	8.4	7.5
25	7.5	7.8	8.2	7.3
50	7.2	7.6	8.2	7.4
100	6.6	7.4	8.2	7.3

Analayses were performed at 0 hr and 48 hr using the 6-hydroxyhexanoic acid peak for quantification. Results are provided below.

Nom. Conc	Measured concentration (mg/l)(% Nominal)		
(mg/L)	0 hr	48 hr (- daphnids)	48 hr (+ daphnids)
0	< 5 (100)	< 5 (100)	< 5 (100)
12.5	14 (117)	15 (120)	12 (96)
100	97 (97)	130 (130)	146 (146)

Result : *Daphnid* swimming ability was not affected at any of the times or concentrations evaluated. Test material recovery rate at 48 hr ranged from 100 – 150%.

Test substance : Dicarboxylic acid solution. Product No. 3265 (Basant); Batch No. 849-2-PRST-71.

Conclusion : The 48 hours EC50 was > 100 mg/L

Reliability : (1) valid without restriction
Well-documented, guideline study

Flag : Critical study for SIDS endpoint

30.12.2003 (9)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : > 5000 mg/kg bw
Species : Rat
Strain : Wistar
Sex : male/female
Number of animals :
Vehicle : other: Dosed neat
Doses : 681, 2150, 3160, and 5000 mg/kg bw
Method :
Year :
GLP : No
Test substance :

Method : Rats were housed at 22 ± 2 °C, 30% - 70% relative humidy and a 12-hr on / 12-hr off light cycle. Test substance was diluted with distilled water and administered to Wistar rats by gavage at a volume of 10 ml/kg. Treated animals (5 males/5 females per group) were observed for 21 days; survivors were sacrificed and subjected to a gross pathological examination. Mean body weights were reported at the time of dosing and at 7, 13 and 21 days post-dosing.

Remark :
Result :

Dose (mg/kg)	Deaths (M = male, F = female)
681	No Deaths
2150	1M (day 21), 1F (day 1)
3160	1F (day 14)
5000	1M (day 7), 2F (days 7, 14)

Dose (mg/kg)	Mean Male Body Weight (g)			
	Start	Day 7	Day 13	Day 20
681	188	258	296	330
2150	188	249	270	326
3160	191	264	298	332
5000	181	218	253	282

Dose (mg/kg)	Mean Female Body Weight (g)			
	Start	Day 7	Day 13	Day 20
681	172	200	210	218
2150	181	217	226	240
3160	188	205	228	239
5000	190	196	225	230

Male Symptoms	Dose (mg/kg)			
	681	2150	3160	5000
Dyspnea	---	1D – 2D	1D - 2D	1D – 14D
Apathy	---	---	!D - 2D	1D – 14D
Staggering	---	1D – 2D	1D - 2D	4D – 15D
Spastic Gait	---	---	---	14D – 15D
Piloerection	---	1D – 2D	1D - 2D	1D – 15D
Impaired General State	---	1D – 2D	---	15D
Poor General State	---	---	1D - 2D	1D – 14D

Female Symptoms	Dose (mg/kg)			
	681	2150	3160	5000
Dyspnea	---	1D – 2D	4H - 2D	1D – 13D
Apathy	---	1D – 2D	4H - 2D	1D – 13D
Staggering	---	1D – 2D	4H - 2D	---
Piloerection	---	1D – 2D	4H - 2D	1D – 15D
Poor General State	---	1D – 2D	4H - 2D	1D – 13D

No abnormalities were noted at necropsy.

Test substance : Abstreifsaeure
Conclusion : The Oral LD50 is greater than 5,000 mg/kg in Wistar rats of each sex.
Reliability : (1) valid without restrictions
Procedure equivalent to OECD 401. Good documentation for an older study.

30.12.2003 (10)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : *Salmonella typhimurium*, Reverse Mutation Assay
System of testing : Reverse mutation, plate incorporation and preincubation methods
Test concentration : 40, 200, 1000, 5000 and 10,000 µg/plate
Cycotoxic concentr. : ≥ 5,000 µg/plate
Metabolic activation : with and without
Result : Negative
Method : OECD 471
Year :
GLP : Yes
Test substance :

Method : The mutagenic potential of dicarboxylic acid solution (DAS) was evaluated using the *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without metabolic activation (S-9). The homogeneity of the test substance was assured by melting at 70 °C and mixing prior to preparation of the test solutions. No test substance precipitation was observed in the studies. Tester strains were exposed according to the direct plate incorporation and preincubation methods. Liver microsomal fractions from male Sprague-Dawley rats (200 - 300 g) were prepared according to established methods. The positive control with S-9 mix was 2-aminoanthracene (dissolved in DMSO) for all 4 strains; positive controls without S-9 mix included: N-methyl-N'-nitro-N-nitrosoguanidine (in DMSO) for TA 100 and TA 1535, 4-nitro-o-phenyldiamine (in DMSO) for TA 98, and 9-aminoacridine chloride monohydrate (in DMSO) for TA 1537. Negative controls were exposed to DMSO only. DAS was dissolved in DMSO and tested at concentrations of 40, 200, 1000, 5000, and 10000 µg/plate. Assays were performed in two independent experiments, using identical procedures, both with and without metabolic activation. Each concentration, including the controls, was tested in triplicate.

In general, positive substances were required to demonstrate (a) doubling of the spontaneous mutation rate, (b) dose-response relationship, and (c) reproducibility of results.

Remark : Test dates: Standard Plate (13-Aug-1996); Preincubation (12-Sep-1996)
Result : Both the direct plate and preincubation assays demonstrated a lack of mutagenic activity DAS. No significant increases in the number of

revertants were found in any strain and DAS treatment group combination relative to the solvent control. In addition, no concentration-dependent enhancement of the revertant number occurred, and no differences were observed between DAS treatments with or without metabolic activation.

Test substance : Dicarboxylic acid solution, batch No. VN-5200, manufactured on 21-Feb-1996.

Reliability : (1) valid without restrictions
GLP guideline study

30.12.2003 (11)

Type : *Escherichia coli*, Reverse Mutation Assay
System of testing : Reverse mutation, plate incorporation and preincubation methods
Test concentration : 40, 200, 1000, 5000 and 10,000 μg/plate
Cycotoxic concentr. : ≥ 5,000 μg/plate
Metabolic activation : with and without
Result : Negative
Method : OECD 472
Year :
GLP : Yes
Test substance :

Method : The mutagenic potential of dicarboxylic acid solution (DAS) was evaluated using the *E. coli* strain WP2 uvrA with and without metabolic activation (S-9). The homogeneity of the test substance was assured by melting at 70 °C and mixing prior to preparation of the test solutions. No test substance precipitation was observed in the studies. The tester strain was exposed according to the direct plate incorporation and preincubation methods. Liver microsomal fractions from male Sprague-Dawley rats (200 - 300 g) were prepared according to established methods. The positive control with S-9 mix was 2-aminoanthracene (dissolved in DMSO); the positive control without S-9 mix was N-ethyl-N'-nitro-N-nitrosoguanidine (in DMSO). Negative controls were exposed to DMSO only. DAS was dissolved in DMSO and tested at concentrations of 40, 200, 1000, 5000, and 10000 μg/plate. Assays were performed in two independent experiments, using identical procedures, both with and without metabolic activation. Each concentration, including the controls, was tested in triplicate.

In general, positive substances were required to demonstrate (a) doubling of the spontaneous mutation rate, (b) dose-response relationship, and (c) reproducibility of results.

Remark : Test dates: Standard Plate (13-Aug-1996); Preincubation (12-Sep-1996)

Result : Both the direct plate and preincubation assays demonstrated a lack of mutagenic activity DAS. No significant increases in the number of revertants were found in any strain and DAS treatment group combination relative to the solvent control. In addition, no concentration-dependent enhancement of the revertant number occurred, and no differences were observed between DAS treatments with or without metabolic activation.

Test substance : Dicarboxylic acid solution, batch No. VN-5200, manufactured on 21 February 1996.

Reliability : (1) valid without restrictions
GLP guideline study

30.12.2003 (11)

(1) BASF Corporation Technical Bulletin. EP-306 Acid Water. February 1997

(2) BASF Aktiengesellschaft Safety Data Sheet. Dicarbonsaeure Loesung A. Ber Trocken. Revised December 15, 2003

(3) EPI Suite (v3.10). KOWWIN (v1.66). USEPA Office of Pollution Prevention and Toxics and Syracuse Research Corporation (April 2001)

(4) EPI Suite (v3.10). WSKOW (v1.40). USEPA Office of Pollution Prevention and Toxics and Syracuse Research Corporation (April 2001)

(5) EPI Suite (v3.10). AOP Program (v1.90). USEPA Office of Pollution Prevention and Toxics and Syracuse Research Corporation (April 2001)

(6) EPI Suite (v3.10). Level III Fugacity Model. USEPA Office of Pollution Prevention and Toxics and Syracuse Research Corporation (April 2001)

(7) BASF Aktiengesellschaft. 10 December 1997. Determination of the biodegradability of dicarboxylic acid solution in the co2-evolution test. Project No.: 97/0071/22/1.

(8) BASF Aktiengesellschaft. 2 December 1987. Report on the study of the acute toxicity of dicarbonsaeureloesung L. Ber. Trocken on the golden orfe (Leuciscus idus L., golden variety). Project No.: 10F0220/875098

(9) BASF Aktiengesellschaft. 18 December 1997. Determination of the acute effect of dicarboxylic acid solution on the swimming ability of the water flea *Daphnia magna Straus*. Project No.: 97/0071/50/1

(10) BASF Aktiengesellschaft. 9 November 1987. Report on the study of acute oral toxicity of abstreifsaeure in the rat. Project No.: 10A0220/871107.

(11) BASF Aktiengesellschaft. 5 May 1998. Report on the study of Dicarbonsaeure-Loesung in the Ames *Salmonella* / mammalian-microsome mutagenicity test and *Escherichia coli* / mammalian-microsome reverese mutation assay (standard plate test and preincubation test). Project No.: 40M0135/964062