201-14963

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

Cycloaliphatic Epoxy Resin ERL-4221

CAS NO. 2386-87-0

Prepared by:

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EXECUTE SUMMARY

The Dow Chemical Company voluntarily submits the following screening information data and Test Plan covering the chemical Cycloaliphatic Epoxy Resin ERL-4221, also known as ERL-4221 (CAS No. 2386-87-0), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

A complete data set exists to evaluate the potential hazards associated with ERL-4221 as pertains to the US HPV program. No additional data needs to be obtained.

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TEST PLAN FOR Cycloaliphatic Epoxy Resin ERL-4221

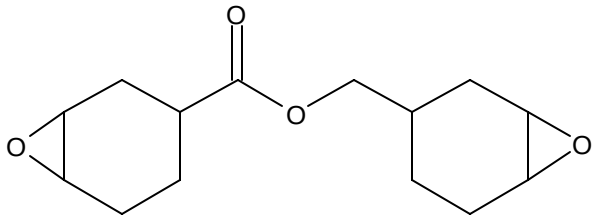
CAS Nos. 2386-87-0

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, The Dow Chemical Company (Dow) has committed to voluntarily compile basic screening data on Cycloaliphatic Epoxy Resin ERL-4221 (ERL-4221). The data included in this Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of ERL-4221, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed by or on behalf of Dow or found in the published scientific literature and fulfills Dow's obligation to the HPV Challenge Program.

A. Structure and Nomenclature

Following is a structural characterization of ERL-4221 and associated nomenclature.



Cycloaliphatic Epoxy Resin ERL-4221
CAS No. : 2386-87-0
Synonyms: ERL-4221

B. Manufacturing & Use

ERL-4221 is produced in an anhydrous peracetic acid based isolated facility. The enclosed unit offers little opportunity for production worker exposure.

Cycloaliphatic epoxies like ERL-4221 are produced by the reaction of peracetic acid with a diolefin precursor to make the diepoxy.

ERL-4221 contains both the desired structure of the diepoxide 'monomer' along with higher molecular weight oligomers and some monoepoxy-monoene. This commercial product containing diepoxy, soluble oligomers and monoepoxy-monoene, cannot be separated by our production unit and is sold as the commercial product ERL-

4221. All tox studies were done on the commercial material. The approximate composition of the commercial product is (by size exclusion chromatography): Diepoxy 82-89%, soluble oligomer 8-13%, monoepoxy-monoene 0-5%.

Shipping/Distribution

Material is shipped in tank and rail cars and drums.

Worker/Consumer Exposure

ERL-4221 is produced in a closed system and thus worker exposure would only occur during upset conditions. Material is shipped in tank and rail cars and drums. The greatest potential for worker exposure would be associated with drumming operations. However, ERL-4221 is a viscous material with a very low vapor pressure, and thus the only routes for human exposure are through accidental contact with skin and eyes. Routine industrial hygiene practices are used in conjunction with monogoggles and protective gloves to minimize skin and eye exposure.

Cycloaliphatic epoxides are reactive acid scavengers and thus are used as stabilizer additives in a number of sensitive organic systems.

ERL-4221 is used to produce cationically UV-cured Zero Volatile Organic Carbon (Zero VOC) coatings and inks for packaging. It is used to formulate encapsulants for various electrical applications.

II. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either:
1) Internal studies conducted by/or for Dow
2) Studies that have been extracted from the scientific literature either as primary references or
3) Studies that were estimated using environmental models accepted by the US EPA (1999b) for such purposes.

This assessment includes information on physico-chemical properties, environmental fate/pathways, and human and environmental effects associated with ERL-4221. The data used to support this program include those Endpoints identified by the US EPA (1998); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VII of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:
1. Valid without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,
2. Valid with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance.

Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).
3. Not Valid – Includes studies in which there are inconsistencies in either the study design or results that provide scientific uncertainty or where documentation is insufficient.
4. Not Assignable – Includes studies in which limited data is provided.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier.

III. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion: All HPV Endpoints have been satisfied with data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation modeling programs. Hence, no further testing for any of the HPV Endpoints is deemed necessary (Table 1).

Physico-chemical Properties: Melting Point, Boiling Point,Vapor Pressure, Water Solubility, and Log Kow were obtained from laboratory measurements performed under GLP (Table 2). The material is a viscous liquid with a negligible vapor pressure at room temperature. The material is moderately soluble in water (13,850 mg/L), and has an accordingly low log K_{ow} (1.34).

Environmental Fate and Pathways: Processes such as hydrolysis and biodegradation were also investigated according to OECD test guidelines, under GLP. Additional fate parameters such as Distribution, Transport Between Environmental Compartments, and Photodegradation were estimated using universally accepted computer estimation methods. (Table 3). Hydrolysis is a dominant mechanism for degradation of ERL-4221 in the environment, with a half-life of approximately 47 hours at 20 °C at pH 7. The rate of hydrolysis is approximately doubled at pH 4 ($t_{1/2}$ = 21 hr.). Hydrolysis of ERL-4221 will result in cleavage of the ester linkage to form cyclohexylcarboxylate and cyclohexyl methanol intermediates, as well as opening of the epoxy rings to yield the dihydroxy forms of these intermediates. Rates of hydrolysis are enhanced with lowered pH. ERL-4221 was rapidly and extensively biodegraded (71% in 28 d) in the OECD Modified Sturm Test of ready biodegradability. While the test results failed to meet stringent criteria for classification as "readily biodegradable", the rate/extent of biodegradation observed indicates that the material will not persist indefinitely in the environment and will undergo substantial biodegradation. Due to a lack of chromophoric functional groups, ERL-4221 is not susceptible to direct photolysis in the atmosphere or hydrosphere. However, a rapid rate of indirect photolysis can be expected in the atmosphere, as the estimated half-life for reaction with photochemically-generated hydroxyl radicals is 7.9 hours. The available data indicate that ERL-4221 has very low potential for accumulation and transport in the environment.

Ecoxicity: The acute toxicity of ERL-4221 to algae, daphnia and fish has been recently evaluated according to OECD test guidelines (Table 4). The acute toxicity to fish was evaluated under flow-through conditions due to the relatively rapid hydrolysis of ERL 4221. Acute toxicity to daphnia and algae were conducted under static conditions. The LC_{50} for fish was 24 mg/L, while the EC_{50} for daphnia and algae were 40 and 90 mg/L, respectively. Therefore, ERL-4221 can be considered as "slightly toxic" to aquatic organisms on an acute basis.

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames and Chromosomal Aberration Testing, Reproductive Toxicity and Developmental Toxicity) have all been considered adequate (Tables 5-7).

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VII of this dossier.

A. Physico-Chemical Data

All measureable HPV Endpoints for Chemical/Physical Properties have been completed (Table 2). At room temperature (25 °C), ERL-4221 is a viscous liquid with a vapor pressure of 2.0×10^{-5} hPa. Thus, a saturated atmosphere contains approximately 0.02 ppm ERL-4221. ERL-4221 is quite water soluble and thus the log Kow is fairly low.

Conclusion – Adequate values are available to provide needed information on the Physical-Chemical Properties associated with ERL-4221. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Pathways

All HPV Endpoints for Environmental Fate have been completed (Table 3). ERL-4221 hydrolyzes in water (Table 2). The half-life of ERL-4221 in water is 47 hours at 20^{o}C and pH 7. Although there is no evidence of direct photolysis, ERL-4221 would be expected to photodegrade indirectly with a half-life of 7.9 hours. Although ERL-4221 did not meet the criteria for 'ready biodegradability', the available data does suggest that it would not persist indefinitely in the environment and will undergo substantial biodegradation. In the event of release to the environment, most of the material will be found in water and pore waters associated with sediments or soil, where it will be readily degraded via hydrolysis and biodegradation.

Conclusion – Adequate values are available to provide needed information on the Environmental Fate and Biodegradation associated with ERL-4221. Therefore, no additional data development is needed for these HPV Endpoints.

C. Ecotoxicity

All HPV Endpoints for Ecotoxicity have been completed (Table 4). The acute LC50 is 24 mg/L in fish using flow-through conditions. The acute EC_{50} values for daphnia and algae range from 40-90 mg/L under static conditions.

Conclusion – Adequate values are available to provide needed information on the Aquatic Toxicity associated with ERL-4221. Therefore, no additional data development is needed for these HPV Endpoints.

D. Mammalian Toxicity

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Table 5. Each report has been further summarized in the Robust Summary section of this Dossier.

1.0 Acute Toxicity

The acute oral and dermal LD50s are 5000 mg/kg and >20 ml/kg, respectively. The material is a mild irritant to the skin and eyes. ERL-4221 is positive in a Guinea Pig maximization assay.

Due in part to the sensitization potential of ERL-4221, protective equipment is required whenever contact with test material is possible.

Conclusion – No additional data development is needed for the Acute Toxicity HPV Endpoint.

2.0 Repeated Dose Toxicity

A 90 day study was completed (Table 6). The NOAEL was 5 mg/kg/day via oral gavage. It was negative in a mouse skin painting study.

Conclusion - No further testing is needed for completion of information related to the Repeat Dose HPV Endpoint.

3.0 Developmental Toxicity

A developmental toxicity study was conducted (Table 6). The maternal NOAEL was 25 mg/kg/day while the developmental NOAEL was 125 mg/kg/day.

Conclusion - No further testing is needed for completion of information related to the Repeat Dose HPV Endpoint.

4.0 Reproductive Toxicity

As part of the 90-day repeated dose study, there was no evidence of an effect on male or female reproductive organs based on absolute and relative organ weight and gross and histopathologic examination (Table 6).

Conclusion - No further testing is needed for completion of information related to the Reproductive Toxicity HPV Endpoint.

5.0 Mutagenicity

5.1 Mutagenicity Testing (in vitro bacterial)

ERL-4221 is positive in strains TA100 and TA1535 with activation in the Ames test.

5.2 - Mutagenicity Testing (in vitro mammalian)

ERL-4221 was negative in the CHO-HGPRT, CHO SCE assays and ambiguous in the rat liver UDS assay.

5.3 - Mutagenicity testing (in vivo mammalian)

ERL-4221 was negative in the rat UDS in vivo, micronucleus and the 32P-postlabeling DNA adduct assays.

Conclusion - Although the Ames test was positive in several strains with activation, all other mutagenicity and chromosomal aberration assays were negative or ambiguous. No further testing is needed for completion of information related to the Mutagenicity HPV Endpoint.

V. REFERENCES

ACGIH TLV (2002). Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists.

Klimisch, H.-J., Andreae, M. and Tillman, U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

US EPA, 1998. Guidance for meeting the SIDS requirements (The SIDS Guide).
Guidance for the HPV Challenge Program (11/31/98).

US EPA, 1999a. Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

US EPA, 1999b. The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

VI. Tables

Tables are appended

VII. ROBUST STUDY SUMMARIES -IUCLID

Data Sets are appended

Table 1. Test Plan Matrix for ERL-4221

	Info available?	OECD?	GLP?	Other study?	Estimated method?	Acceptable?	Testing recommendation?
PHYSICAL CHEMICAL							
Melting Point	Y	Y	Y	N	N	Y, 1A	N
Boiling Point	Y	Y	Y	N	N	Y, 1A	N
Vapor Pressure	Y	Y	Y	N	N	Y, 1A	N
Partition Coefficent	Y	Y	Y	N	N	Y, 1A	N
Water Solubility	Y	Y	Y	N	N	Y, 1A	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	ND	N	N	Y, 2	N
Biodegradation	Y	Y	Y	N	N	Y, 1A	N
Hydrolysis	Y	Follows intent of OECD	Y	N	N	Y, 2E	N
Transport between Environmental Compartmenats (Fugacity)							
Bioaccumulation	N	N	N	N	N	N	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	Y	Y	N	N	Y, 1A	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	Y	N	N	Y, 1A	N
Acute Toxicity to Aquatic Plants	Y	Y	Y	N	N	Y, 1A	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	Y	Y	N	N	Y, 1A	N
Repeated Dose Toxicity	Y	Y	Y	N	N	Y, 1A	N
Genetic Toxicity - Mutation (Ames)	Y	Y	Y	N	N	Y, 1A	N
Genetic Toxicity - Chromosomal Aberrations	Y	Y	Y	N	N	Y, 1A	N
Developmental Toxicity	Y	Y	Y	N	N	Y, 1A	N
Reproductive Toxicity	Y	Y	Y	N	N	Y, 1A	N

Y = Yes; N = No; ND = No Data; S = Supplemental, not required under HPV; - = Not applicable

Table 2. Matrix of Available and Adequate Data on ERL-4221
Physicochemical Properties

Name (CAS No.)	Melting Point (°C)	Vapor Pressure (hPa @ 25°C)	Boiling Point (°C)	Partition Coefficient (log Kow)	Water Solubility (mg/L @ 20C)
ERL-4221 (2386-87-0)	Ca. -30 - -35 (measured)	2.0×10^{-5} (measured)	>300 decomposition noted above 300°C (measured)	1.34 (measured)	13850 (measured)

Table 3. Matrix of Available and Adequate Data on ERL-4221
Environmental Fate

Name (CAS No.)	**Hydrolysis**	**Photodegradation** Half life	**Biodegradation**	**Environmental Transport** Level III 1000 kg/hr released to air, water and soil
ERL-4221 (2386-87-0)	Half life 47 hours at 20°C and pH 7 (measured)	No evidence of direct photodegradation (No absorbance in the range of 290-800 nm) (measured) Estimated half life =7.89 hours or 0.657 days for indirect photolysis	71% in 28 days in OECD 301B test (measured)	Air - 0.00099% Water - 51.3% Soil - 48.7% Sediment - 0.025%

Table 4. Matrix of Available and Adequate Data on ERL-4221
Ecotoxicity

Name (CAS No.)	Acute Fish 96-hour LC50 (mg/l)	Acute Invertebrate 48-hour EC50 (mg/l)	Algal 72-hour growth inhibition EC50 (mg/l)
ERL-4221 (2386-87-0)	24 flow through (measured)	40 (measured)	90 (measured)

Table 5. Matrix of Available and Adequate Data on ERL-4221
Acute Toxicity

Name (CAS No.)	Acute Oral	Acute Dermal	Dermal Irritation	Eye Irritation	Sensitization
ERL-4221 (2386-87-0)	5000 mg/kg	>23,600 mg/kg	Minor erythema	Minor conjunctival irritation	Sensitizer

Table 6. Matrix of Available and Adequate Data on ERL-4221
Repeat-dose Toxicity

Name (CAS No.)	Repeat Dose	Carcinogenicity	Reproductive	Developmental
ERL-4221 (2386-87-0)	90 day study at 5, 50 and 500 mg/kg/day via oral gavage NOAEL = 5 mg/kg LOAEL = 50 mg/kg	Negative in mouse skin painting study	No effect on reproductive organs in 90 day study	Developmental toxicity study at 5, 25, 125 or 500 mg/kg/day via oral gavage Maternal NOAEL = 25 mg/kg/day Developmental NOAEL = 125 mg/kg/day

Table 7. Matrix of Available and Adequate Data on ERL-4221
Genotoxicity

Name (CAS No.)	Genotoxicity (*in vitro* -bacterial)	Genotoxicity (*in vitro* - mammalian)	Genotoxicity (*in vivo*)
ERL-4221 (2386-87-0)	Positive in strains TA100 and TA1535 with activation	Negative in CHO/HGPRT assay Negative in CHO SCE assay Ambiguous in Rat liver UDS assay	Negative in micronucleus assay Negative in rat UDS assay Negative in 32P-postlabeling DNA adduct assay

Table 8
Test Plan Matrix for ERL-4221

	ERL-4221 (2386-87-0)
PHYSICAL CHEMISTRY	
Melting point, °C	Ca. -30 - -35 (measured) A
Boiling point, °C	>300 (measured) A
Vapor Pressure, hPa at 25°C	2.0×10^{-5} (measured) A
Water Solubility , mg/L @20°C	13850 (measured) A
K_{ow}	1.34 (measured) A
ENVIRONMENTAL FATE	
Biodegradation	71% in OECD 301B A
Hydrolysis, half life at 20°C and pH 7	47 hours A
Photodegradability	None A
Transport between Environmental Compartments: (**Fugacity Level III Model**) Default assumption: 1000 kg/hr released into air, water, and soil.	Air - 0.00099% Water - 51.3% Soil - 48.7% Sediment - 0.025% A
ECOTOXICITY	
Acute Toxicity to Fish (96hr LC50)	24 mg/L A
Acute Toxicity to Aquatic Invertebrates (48hr EC50)	40 mg/L A
Toxicity to Aquatic Plants (72hr EC50)	90 mg/L A
TOXICOLOGICAL DATA	
Acute Toxicity (oral), mg/kg	5000 mg/kg A
Acute Toxicity (dermal) ml/kg	>20 ml/kg A
Acute Eye Irritation	Minor conjunctival irritation A
Acute Skin Irritation	Minor erythema

	A
Sensitization	Positive A
Repeated Dose Toxicity	90 day study NOAEL = 5 mg/kg/day A
Genetic Toxicity-Mutation	Positive A
Genetic Toxicity- Chromosomal Aberrations	Negative to ambiguous in vitro Negative in vivo A
Toxicity to Reproduction	Based on 90 day study A
Developmental Toxicity	Maternal NOAEL = 25 mg/kg/day Developmental NOAEL = 125 mg/kg/day A

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties