201-14963

Anh Nguyen
12/23/03 01:42 PM

To: NCIC HPV@EPA
cc:
Subject: Cycloaliphatic Epoxy Resin ERL-4221, CAS Number 2386-87-0

----- Forwarded by Anh Nguyen/DC/USEPA/US on 12/23/2003 01:38 PM -----

"Nitschke, Kenneth (KD)" <kdnitsch@dow.com>
12/23/2003 11:24 AM

To: NCIC OPPT@EPA, Rtk Chem@EPA
cc: Leslie Scott/DC/USEPA/US@EPA, Richard Hefter/DC/USEPA/US@EPA, "Clous, Welmoed (MC)" <wmclous@dow.com>, "Burgert, Linda (LC)" <lburgert@dow.com>
Subject: Cycloaliphatic Epoxy Resin ERL-4221, CAS Number 2386-87-0

> Attached is a submission on behalf of The Dow Chemical Company for Cycloaliphatic Epoxy Resin ERL-4221, CAS Number 2386-87-0, under the US HPV Program.
>
> This submission includes the following attached files:
> * Test Plan
> * IUCLID Dossier
>
> If you have any difficulty opening these files or have any questions, please contact me.
>
> > > <<ERl-4221 Test Plan.doc>> > > <<ERL-4221 Tables.doc>> > > <<2386-87-0.rtf>>
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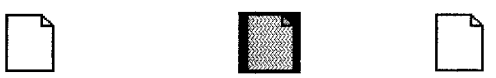


ERl-4221 Test Plan.doc ERL-4221 Tables.doc 2386-87-0.rtf

201-14963

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

Cycloaliphatic Epoxy Resin ERL-4221

CAS NO. 2386-87-0

Prepared by:

The Dow Chemical Company
Midland, Michigan 48674

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.

TABLE OF CONTENTS

TEST PLAN FOR Cycloaliphatic Epoxy Resin ERL-4221

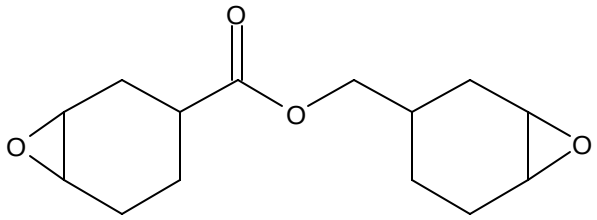
CAS Nos. 2386-87-0

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

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I U C L I D

Data Set

Existing Chemical	:	ID: 2386-87-0
CAS No.	:	2386-87-0
EINECS Name	:	7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate
EINECS No.	:	219-207-4
Molecular Formula	:	C14H20O4
Structural Formula	:	(C6H9O)COOCH2C6H9O

Producer Related Part

Company	:	The Dow Chemical Company
Creation date	:	03.10.2002

Substance Related Part

Company	:	The Dow Chemical Company
Creation date	:	03.10.2002
Memo	:	
Printing date	:	12.12.2003
Revision date	:	
Date of last Update	:	05.09.2003
Number of Pages	:	48
Chapter (profile)	:	
Reliability (profile)	:	
Flags (profile)	:	???

1.0.1 OECD AND COMPANY INFORMATION

Type	:	
Name	:	Dow Chemical Company
Partner	:	
Date	:	
Street	:	
Town	:	48674 Midland, MI
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Source	:	Dow Chemical Company

28.08.2003

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type	:	organic
Physical status	:	liquid
Purity	:	= 82 - 89 % w/w
Source	:	Dow Chemical Company
Reliability	:	(2) valid with restrictions

28.08.2003

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

7-Oxabicyclo[4.1.0]heptane-3-carboxylic acid, 7-oxabicyclo[4.1.0]hept-3-ylmethyl ester
Source : Dow Chemical Company
08.05.1998

Cycloaliphatic Epoxy Resin ERL-4221
Source : Dow Chemical Company
28.08.2003

ERL-4221
Source : Dow Chemical Company
28.08.2003

1.3 IMPURITIES

CAS-No :
EINECS-No :
EINECS-Name : oligomer of ERL-4221
Contents : = 8 - 13 % w/w
Reliability : (1) valid without restriction
22.08.2003 (1)

CAS-No :
EINECS-No :
EINECS-Name : monoepoxide of ERL-4221
Contents : = 0 - 5 % w/w
Reliability : (1) valid without restriction
22.08.2003 (1)

CAS-No : 2611-00-9
EINECS-No :
EINECS-Name : 3-cyclohexene-1-carboxylic acid, 3-cyclohexen-1-ylmethyl ester
Contents : <= .3 % w/w
Reliability : (1) valid without restriction
22.08.2003 (1)

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

Type : industrial
Category : other: coating
Source : Dow Chemical Company
28.08.2003

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	ca. -30 - -35 ° C
Sublimation	:	
Method	:	OECD Guide-line 102 "Melting Point/Melting Range"
Year	:	2000
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A differential scanning calorimeter was used. Approximately 14mg test material was cooled to -120C, held at a steady temperature for two minutes and then scanned upwards to 25C at 10K/min. The test was repeated with the sample cooled to -90C. Due to the effects observed, approximately 5 ml sample of test material was cooled in an open test tube by placing it in a wider tube located in a Drikold bath. Readings were taken of the temperature and visual observations made of the state of the sample. A glass rod was used to help assess fluidity.
Result	:	Using differential scanning calorimetry, there was no evidence of exothermic crystallization nor endothermic melting. A step change at approximately -60C in both directions, however, indicated a glass transition, a property associated with non-crystalline solids. The same result was observed in the repeat test. Using the Drikold bath, the sample became more viscous. At a temperature of approximately -30C the test material was essentially liquid. At -35C, the sample could not be stirred and it was therefore regarded as solid. Cooling was continued to -49C, at which temperature it was hard solid. It was then allowed to warm up smoothly. Above -35C the sample softened and above -30C it was sufficiently mobile to pour. It was therefore regarded as liquid and the viscosity decreased steadily as the temperature rose further. A plot of the temperature vs time showed that during both cooling and warming there was no isothermal stage that would indicate either crystallization or true melting, confirming the DSC observation.
Reliability	:	(1) valid without restriction 1A

23.07.2003 (2)

2.2 BOILING POINT

Value	:	> 300 ° C at 1013 hPa
Decomposition	:	yes
Method	:	OECD Guide-line 103 "Boiling Point/boiling Range"
Year	:	2000
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The test material was too viscous to determine the boiling point by ebulliometry. Therefore differential scanning calorimetry was used instead. A sample of ca 7 mg was heated at 10K/min from 30 to 450C in a nitrogen purge atmosphere. A second sample of ca 5 mg mass was heated similarly to 380C.
Result	:	Irregular exothermic behavior was observed above ca 300C, indicating decomposition in the first sample. The same result was obtained in the second sample. Both crucibles contained a black residue on opening,

confirming that decomposition had occurred.

Reliability : (1) valid without restriction
1A

23.07.2003 (3)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .00002 hPa at 25° C
Decomposition :
Method OECD Guide-line 104 "Vapour Pressure Curve"
Year : 2000
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : The test method was effusion manometry. Temperatures used were 68.1, 82.1 and 110.9C. Data was extrapolated to 25C.
Result : At temperatures of 68.1, 82.1 and 110.9C the vapor pressure was 0.194, 0.779 and 6.35 Pa, respectively.

By extrapolation, the vapor pressure at 25C is 0.002 Pa or 0.00002 hPa.
Reliability : (1) valid without restriction
1A

05.09.2003 (4)

2.5 PARTITION COEFFICIENT

Log pow : = 1.34 at 20° C
Method OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 2000
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : The shake flask method was used. Initially, a nominal concentration of 1000 mg/L test material was prepared for the definitive test.
Result : The average log Pow was 1.34.
Reliability : (1) valid without restriction
1A

23.07.2003 (5)

2.6.1 WATER SOLUBILITY

Value : = 13850 mg/l at 20 ° C
Qualitative : very soluble (> 10000 mg/L)
Pka : at 25 ° C
PH : at and ° C
Method : OECD Guide-line 105 "Water Solubility"
Year : 2000
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Water solubility was measured at 3 nominal concentrations of 5,000, 10,000 and 100,000 mg/L. For the lowest concentration, the solution was prepared at the beginning of the study to be held at 30C then equilibrated at 20C for 24 hours.

For the nominal concentration of 10,000 mg/L, the solution was maintained at 20C. This was analyzed at 0 hours and regular intervals thereafter.

In the final definitive run at 100,000 mg/L, the solution was maintained at 20C. Samples were analyzed at 0, 2.5, 5.5, 24.5, 30, 48, 53, 78, 144, 168, 191, 215.5, 239.5, 312.5, 340.5, 360, 383.5 and 407.5 hours.

Result : At the lowest nominal concentration, 5,000 mg/L, the measured concentrations showed a continual decrease due to hydrolysis. For a nominal concentration of 5000 mg/L, measured values were 3631, 2321, 3092, 875, 1362, 1310, 1523, 608 and 204 mg/L for 24, 44, 52, 69, 76, 93, 101, 116 and 143 hours, respectively.

At 10,000 mg/L, the measured concentration showed that the test substance had gone fully into solution after 30 hours indicating that solubility must lie above 10,000 mg/L.

In the final definitive run, the overall mean solubility on day 18 was 13,850 mg/L based on 19 measured values. Individual values ranged from 10,600 to 17,360 mg/L.

The temperature of the 20C water bath ranged from 20.2 to 20.4C. During the definitive study, the pH measurements were all 7 for the nominal 100,000 mg/L test solution.

Reliability : (1) valid without restriction
1A

23.07.2003 (6)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Deg. Product	:	
Method	:	
Year	:	2003
GLP	:	
Test substance	:	other TS: estimate conducted for pure double epoxy compound
Method	:	Used AOP v1.90 EPIWIN to calculate indirect photolysis.
Result	:	Estimated half-life for reaction with photochemically generated hydroxyl radical is 7.9 hours or 0.657 days.
Reliability	:	(2) valid with restrictions 2E

28.08.2003

Type	:	water
Light source	:	Sun light
Light spect.	:	ca. 290 - 800 nm
Rel. intensity	:	based on Intensity of Sunlight
Conc. of subst.	:	40 mg/l at degree C
Deg. Product	:	
Method	:	EPA OPPTS 835.2210
Year	:	2000
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	ERL-4221 has no absorbance in the range of 290-800 nm indicating that no direct photolysis takes place in sunlight.
Reliability	:	(2) valid with restrictions 2E

28.08.2003 (7)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	= 21 hour(s) at 20 degree C
t1/2 pH7	:	= 47 hour(s) at 20 degree C
t1/2 pH9	:	= 42 hour(s) at 20 degree C
Deg. Product	:	
Method	:	other: follow parts of OECD 111
Year	:	2000
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Nominal solutions of 5000 mg/L were prepared in deionized water and remained at room temperature, 20C. Samples were analyzed at 0 and 72 hours. In addition, as part of the solubility determination, nominal concentrations of 5000 mg/L were prepared, held at 30C for 24 hours and then at 20C for up to 143 hours. The concentration of test material was determined at various time points between 24 and 143 hours.
Result	:	The analytical concentration of test material was determined at 0 and 72 hours at pH 4, 7 and 9 (Table 1). Based on this data, the half life at pH4, 7 and 9 is 21, 47 and 42 days.

Table 1

pH	Analytical Conc. 0 hour	72 hours	Percentage loss (%)
4	33	3.0*	91
7	49	17	65
9	59	18	69

Nominal concentrations of 50 mg/L were prepared
* limit of detection.

The above data is confirmed with data obtained from the water solubility experiment (Table 2). At an approximate pH of 7.3, the half life was approximately 2 days.

Table 2

Time	pH	Analytical Conc. mg/L	Percentage loss (%)
24	7.14	3630	27
44	7.48	2320	54
52	7.36	3090	38
69	7.30	875	82
76	7.36	1360	73
93	7.32	1310	74
101	7.25	1520	70
116	7.32	610	88
143	7.26	200	96

Reliability : (2) valid with restrictions
2E

23.07.2003 (8)

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level I
Media :
Air (level I) : .0007
Water (level I) : 98.1
Soil (level I) : 1.9
Biota (level II / III) :
Soil (level II / III) :
Method :
Year : 2003
Method : Level I model version 2.11. Obtained from the Canadian Environmental Modeling Center, Trent University, Peterborough, Ontario, Canada

Input Parameters for Level I Models:

Property	Value	Source
Data Temperature (^{0}C)	25	
Chemical Type	1	Type 1 indicates chemical can

partition into all environmental compartments
Molecular Mass (g/mol) 252.31 Calculated from molecular structure
Water Solubility (g/m3) 13,850 Measured value [1]
Vapor Pressure @ 25 ^{0}C (Pa) 0.002 Measured value [1]
Melting Point (^{0}C) -32.5 Measured value [1]
Estimated Henry's Law Constant (H)
(Pa m3/mol) 0.000036 Calculated by Level I Fugacity Model [2]
Log Kow Octanol-Water Partition Coefficient
1.34 Measured value [1]
Amount of Chemical input to Level I Model (kg)
100,000 Level I Default Value[2]

REFERENCES
1. Data from The Dow Chemical Company present in dossier.
2. Mackay, D., 2001. Multimedia Environmental Models: The Fugacity Approach. Lewis Publishers, CRC Press, Boca Raton, FL. Models available at: http://www.trentu.ca/cemc/models.html

Result :
RESULTS
Media: Distribution among air, water, soil, and sediments

Emission Scenario	Percentage and amount distributed to			
	Air	Water	Soil	Sediment
Level I: 100,000 kg total emissions				
Percentage	0.00072	98.1	1.9	0.042
Amount, kg	0.72	98000	1900	42

Reliability :
(2) valid with restrictions
2E

05.09.2003

Type : fugacity model level III
Media :
Air (level I) :
Water (level I) :
Soil (level I) :
Biota (level II / III) :
Soil (level II / III) :
Method :
Year : 2003
Method :
Remarks: Level III model version 2.70. Obtained from the Canadian Environmental Modeling Centre, Trent University, Peterborough, Ontario, Canada

Input Parameters for Level III Models:

Property	Value	Source
Data Temperature (^{0}C)	25	
Chemical Type	1	Type 1 indicates chemical can partition into all environmental compartments
Molecular Mass (g/mol)	252.31	Calculated from molecular structure
Water Solubility (g/m3)	13,850	Measured value [1]
Vapor Pressure @ 25 ^{0}C (Pa)	0.002	Measured value [1]
Melting Point (^{0}C)	-32.5	Measured value [1]
Estimated Henry's Law Constant (H) (Pa m3/mol)	0.000036	Calculated by Level I Fugacity Model [2]

Log Kow Octanol-Water Partition Coefficient
1.34 Measured value [1]
Amount of Chemical input to Level I Model (kg)
100,000 Level I Default Value[2]
Reaction Half-lives (hr.) Input to Level III Model

Air (vapor phase)	7.9	Estimated value [3]
Water (no susp. solids)	1200	Based on measured ready biodegradability [1]**
Soil	2160	Based on measured ready biodegradability [1]**
Sediment	2160	Based on measured ready biodegradability [1]**
Suspended Sediment	*1.0 x 10(11)	Not expected to adsorb to susp. sediment
Fish	*1.0 x 10(11)	No uptake/bioaccumulation is expected
Aerosol	*1.0 x 10(11)	Aerosol emissions not expected

**Compound is readily biodegradable, half-lives extrapolated from ready biodegradability classification, according to Technical Guidance Document of the European Commission [4].

REFERENCES

1. Data from The Dow Chemical Company present in dossier.
2. Mackay, D., 2001. Multimedia Environmental Models: The Fugacity Approach. Lewis Publishers, CRC Press, Boca Raton, FL. Models available at: http://www.trentu.ca/cemc/models.html
3. U.S. EPA. 2000. AOPWIN software, version v1.90. United States Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D. C. Available at: http://www.epa.gov/oppt/exposure/docs/episuitedl.htm
4. European Commission. 1996. Technical Guidance Documents in support of the commission directive 93/67/EEC on risk assessment for new notified substances and commission regulation. European Commission, Brussels, Belgium.

Result : Media: Distribution among air, water, soil, and sediments

Emission Scenario	Percentage and amount distributed to			
	Air	Water	Soil	Sediment
Level III:				
1,000 kg/hr to Air				
Percentage, %	0.0026	39.4	60.5	0.019
Amount, kg	31	470000	730000	230
1,000 kg/hr to Water				
Percentage, %	0.000000011	99.9	0.00027	0.048
Amount, kg	0.000071	630000	1.7	300
1,000 kg/hr to Soil				
Percentage, %	0.0000027	38.1	61.9	0.018
Amount, kg	0.034	480000	770000	230
Level III:				
1,000 kg/hr simultaneously to Air, Water, and Soil				
Percentage, %	0.00099	51.3	48.7	0.025
Amount, kg	31	1600000	1500000	760

Conclusion : This material has high water solubility, low vapor pressure, and low log

Kow. These properties dictate that the material has low potential to volatilize from water or soil to air, or adsorb from water to soil and sediments. When released to water, the material will remain dissolved in water and be removed through hydrolysis and biodegradation. When released to soil, the material will remain dissolved in soil pore water, and be removed through hydrolysis and biodegradation.

Reliability : (2) valid with restrictions
2E

05.09.2003

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge, domestic
Contact time	:	
Degradation	:	= 71 % after 28 day
Result	:	
Deg. Product	:	
Method	:	OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO_2 evolution)"
Year	:	1999
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The inoculum used was activated sludege obtained from Newton Abbot sewage treatment works in England. The sewage treatment plant treats sewage predominantly of domestic origin. This was washed by centrifugation and re-suspension in test medium and maintained, aerated at room temperature until required.
Result	:	After 3, 6, 10, 20 and 28 days, 0, 8, 28, 56 and 71% of the available ERL-4221 was biodegraded, respectively. Although 71% of ERL-4221 was biodegraded within 28 days it did not achieve the pass window of 60% in 10 days. Thus, although ERL-4221 undergoes substantial biodegradation, it does not meet the formal definition of readily biodegradable.
Reliability	:	(1) valid without restriction 1A

19.08.2003 (9)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m = 3.2
LC100	:	m = 32
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	2000
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A stock concentrate was prepared at 320 g/L of ERL-4221 in dimethylformamide (DMF) and diluted by the appropriate amount of DMF to give a 300 ml solution at the correct nominal concentrations. The resultant test solutions were clear and colorless up to 100 g/L, clear and very pale yellow in color at 180 g/L and clear and pale yellow in color at 320 g/L. Stock solutions were prepared from the stock concentrate. Stock solutions were further diluted to produce the desired concentrations fish were exposed to. Nominal concentrations fish were exposed to was 0 (control), 1.8, 3.2, 5.6, 10, 18 and 32 mg/L.
Remark	:	ERL-4221 is rapidly hydrolyzed in water.
Result	:	For nominal concentrations of 1.8, 3.2, 5.6, 10, 18 and 32 mg/L the mean measured concentration at 0, 48 and 96 hours was 2.7, 2.9, 5.4, 10, 19 and 31 mg/L, respectively. Except for the lowest concentration, all values were within 10% of the target concentrations. The reason for the high analytical result for the lowest concentration of ERL-4221 is unknown. At the highest analytical concentration, 31 mg/L, all animals died within 96 hours. At all lower concentrations, all animals survived. No clinically visible effects were noted at analytical concentrations of 2.7 and 2.9 mg/L. At 5.6 mg/L, dark discoloration was noted in the fish. At 10 mg/L, dark discoloration and sounding was noted. At 18 mg/L, dark discoloration, sounding, irregular respiration, surfacing and quiescense were reported. Thus, the 96 hour LC50 was calculated to be 24 mg/L and the NOEC was 3.2 mg/L based on nominal concentrations. The pH values ranged from 7.4 to 7.7, dissolved oxygen concentrations ranged from 9.8 to 10.4 mg/L, and the temperatures recorded were within the range 15+/-1C. The total hardness (as CaCO3) 45.7 -48.3 mg/L and conductivity at 25C was 208-214 uS/cm.
Reliability	:	(1) valid without restriction 1A

17.10.2002 (10)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
Method	:	OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"

Year	:	1999
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 5 Daphnia magna/replicate were tested in 4 replicates to nominal concentrations of 0 (control), 5.6, 10, 18, 32, 56, 100 and 180 mg/L. The test solution temperature was maintained at 20+/-1C. A photoperiod of 16 hours light:8 hours dark with 20 minute transition periods was provided. The test solutions were not aerated. Daphnia were not fed during the course of the study. Due to differences between nominal and analytical concentrations at the two highest concentrations, data from these two concentrations were excluded when calculating the 48-hour EC50 using Stephan's method. Stephan, C.E. (1977). Methods for calculating an LC50. InAquatic Toxicology and Hazard Evaluation. Mayer, F.L. and Hamelink, J.L editors. Proceedings 1st Annual Symposium on Aquatic Toxicology. ASTM, 1977, STP 634 65-8.
Remark	:	ERL-4221 is rapidly hydrolyzed in water.
Result	:	The nominal concentrations of 5.6, 10, 18, 32, 56, 100 and 180 mg/L resulted in mean analytical concentrations of 5.2, 9.4, 16, 28, 57, 101 and 160 mg/L, respectively, based on arithmetic means of the 0, 24 and 48 hour concentrations. The resultant solutions were clear and colorless except for the nominal 100 mg/L concentration where a slight film was visible on the surface and 180 mg/L with a slight film on the surface and fine white globules on the base of the test vessel. After 24 hours, 2 daphnia at 180 mg/L were immobilized. After 48 hours, the number immobilized was 0, 0, 0, 2, 10, 11, 1 and 4 for nominal concentrations of control, 5.6, 10, 18, 32, 56, 100 and 180 mg/L, respectively. The 48 hour NOEC was 10 mg/L and the 48-hour EC50 was 40 mg/L based on nominal concentrations. The EC100 was not determined. Dissolved oxygen concentrations ranged from 8.8 to 9.2 mg/L and the pH values ranged from 7.84 to 8.05. The mean total hardness of the reconstituted dilution water batches was 609 mg/L CaCO3.
Reliability	:	(1) valid without restriction 1A 1A

23.07.2003 (11)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m = 22
LOEC	:	m = 27
EC50	:	m = 90
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	2000
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Nominal exposure concentrations of 0 (control), 5.6, 10, 18, 32, 56, 100

and 180 mg/L were used.

Remark : ERL-4221 is rapidly hydrolyzed in water.

The analytical data for the three highest concentrations is not consistent.

Table 1

Measured concentration of ERL-4221

Nominal Conc	Analytical Conc, mg/L 0 hr	72 hr
56	42	20
100	110	6.5
180	190	55

Data is based on centrifuged values.

The half life, based on hydrolysis, is expected to be 1-2 days. Thus one would expect approximately 75% of the material to be hydrolyzed within 72 hours. The difference noted at 72 hr for the nominal concentration of 100 mg/L is probably due to an analytical error.

Result : For the nominal concentrations of 5.6, 10, 18, 32, 56, 100 and 180 mg/L, the geometric mean measured concentration was 3.7, 6.6, 11, 22, 30, 27 and 110 mg/L, respectively, based on values obtained at 0 and 72 hours. The percent loss of ERL-4221 during the 72 hours was 46, 49, 53, 47, 48, 94 and 72% for nominal concentrations of 5.6, 10, 18, 32, 56, 100 and 180 mg/L, respectively.

For the measured concentrations of 0(control), 3.7, 6.6, 11, 22, 30, 27 and 110 mg/L, the average algal cell density from six r eplicates at 72 hours was 99.3, 99.1, 90.6, 97.0, 118, 104, 67.7 and 19.6 cells/ml (x10+4), respectively. The no-observed-effect-concentration (NOEC) was 22 mg/L and the lowest significant effect concentration was 27 mg/L

At the start of the test the pH of the test solutions ranged from 7.3 to 7.4 and at the end of the test the range was 7.3 to 8.2. During the course of the test the pH of the control culture medium solutions increased by 0.4 units.

Daily temperature measurements ranged from 24.1 to 24.3 C.

The light intensity, measured once during the study, was 8040 lux.

Reliability : (1) valid without restriction
1A

23.07.2003 (12)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	
Value	:	= 4.49 ml/kg bw
Method	:	
Year	:	1961
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 5 male rats were dosed orally with 2.0, 4.0, 8.0 or 16.0 ml/kg and observed for 14 days. Gross pathologic exam was performed on animals that died. Animals were weighed prior to dosing and survivors were weighed 14 days later. The method of moving average for calculating the median-effective dose was applied to the 14-day mortality data.
Remark	:	The specific gravity of the test material was 1180 mg/ml. The oral LD50 of 4.49 ml/kg corresponds to 5300 mg/kg which is in very close agreement with the study conducted in 1999.
Result	:	Animals weighed between 99 and 120 grams on the day of dosing. The number of animals dying was 2, 2, 3 and 5 at doses of 2.0, 4.0, 8.0 and 16.0 ml/kg. Deaths in the highest dose group occurred within 18 hours after dosing while most of those on the lower levels were delayed from two to four days. Gross pathological findings included congestion of the lungs, stomachs, intestines and adrenals; paleness of the kidneys; and congestion of the livers with priminent acini and burned areas discernible on surfaces that had been in opposition to stomachs that still contained part of the dose. Animals that survived gained between 58 and 110 grams. The oral LD50 was 4.49 ml/kg.
Reliability	:	(2) valid with restrictions 2E

28.08.2003 (13)

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	20
Vehicle	:	
Value	:	ca. 5000 mg/kg bw
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1999
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 5 male and 5 female rats were dosed via oral gavage with 2959 and 5000 mg/kg.
Remark	:	The specific gravity of the test material was 1180 mg/ml. Thus 5000 mg/kg corresponds to 4.24 ml/kg which is in very close agreement with the study conducted in 1961.
Result	:	Three males and two females in the 5000 mg/kg group died within six days of dosing. Mortality was 0/10 and 5/10 for the 2959 and 5000 mg/kg groups, respectively. Clinical findings were noted in both dose groups during the first week of the

study. Four animals in the 2959 mg/kg group and all animals in the 5000 mg/kg group were noted with various discolored areas due to discharges/excretions, hypoactivity and/or impaired muscle coordination. Three animals in the 5000 mg/kg group were noted with decreased defecation, decreased urination, labored respiration and/or convulsions. There were no other clinical findings. All surviving animals appeared normal by day 6 and throughout the remainder of the study.

There were no remarkable body weight changes observed during the study.

Three animals that died were noted with gastric abnormalities. There were no other internal gross necropsy findings for animals found dead.

At the terminal necropsy, findings included capsular scarring on the spleen for one male in the 5000 mg/kg group. There were no other findings for any examined tissues at the scheduled necropsy.

The LD50 of cycloaliphatic epoxy resin ERL-4221 was found herein to be approximately 5000 mg/kg in fasted male and female Sprague Dawley rats when administered once orally via gavage.

Reliability : (1) valid without restriction
1A

28.08.2003 (14)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Species	:	rat
Strain	:	
Sex	:	female
Number of animals	:	6
Vehicle	:	
Exposure time	:	8 hour(s)
Method	:	
Year	:	1961
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 6 female rats was exposed to saturated vapors of EP-221 for 8 hours. Saturated vapors were generated at a temperature of 21C by passing dried air at the rate of 2.5 liters/minute through a fritted glass disc immersed to a depth of at least one inch in 50 ml of EP-221. The animals were observed for 14 days and a gross necropsy exam was conducted on surving animals as well as those that died during the observa tion period.
Remark	:	Based on the low vapor pressure, 0.00002 hPA, a saturated atmosphere contains approximately 0.02 ppm EP-221.
Result	:	All animals survived the 8 hour exposure period as well as the 14 day post exposure observation period. The animals gained weight during the subsequent two week observation period and exhibited no grossly visible effects upon gross examination.
Reliability	:	(2) valid with restrictions 2E

28.08.2003 (13)

Type	:	LC50
Species	:	rat
Strain	:	
Sex	:	female

Number of animals	:	6
Vehicle	:	
Exposure time	:	8 hour(s)
Method	:	
Year	:	1961
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 6 female rats was exposed to a condensation aerosol and any decomposition products of EP-221 for 8 hours. The condensation aerosol was generated by passing dried air at the rate of 2.5 liters/minute through a fritted glass disc immersed to a depth of at least one inch in 50 ml of EP-221. The glass disc from submerged in a silicone oil bath maintained at a temperature sufficiently high to keep the EP-221 at approximately 162C. The ambient air temperature in the chamber never exceeded 28C. The animals were observed for 14 days and a gross necropsy exam was conducted on surving animals as well as those that died during the observation period.
Result	:	Five of six rats survived after eight hours in this atmosphere. The lone death occurred the day after inhalation and autopsy revealed from 70 to 80% lung hemorrhage. The five survivors gained weight normally during the subsequent two week observation period. There were no grossly visible changes observed in any of the surviving rats at the conclusion of the two week observation period.
Reliability	:	(2) valid with restrictions 2E

06.08.2003 (13)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	4
Vehicle	:	
Value	:	> 20 ml/kg bw
Method	:	
Year	:	1961
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 4 male New Zealand White rabbits, 3-5 months of age and averaging 2.5 kg were dosed dermally with 20 ml/kg of ERL-4221. The hair on the trunk of the rabbits was removed prior to treatment. The test material was applied and a sheet of VINYLITE was placed on the application site to retain the dose in contact with the skin. The rabbits were immobilized during the 24 hour dermal contact period. After 24 hours, the sheeting was removed and the animals were caged for the remainder of the 14-day observation period. Body weights were obtained prior to dosing and at the end of the observation period.
Result	:	One of four rabbits dosed dermally with 20 ml/kg died four days after dosing. The cause of death could not be determined. Two of three survivors lost weight (20 and 408 gram) during the two-week observation period. No additional information supplied in report.
Reliability	:	(2) valid with restrictions 2E

06.08.2003 (13)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	
Exposure time	:	4 hour(s)
Number of animals	:	6
PDII	:	
Result	:	
EC classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 6 rabbits, 3 males and 3 females, was used. A volume of 0.5 ml was applied to the dorsal area of the trunk of each rabbit which had been previously clipped free of hair. A 1-inch square gauze patch was placed over the dose site and was secured by adhesive tape. Polyethylene sheeting was placed loosely around the trunk and secured. The animal was restrained for the 4-hour contact period after which the coverings and excess test material were removed. Readings were made starting at 1, 24, 48 and 72 hours and at 7 and 14 days after the 4 hour contact period using the Draize method (Draize, 1959). Draize, J.H. (1959). The appraisal of chemicals in foods, drugs and cosmetics. The Association of Food and Drug Officials of the United States.
Result	:	Application of 0.5 ml of Cyracure UVR-6110 to covered rabbit skin for a 4-hour contact period produced minor erythema on 6 of 6 rabbits. Minor transient edema was produced on 3 animals. There was no edema present on any animal by 2 days. Erythema subsided on 5 of 6 rabbits within 7 days and the last rabbit within 14 days. The modified primary irritation score (average of 1 and 24 hour mean values) was 1.35. This material is not irritating or corrosive to skin.
Reliability	:	(1) valid without restriction 1A

07.08.2003 (15)

Species	:	rabbit
Concentration	:	
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
PDII	:	
Result	:	
EC classification	:	
Method	:	
Year	:	1984
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 3 male and 3 female rabbits were dosed with 0.5 ml of test material applied to the clipped, intact skin under a gauze patch. The patch is loosely covered with impervious sheeting. The animals are restrained for

		the 24 hour contact period. Excess sample is removed after contact. Skin reaction is scored, by the method of Draize, at one day (shortly after removing the patch and impervious sheeting), 2 days, 3 days and, depending upon the local skin reaction, possibly 7, 10 and 14 days after dosing.
Result	:	There was no evidence of edema observed after the 24 hour application of test material. Very slight erythema was noted in 3 of 6 rabbits, 1 male and 2 females, shortly after removal of the patch containing test material. Approximately 24 hours after removing the patch very slight erythema was still noted in one male rabbit. Desquamation was noted in one and two male rabbits two and 6 days after removing the patch. The study was concluded on day 6 after removal of the patch. CYRACURE Resin UVR-6110 produced minor irritation on rabbit skin following a 24-hour occluded application.
Reliability	:	(2) valid with restrictions 2E

07.08.2003 (16)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	
Exposure time	:	
Number of animals	:	5
PDII	:	
Result	:	
EC classification	:	
Method	:	
Year	:	1961
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Undiluted EP-221 was applied undiluted to clipped skin on the belly of the rabbit. The dosage was 0.01 ml. No additional information provided.
Remark	:	No information provided in the report on the length of the exposure to test material. The amount used, 0.01 ml, is much lower than currently required in OECD guidelines, 0.5 mls. Thus the study is considered to be invalid.
Result	:	There was no reaction on four animals and marked capillary injection on a fifth. No additional information provided
Reliability	:	(3) invalid 3B

06.08.2003 (13)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure Time	:	
Comment	:	
Number of animals	:	4
Result	:	
EC classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1992

GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A total of 4 rabbits, 2 males and 2 females, were used. A volume of 0.1 ml of test material was placed into the conjunctival sac of 1 eye/rabbit. The other eye of each animal served as the control. The eye was examined at 1, 24, 48 and 72 hours and at 7 and 9 days following instillation. Fluorescein staining was performed at day 1 and each subsequent examination. Grading and scoring followed the Draize system (Draize, 1959). Draize, J.H. (1959). The appraisal of chemicals in foods, drugs and cosmeti cs. The Association of Food and Drug Officials of the United States.
Result	:	A volume of 0.1 ml of test material instilled into rabbit eyes produced no corneal injury or irits in any of 4 rabbits dosed. Minor conjunctival irritation consisting of slight erythema, slightly swollen conjunctiva and slight discharge, was observed in all 4 rabbits within 1 hour. The dosed eye of 1 rabbit healed within 48 hours. The 3 remaining rabbits had a normal ocular appearance within 72 hours to 9 days. The material is not an ocular irritant using the Draize/FHSA interpretation. FHSA (1989). Consumer Product Safety Commission (1989). Regulations under FHSA, Title 16, Code of Federal Regulations, Ch. II, Commercial Practices, Sectoin 1500.
Reliability	:	(1) valid without restriction 1A

07.08.2003 (15)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure Time	:	
Comment	:	
Number of animals	:	6
Result	:	
EC classification	:	
Method	:	
Year	:	1984
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 3 male and 3 female rabbits were dosed with 0.1 ml of test material. The dose is instilled into the lower conjunctival sac of one eye per animal or is placed directly on the eye. The eyes are held together for one second. Six eyes are dosed per test volume. The eyes are scored at one and 4 hours and 1, 2 and 3 days after dosing. The eyes were scored using a modification of the Draize score.
Result	:	There was no observable effect on the cornea or iris at any time point post dosing. The most severe effects on the conjunctiva occurred one hour after dosing and all effects were absent within 48 hours. Conjunctival redness varied from 0 (normal) to 2 (diffuse, deep crimson red) one hour after dosing. The mean score was 1.5. By 24 hours after dosing, 2 rabbits still exhibited slight conjunctival redness. All animals appeared normal within 48 hours after dosing. The swelling ranged from 0 (normal) to 2 (obvious swelling with partial eversion of eyelids). The mean score was 0.8. By 24 hours there was no visible evidence of swelling. The eye discharge ranged from 0 (normal) to 2 (discharge moistening lids and hairs adjacent to lids). The mean score was 1.0. By 24 hours there was no visible evidence of a discharge. Instillation of 0.1 ml of sample into rabbit eyes produced minor transient

irritation. All animals appeared normal within 48 hours after dosing.

Reliability : (2) valid with restrictions
2E

07.08.2003 (16)

Species : rabbit
Concentration : undiluted
Dose : .5 ml
Exposure Time :
Comment :
Number of animals : 5
Result :
EC classification :
Method :
Year : 1961
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : Five rabbits had 0.5 ml of EP-221 instilled into the eye.

No additional information provided.

Remark : Although the dose volume was much greater than currently recommended, the very slight irritation observed suggests minimal or no eye irritation at recommended dose volumes.

Result : Three rabbit eyes were apparently unharmed and two others had only trace injuries.

Reliability : (2) valid with restrictions
2E

07.08.2003 (13)

5.3 SENSITIZATION

Type : Guinea pig maximization test
Species : guinea pig
Concentration : Induction 5 % intracutaneous
Induction 100 % occlusive epicutaneous
Challenge 100 % occlusive epicutaneous
Number of animals :
Vehicle : other: propylene glycol was used for intracutaneous administration
Result : sensitizing
Classification : sensitizing
Method : other: essentially follows OECD 0406
Year : 1991
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : Range finding study - Groups of 2 guinea pigs were administered intradermal injections (2 sites per animal) of a 5.0% v/v concentration of the test material in propylene glycol. Animals were observed at 24 and 48 hours for necrosis and ulterations.

Range finding study - A topical range-finding study was performed to determine the lowest concentration which produced mild irritation (to be used for induction) and the highest concentration which did not produce irritation (to be used for challenge. Six guinea pigs, 3 male and 3 female were used. Each animal was dosed with 10, 25, 50% v/v and 100% test material. The vehicle used was 70% ethanol. A 0.1 ml sample of test material was placed on each application site and the sites were covered with plastic sheeting which was secured with elastic adhesive bandage. After 24 hours, the bandages, sheeting and patches were removed.

Observations for signs of dermal irritation (erythema, edema and eschar formation) were made approximately 24 and 48 hours after removal of the patches.

Definitive study - A group of 10 male and 10 female guinea pigs were used in the guinea pig maximization test. For intradermal doses, a 5% concentration of ERL-4221 dissolved in propylene glycol was used. For the topical application neat ERL-4221 was used. Since the test material was non-irritating at 100% concentration, the area was pre-treated with 10% sodium lauryl sulfate (SLS) in petrolatum 24 hours before the material was applied in order to provoke a mild inflammatory reaction. The SLS was massaged into the skin with gloved fingers. An additional group of 5 male and 5 female guinea pigs were used as irritation controls. For the irritation controls, neat propylene glycol was used for intradermal doses while 70% ethanol was used topically.

For the challenge phase, 0.1 ml of test material was applied and remained on the skin for 24 hours on day 21 for animals from the definitive study and irritation controls. Dermal readings were made on all animals 24 and 48 hours after removal of the patches.

Result : Range finding study - For the intradermal injection, a 5.0% solution in propylene glycol was injected in two sites in two animals. Local necrosis was the only effect observed. There was no evidence of extensive necrosis or ulceration. Therefore this concentration was used for the intradermal induction administration.

Range finding study - For the topical application, six animals, 3 females and 3 males, were used. Concentrations of 10, 25 and 50% v/v and 100% were placed on one of four sites on each animal. The undiluted material was non-irritating and was therefore administered at a 100% concentration for both induction and challenge.

Definitive study - One male guinea pig died 4 days after the topical application. Gross postmortem observations revealed discolored lungs, the surface of liver was yellow and the abdominal cavity was filled with yellow fluid. Since all remaining animals were free of any signs of toxicity, this death was probably not related to test material administration. During the challenge phase 19 of 19 guinea pigs exhibited a score of 0.5 or greater and 12 of 19 had a score of 1.0. For the irritation control animals, 0 of 10 guinea pigs exhibited a score of 0.5 or greater.

Based on this study, ERL-4221 exhibited a potential to produce dermal sensitization in the guinea pig.

Reliability : (1) valid without restriction
1A

28.08.2003 (17)

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	other: CFE albino strain
Route of admin.	:	oral feed
Exposure period	:	97 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	0, 31.25, 125, 500 and 2000 mg/kg/day

Control group	:	yes, concurrent no treatment
Method	:	
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 10 male and 10 female rats were fed diets containing 0, 31.5, 125, 500 or 2000 mg/kg/day epoxide 221. Rats were fed twice weekly during the first week of the study and weekly thereafter. Animals were observed daily for symptoms of abnormalities. Animals that died were necropsied. Animals that survived to the end of the study were necropsied and liver and kidney weights were obtained.
Result	:	Mortality was not substantially affected at any dose level. None, one or two rats of each sex died during the three month period. All deaths, decept one where autolysis concealed the cause, were attributed to lung infections. Feed consumption was decreased at all dose levels for the females and at 0.125 and 2.0 mg/kg/day for the males. Similarly body weight gain for 125, 500 and 2000 mg/kg/day females was significantly lower than that of the controls, while only the 2000 mg/kg/day male group was affected. Relative liver weights of the 2000 mg/kg/day male group and 500 mg/kg/day female group were significantly higher than control values. Kidney weights of 500 and 2000 mg/kg/day male and female groups were significantly increased. However, there were no gross or histopathological effects noted in the liver or kidney or any of the other organs examined from those of the control animals.
Reliability	:	(3) invalid 3B Pulmonary infections affected survival in all groups.

08.08.2003 (18)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	14 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	0, 111, 556, 834 and 1113 mg/kg/day
Control group	:	yes, concurrent vehicle
LOAEL	:	= 100 mg/kg bw
Method	:	
Year	:	2000
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 10 male and 10 female rats received 0, 111, 556, 834 and 1113 mg/kg/day of ERL-4221 via oral gavage for 14 consecutive days. The vehicle for all dose levels was Mazola corn oil. In-life observations included clinical observations each day. Body weight and feed consumption were measured on a weekly basis. At the end of the study, the animals were fasted prior to necropsy. A complete necropsy was conducted on all animals. With two exceptions, a complete set of tissues were placed in 10% neutral buffered formalin. Testes were preserved in Bouin's solution and poles of the left kidney and one half of the right kidney and part of the left lobe of the liver were frozen and stored at -70C. The frozen kidney and liver were evaluated for 32P-postlabeling of DNA adducts (reported in in-vivo genetics section of dossier). Standard tissues were weighed at necropsy. Microscopic examination was conducted on the adrenal glands, kidneys, lungs, spleen, stomach and gross lesions from five randomly selected animals/sex/group in the control and 1000 mg/kg/day groups. The livers (males and females) and

testes (males) were examined from each of the lower dose levels.

Statistical analysis of body weights, body weight changes, feed consumption and absolute and relative organ weights was conducted using a one-way analysis of variance (ANOVA) followed by Dunnett's test if the ANOVA revealed statistical significance ($p<0.05$).

Remark : Although the report states that the hepatocellular vacuolization was minimal in females, both control and treated female rats exhibited effects ranging from mild to minimal in severity. In males, the effect was mild at all dose levels, except control, where 1 of 10 exhibited an effect.

Result : Test material-related clinical observations consisted of evidence of increased salivation in males and females receiving 500, 750 and 1000 mg/kg/day and yellow material in the urogenital area of females receiving 750 and 1000 mg/kg/day. These clinical signs were observed in some animals from each of the groups, most frequently, but not exclusively, at the 1-hour post-dosing interval. There was no affect on survival. All rats survived until the scheduled sacrifice.

Dose-related decreases in body weight and weight gain were observed for males dosed at 500 mg/kg/day and above and for females at 1000 mg/kg/day (Table 1). Decreased mean feed consumption was observed in the 750 and 1000 mg/kg/day group males during the first week of the study.

Table 1

Body weights (g) of rats in range-finding study

	mg/kg/day				
Week	0	100	500	750	1000
			males		
0	291+/-24.4	291+/-24.7	287+/-22.1	286+/-27.1	287+/-21.6
1	323+/-30.7	323+/-34.1	306+/-29.7	296+/-37.9	299+/-24.7
2	354+/-37.3	353+/-38.8	333+/-31.4	321+/-41.4	316+/-27.1
			females		
0	197+/-16.7	198+/-12.9	198+/-15.0	202+/-16.6	200+/-14.0
1	214+/-14.5	212+/-17.8	210+/-14.3	215+/-17.6	208+/-16.4
2	229+/-15.2	225+/-19.2	226+/-19.8	224+/-18.5	215+/-17.8

No values were statistically significantly different from control value, $p<0.05$.

In males, increased mean absolute and relative (to final body weight) liver weights were observed in the 100, 500, 750 and 1000 mg/kg/day groups (Table 2). Test material related increases in mean absolute and relative (to final body weight and to brain weight) liver weights were noted for the 500, 750 and 1000 mg/kg/day group females. There was no clear dose response for these increases. These changes in liver weights correlated with an increased incidence and/or severity of periportal hepatocellular vacuolation observed microscopically in the 100 mg/kg/day group males and in the 500, 750 and 1000 mg/kg/day group males and females, although the changes in the livers of the females was minimal.

Table 2

Absolute and relative weights of rats in range-finding study

	mg/kg/day				
Parameter	0	100	500	750	1000
			males		

Body Wt.	328+/-35	323+/-37	304+/-29	293+/-39	290+/-24*
Liver	11.1+/-1.8	13.4+/-2.1	12.8+/-2.0	12.3+/-2.0	11.8+/-1.0
Liver/BW	3.36+/-0.25	4.12+/-0.26**	4.17+/-0.28**	4.19+/-0.18**	4.08+/-0.25**

females

Body Wt.	213+/-13	208+/-18	208+/-18	207+/-18	201+/-16
Liver	7.9+/-0.7	8.4+/-0.81	9.5+/-1.1**	9.4+/-0.9**	9.3+/-1.2**
Liver/BW	3.73+/-0.36	4.06+/-0.15	4.58+/-0.32**	4.56+/-0.35**	4.64+/-0.37**

Parameters expressed as means +/- S.D. in grams and due to space limitations have been rounded off.
** Statistically significantly different from control value, p<0.01.

The Lowest-Observed-Effect-Level was 100 mg/kg/day, the lowest dose studied. Thus, a No-Observed-Effect-Level was not established in this study.

Reliability : (1) valid without restriction
1E

30.07.2003 (19)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	90 day
Frequency of treatment	:	daily
Post obs. period	:	28 day
Doses	:	0, 5, 50 and 500 mg/kg/day based on epoxy equivalent factor of 92.5%
Control group	:	yes, concurrent vehicle
NOAEL	:	= 5 mg/kg bw
LOAEL	:	= 50 mg/kg bw
Method	:	OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year	:	2001
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of Sprague Dawley rats were orally gavaged with 0, 5, 50 or 500 mg/kg/day of ERL-4221. The control and high dose consisted of 25 males and 25 females in each group while the intermediate doses consisted of 20 males and 20 females in each group. Doses were based on an epoxy correction factor of 92.5%. The vehicle was Mazola corn oil. Groups of 15 rats/sex/dose level were assigned to the primary necropsy and groups of 5 rats/sex/dose level from the intermediate dose groups or 10 rats/sex/dose level from the control and top dose group was assigned to a 28-day recovery period. Parameters evaluated included clinical observations, body weights, feed consumption, clinical pathology (hematology, serum chemistry and urinalysis), ophthalmology, vaginal cytology and spermatogenic endpoints. Complete necropsies were performed on all animals and selected organs were weighed. Selected tissues were examined microscopically at the primary necropsy as well as the 28-day recovery period.
Result	:	All animals survived to the scheduled sacrifice periods. Increased salivation and yellow material on the fur were observed primarily after dosing the 500 mg/kg/day males and females. Body weights of the 500 mg/kg/day males were decreased, although not statistically significant, throughout the study. Feed consumption was unaffected in male or female rats receiving up to 500 mg/kg/day. Hematological parameters also appeared to be unaffected in male or female rats receiving up to 500 mg/kg/day. There were no test material-related changes in estrous cycle or spermatogenic endpoints. At the end of the 13-week dosing period, effects were noted in the kidney, liver and olfactory epithelium of the nasal tissues. Slight effects in absolute and

relative kidney weights in the 500 mg/kg/day group and correlating serum chemistry (increased serum urea nitrogen and phosphorous) and urinalysis (decreased pH and urine creatinine levels (males only)) changes in the 50 and 500 mg/kg/day groups were observed. There were no histopathologic changes noted in the kidneys.

SLight effects were noted in absolute and relative liver weights in the 50 and 500 mg/kg/day groups. Slight changes in liver function, as indicated by serum chemistry alterations (reduced cholesterol levels and increased direct bilirubin and sorbitol dehydrogenase levels), were observed in the 50 and 500 mg/kg/day groups. These effects were accompanied by minimal to mild histopathologic changes in the liver.

Degeneration of the olfactory epithelium in the nasal tissues was seen in the 50 and 500 mg/kg/day group males and females but not in any of the control group animals.

Following a 28-day recovery period, mean body weight of the males from the 500 mg/kg/day dose group remained lower than the controls although weight gain during the period was similar. Olfactory epithelial degeneration was observed in both males and females from the 50 and 500 mg/kg/day groups, although at a lower incidence. In addition, regenerative changes were also evident in the olfactory epithelium.

In conclusion, based on the results of this study, the no-observed-effect-level (NOEL) for oral administration of ERL-4221 to rats for a minimum of 90 days was 5 mg/kg/day for both males and females. Both males and females from the 50 mg/kg/day group showed evidence of recovery from all effects following a four-week recovery period; however, lesions in the nasal tissues persisted.

Reliability : (1) valid without restriction
1A

06.08.2003 (20)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	
Concentration	:	
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	positive
Method	:	other: essentially follows OECD 471
Year	:	1985
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	For the preliminary toxicity screen, dose levels of 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 and 117.5 mg/plate were used with strain Salmonella typhimurium strain TA100 only. For the definitive study, dose levels of 0.1, 0.3, 1, 3 and 10 mg/plate were run in triplicate for each strain of bacteria used. Strains TA98, TA100, TA1535, TA1537 and TA1538 were used. Concurrent solvent, dimethylsulfoxide, and positive controls were run with each test. Both activation-dependent and activation-independent positive controls were used. The activation-independent controls were 4-nitro-o-phenylenediamine for TA98 and TA1538, sodium azide for TA100 and TA1535, and 9-aminoacridine for TA1537. The activation-dependent control in 2-aminoanthracene (2-anthramine) for all strains.

Result : For metabolic activation, samples of Aroclor -1254 induced, rat liver homogenate (S9) was prepared
In the preliminary screen, complete inhibition of the background lawn growth was observed at doses of 10, 30 and 117.5 mg/plate. Based on these results, mutagenicity testing for the definitive study was conducted at 0.1, 0.3, 1.0, 3.0 and 10 mg/plate.

For the definitive study toxicity was noted at the highest dose, 10 mg/plate, in each strain with and without metabolic activation (Table 1). The only increase in mutagenic activity was observed in strains TA100 and TA1535 with metabolic activation. There was no increase in mutagenic activity in strains TA98, TA1537 or TA1538 with metabolic activation and in any strain without metabolic activation.

Table 1
Results in Ames test with various strains

		Activation	
Strain	Dose, mg/plate	without	with
TA98	Solvent	26+/-3.6	21+/-1.2
	0.1	28+/-6.5	20+/-1.5
	0.3	22+/-4.5	18+/-2.1
	1	24+/-2.6	29+/-1.5
	3	20+/-3.5	27+/-10.1
	10	Toxic	Toxic
	Positive Control	885+/-67.0	1490+/-280.9
TA100	Solvent	134+/-4.5	100+/-13.0
	0.1	133+/-8.2	100+/-8.3
	0.3	131+/-6.7	114+/-10.4
	1	135+/-8.5	140+/-7.2
	3	132+/-9.3	253+/-8.7
	10	Toxic	Toxic
	Positive Control	2210+/-117.2	1223+/-42.8
TA1535	Solvent	35+/-9.6	9+/-2.1
	0.1	45+/-10.7	14+/-4.7
	0.3	40+/-2.5	18+/-8.5
	1	39+/-12.9	51+/-4.7
	3	39+/-6.1	138+/-15.1
	10	Toxic	Toxic
	Positive Control	2256+/-147.0	75+/-10.2
TA1537	Solvent	5+/-1.7	6+/-1.5
	0.1	5+/-1.5	5+/-2.5
	0.3	5+/-1.5	3+/-0.6
	1	7+/-3.1	3+/-2.0
	3	6+/-4.2	8+/-2.6
	10	Toxic	Toxic
	Positive Control	91+/-12.1	63+/-27.1
TA1538	Solvent	9+/-1.5	15+/-6.8
	0.1	12+/-4.4	14+/-4.6
	0.3	7+/-1.2	7+/-2.3
	1	5+/-1.0	16+/-3.1
	3	7+/-2.1	14+/-1.0
	10	Toxic	Toxic
	Positive Control	1032+/-22.5	206+/-21.1

Reliability : (2) valid with restrictions
2E

24.07.2003 (21)

Type : Ames test
System of testing : preincubation method
Concentration : 156 - 5000 ug/plate
Cycotoxic conc. :
Metabolic activation : with and without
Result : positive
Method : Guidelines for screening mutagenicity testing of chemicals, JAPAN
Year : 1995
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : Salmonella typhimurium TA98, TA100, TA1535, TA1537 and E coli strain WP2 uvrA- were used at dose levels of 156 to 5000 ug/plate of UVR-6110. The preincubation method was used. Dimethylsulfoxide (DMSO) was used as the vehicle.

Positive controls used were 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, AF-2
sodium azide, NaN3
9-aminoacridine, 9-AA
N-ethyl-N'-nitro-N-nitrosoguanidine, ENNG
2-aminoanthracene, 2-AA

The S9 mix was prepared from liver homogenate of Sprague-Dawley rats which had received ip injection of phenobarbital and 5,6-benzoflavone.

Result : There was no effect on any strains without metabolic activation (Table 1) and on strains TA98, TA1537 and WP2 uvrA- with metabolic activation (Table 2). The number of revertants induced by the test substance were more than double of the solvent control in strains TA100 and TA1535 with metabolic activation. Microbial growth inhibition was observed, typically at the highest dose. Undissolved test substance was observed on the agar plate at 5000 ug/plate.

Table 1
Results of Ames test without metabolic activation

Strain	Dose/plate (mg)	Average
TA98	Solvent	12
	0.156	12
	0.313	12
	0.625	15
	1.25	15
	2.50	21
	5.00	Toxic
	Positive Control	616
TA100	Solvent	112
	0.156	115
	0.313	133
	0.625	127
	1.25	107
	2.50	49-Toxic
	5.00	Toxic
	Positive Control	507
TA1535	Solvent	11
	0.156	10
	0.313	10

	0.625	15
	1.25	12
	2.50	9
	5.00	Toxic
	Positive Control	216
TA1537	Solvent	4
	0.156	2
	0.313	3
	0.625	4
	1.25	6
	2.50	3
	5.00	Toxic
	Positive Control	796
WP2	Solvent	34
	0.156	33
	0.313	30
	0.625	35
	1.25	38
	2.50	29
	5.00	Toxic
	Positive Control	969

Positive control was 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide at 100 mg for strain TA98 and 10 mg for strain TA100, sodium azide at 500 mg for strain TA1535, 9-aminoacridine at 0.08 mg for strain TA1537 and N-ethyl-N-nitro-N-nitrosoguanidine at 0.002 mg for WP2
No standard deviation provided in report.

Table 2
Results of Ames test with metabolic activation

Strain	Dose/plate (mg)	Average
TA98	Solvent	19
	0.156	23
	0.313	18
	0.625	25
	1.25	23
	2.50	23
	5.00	9-Toxic
	Positive Control	214
TA100	Solvent	131
	0.156	149
	0.313	145
	0.625	157
	1.25	193
	2.50	288
	5.00	Toxic
	Positive Control	815
TA1535	Solvent	17
	0.156	23
	0.313	31
	0.625	43
	1.25	101
	2.50	189
	5.00	Toxic
	Positive Control	79

TA1537	Solvent	9
	0.156	5
	0.313	5
	0.625	8
	1.25	7
	2.50	7
	5.00	1-Toxic
	Positive Control	125
WP2	Solvent	35
	0.156	35
	0.313	31
	0.625	30
	1.25	34
	2.50	40
	5.00	15-Toxic
	Positive Control	947

Positive Control was 2-aminoanthracene at 0.0005 mg for strain TA98, 0.001 mg for strain TA100, 0.002 for strains TA1535 and TA1537 and 0.001 mg for strain WP2.
No standard deviation provided in report.

Reliability : (1) valid without restriction
1A

04.08.2003 (22)

Type : HGPRT assay
System of testing : Chinese Hamster ovary cells
Concentration :
Cycotoxic conc. :
Metabolic activation :
Result : negative
Method :
Year : 1980
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : In the first study, Chinese Hamster ovary cells were exposed for 16 hours to five concentrations of epoxy resin ERL-4221 without the addition of S9 metabolic activation system and for 5 hours to an identical range of concentrations with S9 activation. The 5 concentrations examined were 0.000625, 0.00125, 0.0025, 0.0050 and 0.001%, v/v. The cells used for 5 hours with S9 activation were not assessed for mutant induction because the CO2 concentration in the incubator used for these plates was abnormally high (due to a malfunction) and this malfunction inhibited or killed the cells. In addition, 2 controls were used. A solvent control using DMSO at 20 ul/ml and a H2O control at 20 ul/ml were used for the 3 controls. Positive controls, ethylmethanesulfonate (EMS) at 200 ug/ml without metabolic activation and dimethylnitrosamine at 740 and 3700 ug/ml with metabolic activation, were used also. The surviving fraction was determined at 20 to 24 hours after treatment and the mutant fraction was determined after a 7- to 9-day period to allow the mutant phenotype to express itself. Only the top five concentrations which allowed sufficient cell survival were assessed for survival and induction of mutants. Analysis of mutation frequencies in the CHO test followed the procedure of Irr and Snee which transforms the data prior to parametric analysis using s Student's t test.

The study was repeated with and without S9 activation. Without S9 activation, identical concentrations were used. With S9 activation, concentrations of 0.00125, 0.0025, 0.0050, 0.001 and 0.002%. All other

parameters were the same as in the first study.

Result : ERL-4221 was not active in stimulating a dose-related increase of mutant cells when tested either with or without the presence of an S9 metabolic activation system (Table 1). Neither of two experiments provided any indication of a statistically significant mutagenic effect of the test agent. ERL-4221 was considered inactive as an agent for inducing mutation of CHO cells in culture.

Table 1

Chinese Hamster Ovary mutation assay results

Test Chemical	Conc	Total # Viable	Mutant fraction	Mutants Colonies /10(6) viable cells
Experiment 1 without S9				
ERL-4221	0.000625%	0.507	0	0
	0.00125%	0.480	2	4.2
	0.0025%	0.480	0	0
	0.0050%	0.273	1	3.7
	0.0100%	0.163	0	0
DNSO	20 ul/ml	0.900	1	1.1
H2O	20 ul/ml	0.677	1	1.5
medium	-	0.850	0	0
EMS	200 ul/ml	0.600	22	36.7
Experiment 2 without S9				
ERL-4221	0.000625%	0.465	3	6.5
	0.00125%	0.430	2	4.7
	0.0025%	0.342	0	0
	0.0050%	0.218	3	13.8
	0.0100%	0.190	0	0
DNSO	20 ul/ml	0.528	3	5.7
H2O	20 ul/ml	0.615	2	3.3
EMS	200 ul/ml	0.450	124	275.6***
Experiment 2 with S9				
ERL-4221	0.00125%	0.882	14	15.9
	0.0025%	0.722	3	4.2
	0.0050%	0.782	15	19.2
	0.0100%	0.832	15	18.0
	0.0200%	0.780	2	2.6
DNSO	20 ul/ml	0.905	18	19.9
H2O	20 ul/ml	0.965	5	5.2
DMN	3700 ul/ml	0.495	63	127.3***
DMN	740 ul/ml	0.658	30	45.6*

Significantly different from solvent control value, * p<0.05 *** p<0.001

Reliability : (2) valid with restrictions
2E

08.08.2003 (23)

Type : Sister chromatid exchange assay
System of testing : Chinese Hamster ovary
Concentration :
Cycotoxic conc. :
Metabolic activation :
Result :
Method : other: essentially follows OECD 479 guideline
Year : 1980
GLP : no

Test substance : as prescribed by 1.1 - 1.4
Method : In general follows OECD 479 guideline.

A range-finding study was conducted to determine the maximum dose level which would permit survival of at least 50% of the treated cells was based on the prescreening test for cytotoxicity performed as part of the CHO Mutation test.

Concentrations of ERL-4221 tested in the definitive study ranged from 0.00031225 to 0.0100% (by volume). Concentrations tested were 0.0003125, 0.000625, 0.0012.5, 0.0025, 0.0050 and 0.0100% v/v. Negative controls were DMSO at 5 ul/ml and H2O at 5 ul/ml. Positive control was ethylmethanesulfonate (EMS) at 100 ug/ml. CHO cells were exposed to ERL-4221 or appropriate controls for 5 hours without S9 activation. Indirect mutagenic action, required metabolic activation by liver S9 homogenate, was not studied because a highly significant positive response was obtained without metabolic activation which indicated a direct-acting mechanism for this material. Bromodeoxyuridine (BrdU) required to differentiate between the individual 'sister' chromatids by SCE staining, was present at a concentration of 3 g/ml in the growth medium during treatment and during culture period following exposure. A total of 15 cells/dose level and 5 dose levels without metabolic activation were examined. The number of SCE/cell, mean # of SCE/chromosome and the level of statistical significance of the increases above concurrent solvent control values were determined. Data was analyzed using parametric statistical procedres with Student's t-test.

Result : ERL-4221 produced statistically significant increases in the SCE frequency at 3 of the 6 dose levels tested in the absence of a metabolic activation system (Table 1). The increase in the numbers of SCE was dose dependent. The test without S9 activation was considered an indication of a significant direct mutagenic action of ERL-4221.

Table 1

Chinese Hamster Ovary Sister Chromatid Exchange results

Test Chemical	Conc	SCE /Cell	Mean # SCE/Chromosome
Without S9			
ERL-4221	0.0003125%	15.53	0.779+/-0.238
	0.000625%	14.67	0.743+/-0.233
	0.00125%	21.07	1.041+/-0.316***
	0.0025%	27.67	1.379+/-0.184***
	0.0050%	38.13	1.869+/-0.301***
	0.0100%	11.60	0.626+/-0.212
DNSO	5 ul/ml	12.13	0.628+/-0.214
H2O	5 ul/ml	13.33	0.680+/-0.169
EMS	100 ul/ml	28.20	1.417+/-0.242***

*** Statistically significant above solvent control, p<0.001

Reliability : (2) valid with restrictions
2E

08.08.2003 (23)

Type : Unscheduled DNA synthesis
System of testing : Rat liver cells
Concentration :
Cycotoxic conc. :
Metabolic activation :

Result : ambiguous
Method : other: essentially follows OECD 482 guideline
Year : 1980
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : UDS assay was conducted at concentrations of 0.0001, 0.0010, 0.0030, 0.0100, 0.0300 and 0.1% v/v ERL-4221. The negative solvent control was conducted at 3.0%. Positve controls were 4-nitroquinoline oxide (4-NQO) and DMN. Positive controls were studied at 3-6 concentrations.
Result : In hepatocytes treated with ERL-4221, two of the six concentrations, 0.0010 and 0.0001% tested for potential activity induced a statistically significant increase in the amounts of 3H-thymidine incorporation in the DNA (Table 1). Although there was no indication of a dose-response relationships due to treatment with the test material, the UDS values were sufficiently elevated to suggest a very weak level of mutagenic activity. These data were considered equivocal but sugges tive of a questionable-to-weak activity for ERL-4221.

Table 1

Results of unscheduled DNA synthesis in rat hepatocyte

Test Chemical	Conc	Radioactivity in DNA Mean+/-S.D.	% of solvent Control Mean+/-S.D.
ERL-4221	0.0001%	14629+/-993	171.4+/-11.6%**
	0.0010%	12172+/-242	142.6+/-2.8%
	0.0010%	14760+/-1453	172.9+/-17.0%**
	0.0100%	10882+/-1198	127.5+/-14.0%
	0.0300%	7864+/-307	92.1+/-3.6%
	0.1000%	495+/-289	5.8+/-3.4%
DNSO	3.0%	8537+/-3379	100.0+/-39.6%
4-NQO	0.3 ug/ml	10219+/-757	119.7+/-8.9%
	1.0 ug/ml	12011+/-3654	140.7+/-42.8%
	3.0 ug/ml	16720+/-940	195.0+/-11.0%***
DMN	1 ug/ml	16243+/-1690	190.3+/-19.8%***
	10 ug/ml	12198+/-3117	142.9+/-36.5%
	30 ug/ml	13322+/-4554	156.0+/-53.3%**
	100 ug/ml	13195+/-681	154.6+/-8.0%**
	300 ug/ml	14608+/-1669	171.1+/-19.5%**
	1000 ug/ml	9818+/-786	115.0+/-9.2%

Statistically significant above solvent control, ** 0.05>p>0.01 *** 0.01>p>0.001

Reliability : (2) valid with restrictions
2E

08.08.2003 (23)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : Swiss
Route of admin. : i.p.
Exposure period :
Doses : 500, 1000 and 2250 mg/kg
Result : negative

Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 1991
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : Probe study - Groups of 3 male and 3 female mice were dosed ip with 500, 1000, 1250, 1500, 1750, 2000, 2250, 2500 and 4000 mg/kg ERL-4221. The test material was dissolved in peanut oil. Mortality and clinical observations were observed during the first day after dosing.

Definitive study - Groups of 18 male and 18 female mice received 0, 500, 1000 and 2250 mg/kg ip. Additional groups of 5 male and 5 female mice received 25 and 40 mg/kg cyclophosphamide in isotonic saline. The same vehicle was used as for the probe study. Bone marrow smears, of 5 animals/dose group, were made at approximately 24, 48 and 72 hours after treatment. For the positive control groups, bone marrow smears were only made at 24 hours. Slides were fixed in methanol and stained with 5% Giemsa for approximately 20 minutes. The percentage of polychromatic erythrocytes (PCE) was counted for a minimum of 1000 erythrocytes.

One-tailed Fisher exact tests and binomial approximation tests were performed to determine if there was a statistically significant increase in the frequency of micronucleated cells in the treated groups. Since multiple comparisons were made, Bonferroni corrections were made to adjust the probability value required for significance. If no difference was detected at the 5% level of significance, the results were negative. If a difference was detected, the dose response was analyzed using the one-tailed Cochran-Armitage test for trend in binomial proportions. If this test detected a trend at the 5% level, the results were cosidered to be positive. If a trend was not detected, the Study Director evaluated the variability observed in the vehicle control and the nature of the statistically significant responses.

Result : Probe study - Mortality was observed within 24 hours of dosing in the 2500 and 4000 mg/kg groups. In addition, decreased motor activity, ataxia, collapse and labored breathing was observed at these dose levels and also at 2250 mg/kg. Based on these results, dose levels of 500, 1000 and 2250 mg/kg were selected for the definitive study.

Definitive study - Clinical signs of toxicity were observed in animals receiving ip doses of 2250 mg/kg. Clinical signs noted were decreased motor activity, collapse, weakness, ataxia and labored breathing.

Cytotoxicity was observed in low and high dose females. Only the increase observed in males treated with 1000 mg/kg and sampled at 48 hours was statistically significant when analyzed with the Fisher exact or binomial approximation test with the Bonferroni correction for multiple comparisons. This increase was not dose-responsive when analyzed with the Cochran-Armitage test for trend in binomial proportions. It is likely that the significance of that response is due to the unusually low spontaneous rate in the control group for that sampling time; therefore the response is not considered to be biologically significant.

Table 1

Frequency of micronucleated polychromatic erythrocytes (MN-PCE)/1000 PCE in bone marrow of mice treated with ERL-4221

	MN-PCE/1000 PCE		
Treatment group	24 hours	48 hours	72 hours
Males			
Control	1.2	0.0	0.4

500 mg/kg	0.8	1.0	0.8
1000 mg/kg	1.0	1.4	0.8
2250 mg/kg	2.0	0.6	0.6
Cyclophosphamide			
25 mg/kg	9.8*		
40 mg/kg	14.2*		
Females			
Control	0.4	0.2	0.2
500 mg/kg	1.8	0.2	1.2
1000 mg/kg	0.6	0.6	0.6
2250 mg/kg	0.8	0.2	1.4
Cyclophosphamide			
25 mg/kg	11.0*		
40 mg/kg	16.2*		

1000 PCE scored/animal, 5 animals scored/dose level

Table 2

Frequency of micronucleated polychromatic erythrocytes (MN -PCE)/5000 PCE in bone marrow of mice treated with ERL-4221

	MN-PCE/5000 PCE		
Treatment group	24 hours	48 hours	72 hours
Males			
Control	6	0	2
500 mg/kg	4	5	4
1000 mg/kg	5	7	4
2250 mg/kg	10	3	3
Cyclophosphamide			
25 mg/kg	49*		
40 mg/kg	71*		
Females			
Control	2	1	1
500 mg/kg	9	1	6
1000 mg/kg	3	3	3
2250 mg/kg	4	1	7
Cyclophosphamide			
25 mg/kg	55*		
40 mg/kg	81*		

5000 PCE scored/animal, 5 animals scored/dose level

Reliability : (1) valid without restriction
1A

01.08.2003 (24)

Type : Unscheduled DNA synthesis
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period :
Doses : 0, 500, 1000 and 2000 mg/kg
Result : negative
Method : other: OECD 486
Year : 1999
GLP : yes

Test substance : as prescribed by 1.1 - 1.4

Method : For the range-finding study, groups of 5 male Sprague Dawley rats were dosed with 1000, 2000, 4000 or 5000 mg/kg via oral gavage. The animals were observed immediately after dosing and daily thereafter for 3 days. Body weights were recorded prior to dose administration and on days 1 and 3 post-dosing.

For the definitive UDS assay, groups of 10 male rats were dosed with 0, 500, 1000 or 2000 mg/kg ERL-4221. Water was used as the vehicle for ERL-4221. A positive control group of the same size received 35 mg/kg dimethylnitrosamine (DMN). Of the ten rats in each group, 3 animals were sacrificed at each time point for hepatocyte culture. Time points were after 2-4 hours and 12-16 hours.

Any mean net nuclear count which was increased by at least 5 counts over the negative control was considered significant. The test article was judged positive if it induced a dose-related increase with no less than one dose significantly elevated above the negative control.

Result : For the range-finding study, all 5 animals died within 3 days of dosing at 4000 and 5000 mg/kg. All animals survived at the two lower dose levels, 1000 and 2000 mg/kg. Clinically, lethargy and piloerection were routinely noted one day after dosing at 2000 mg/kg and greater. All animals appeared to be normal after dosing at 1000 mg/kg.

For the definitive UDS assay, there was no significant increase in the mean number of net nuclear grain counts (i.e., an increase of at least 5 counts over the negative control) after 2-4 hours or 12-16 hours post-dosing (Table 1). The mean number of cells in repair ranged from 4-6% in the controls to 2-3, 2-3 and 2-9 % in the 500, 1000 and 2000 mg/kg groups, respectively, during the two sampling points. The positive control group exhibited 81-99% of the cells undergoing repair. Under these test conditions, ERL-4221 was concluded to be negative in the unscheduled DNA synthesis (UDS) test with mammalian liver cells in vivo.

Table 1
Summary of UDS assay with ERL-4221

Dose Group mg/kg	Time Period	net nuclear grain counts Mean +/- SD
Control	2-4	0.2+/-0.9
500	2-4	0.1+/-0.7
1000	2-4	-0.2+/-0.9
2000	2-4	-0.3+/-0.7
DMN, 35 mg/kg	2-4	17.6+/-1.2*
Control	12-16	-0.2+/-0.4
500	12-16	-0.4+/-0.3
1000	12-16	-0.2+/-0.7
2000	12-16	0.4+/-1.4
DMN, 35 mg/kg	12-16	10.5+/-3.2*

Significantly different from control values.

Reliability : (1) valid without restriction
1A

05.08.2003 (25)

Type : other: 32P-postlabeling analysis of in vivo DNA adducts
Species : rat
Sex : male/female
Strain : Sprague-Dawley

Route of admin.	:	gavage
Exposure period	:	90-day
Doses	:	0 and 500 mg/kg/day
Result	:	negative
Method	:	
Year	:	2000
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Samples of liver, kidney and stomach from 5 male rats and liver and kidney from 5 female rats were obtained from the vehicle control and 500 mg/kg/day groups at the time of necropsy in the 90 day study (Padgett, 2001). Groups of 5 male and 5 female rats were treated with mitomycin C as positive controls. No additional information was provided in this report on the positive control group. Tissue samples were frozen in liquid nitrogen until used. Techniques used to analyze DNA adducts included isolation of DNA from liver, kidney and stomach tissue from male rats and liver and kidney from female rats. Once the DNA was isolated, samples were spectrophotometrically quantified as to purity and amount of DNA. Next, samples of DNA were digested by micrococcal nuclease (MN) and calf spleen phosphodiesterase (SPD) and processed using nuclease P1 as well as butanol enrichment. DNA from mitomycin-C treated animal tissues were analyzed by the nuclease P1 method using TLC Condition 1 only since the adducts of mitomycin-C are adequately purified and identified using these procedures. The nuclease P1 and butanol enriched DNA digests were 32P-postlabeled with 32P-ATP. The labeled adducts were chromatographed on anion exchange polyethyleneimine (PEI)-cellulose TLC using two different sets of buffers (TLC Conditions 1 and 2). TLC Condition 1 was used to resolve bulkier base modifications of medium to low polarity. Since it was considered possible that, the test article may have broken down in vivo to smaller components, a different set of buffers (TLC Condition 2) was used to resolve any more polar adducts resulting from the modification of base(s) by smaller molecule(s) derived from the test article. TLC Condition 1 used 1.7M sodium phosphate for approximately 16 hours which was subsequently followed by 1.7M lithium formate and 3.2M urea. TLC Condition 2 used 1.5M formic acid for approximately 16 hours followed by 0.6M ammonium formate. All the chromatograms from the above TLC developments were dried and scanned using a Packard InstantImager. The chromatograms of control and ERL-4221 treated DNAs were compared to detect any exposure-related new spots. Endogenous spots common to both vehicle control and treated samples were also quantified, when appropriate, to determine if radioactivity of a preexisting spot was affected by treatment.
Remark	:	The study was conducted in the spirit of compliance with Good Laboratory Practice (GLP) regulations.
Result	:	Based on the enrichment, labeling and TLC conditions used in this assay, exposure to the highest dose of ERL-4221 (500 mg/kg/day for 90 days) did not induce detectable amounts of new DNA adducts or enhance existing adducts in liver or kidney DNA from male and female Sprague-Dawley rats.
Reliability	:	(2) valid with restrictions 2E

06.08.2003 (26)

Type	:	other: 32P-postlabeling analysis of in vivo DNA adducts

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	14 day
Doses	:	0 and 1113 mg/kg/day
Result	:	negative
Method	:	
Year	:	2000
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Samples of liver and kidney from 5 male and 5 female rats were obtained from the vehicle control and 1000 mg/kg/day groups at the time of necropsy in the 14 day study (Padgett, 2000). Groups of 5 male and 5 female rats were treated with mitomycin C as positive controls. No additional information was provided in this report on the positive control group. Tissue samples were frozen in liquid nitrogen until used. Techniques used to analyze DNA adducts included isolation of DNA from liver and kidney from male and female rats. Once the DNA was isolated, samples were spectrophotometrically quantified as to purity and amount of DNA. Next, samples of DNA were digested by micrococcal nuclease (MN) and calf spleen phosphodiesterase (SPD) and processed using nuclease P1 as well as butanol enrichment. DNA from mitomycin-C treated animal tissues were analyzed by the nuclease P1 method using TLC Condition 1 only since the adducts of mito mycin-C are adequately purified and identified using these procedures. The nuclease P1 and butanol enriched DNA digests were 32P-postlabeled with 32P-ATP. The labeled adducts were chromatographed on anion exchange polyethyleneimine (PEI)-cellulose TLC using two different sets of buffers (TLC Conditions 1 and 2). TLC Condition 1 was used to resolve bulkier base modifications of medium to low polarity. Since it was considered possible that, the test article may have broken down in vivo to smaller components, a different set of buffers (TLC Condition 2) was used to resolve any more polar adducts resulting from the modification of base(s) by smaller molecule(s) derived from the test article. TLC Condition 1 used 1.7M sodium phosphate for approximately 16 hours which was subsequently followed by 1.7M lithium formate and 3.2M urea. TLC Condition 2 used 1.5M formic acid for approximately 16 hours followed by 0.6M ammonium formate. All the chromatograms from the above TLC developments were dried and scanned using a Packard InstantImager. The chromatograms of control and ERL-4221 treated DNAs were compared to detect any exposure-related new spots. Endogenous spots common to both vehicle control and treated samples were also quantified, when appropriate, to determine if radioactivity of a preexisting spot was affected by treatment.
Remark	:	The study was conducted in the spirit of compliance with Good Laboratory Practice (GLP) regulations.
Result	:	Based on the enrichment, labeling and TLC conditions used in this assay, exposure to the highest dose of ERL-4221 (1000 mg/kg/day for 14 days) did not induce detectable amounts of new DNA adducts or enhance existing adducts in liver or kidney DNA from male and female Sprague-Dawley rats.
Reliability	:	(2) valid with restrictions 2E

07.08.2003 (27)

06.08.2003

5.7 CARCINOGENITY

Species	:	mouse
Sex	:	male
Strain	:	
Route of admin.	:	dermal
Exposure period	:	3 days/week (Monday, Wednesday and Friday)
Frequency of treatment	:	
Post. obs. period	:	
Doses	:	undiluted
Result	:	negative
Control group	:	other: acetone treated
Method	:	
Year	:	1964
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 40 C3H/Anf mice were painted on Monday, Wednesday and Friday of each week until they died. The control mice received acetone while the treated mice received undiluted EP-221. The positive control mice received 0.2% methyl cholanthrene dissolved in acetone. The hair of the mice was clipped once/week. The material was applied to the mouse skin with one brushfull from a series 197 #1 Grumbacher brush for each application. Mice receiving EP-221 were painted for 28 months while the vehicle controls were painted with acetone for 26 months and the positive controls were painted with methyl cholanthrene for 13 months.
Remark	:	A brushfull is approximately 24.8 mg EP-221. Assuming the average weight of the male mouse was 40 grams, this corresponds to 620 mg/kg.
Result	:	Survival of EP-221 treated mice was slightly better than vehicle control mice (Table 1). For EP-221, after 23 months of skin painting, only one tumor was observed at the application site. No additional information provided.

Table 1
Summary of skin painting results

	Vehicle control	Positive control	EP-221
Initial Number of mice	40	40	40
# alive after 12 months	32	2	39
# alive after 18 months	26	0	31
# alive after 24 months	4	0	12
First tumor observed	23	3	23
# of mice with tumors	2	39	1

Reliability	:	(2) valid with restrictions 2E

05.08.2003 (28)

5.8 TOXICITY TO REPRODUCTION

Type	:	other: 90 day oral gavage study
Species	:	rat

Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	90 day
Frequency of treatment	:	
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
Doses	:	0, 5, 50 and 500 mg/kg/day based on epoxy equivalent factor of 92.5%
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	>= 500 - mg/kg bw
Method	:	other: OECD 408
Year	:	2001
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of Sprague Dawley rats were orally gavaged with 0, 5, 50 or 500 mg/kg/day of ERL-4221. The control and high dose consisted of 25 males and 25 females in each group while the intermediate doses consisted of 20 males and 20 females in each group. Doses were based on an epoxy correction factor of 92.5%. The vehicle was Mazola corn oil. Groups of 15 rats/sex/dose level were assigned to the primary necropsy and groups of 5 rats/sex/dose level from the intermediate dose groups or 10 rats/sex/dose level from the control and top dose group were assigned to a 28-day recovery period. Parameters evaluated included clinical observations, body weights, feed consumption, clinical pathology (hematology, serum chemistry and urinalysis), ophthalmology, vaginal cytology and spermatogenic endpoints. Vaginal cytological endpoints included vaginal smears beginning 22-23 days prior to the primary necropsy and continued to the day of necropsy. The average cycle length was calculated for complete estrous cycles. Spermatogenic endpoints included as assessment of sperm motility and morphology. At least 200 (if possible) sperm were analyzed for motility and morphology from each animal. Complete necropsies were performed on all animals and selected organs were weighed. These organs included epididymides (total and cauda), testes, uterus (with cervix) and ovaries (with oviducts). Selected tissues were examined microscopically at the primary necropsy as well as the 28-day recovery period. These selected tissues included epididymides, prostate and testes of males and mammary gland, ovaries with oviducts, uterus with cervix and vagina of females. The right testis and epididymis were fixed in Bouin's solution prior to histopathologic examination.
Result	:	Subchronic toxicity endpoints are discussed in the repeated dose section of this dossier. There were no test material-related changes in estrous cycle or on spermatogenic endpoints (mean testicular and epididymal sperm numbers, sperm production rate and sperm molity and morphology) observed (Table 1).

Table 1
Results of estrous and spermatogenic endpoints

	Dose Level, mg/kg/day			
Parameter	0	5	50	500
Females				
estrous cycle length, days	4.6+/-0.93	4.7+/-0.91	5.2+/-1.81	4.9+/-1.27

Males
sperm/gram tissue in left testis, in millions
95.4+/-21.01 110.7+/-32.04 113.6+/-22.35 102.3+/-14.13
sperm/gram tissue in left epididymis, in millions
348.9+/-108.9 340.6+/-79.8 381.8+/-153.46 385.0+/-147.58
sperm motility assessment, %
82.9+/-9.92 83.3+/-7.76 81.0+/-13.5 74.4+/-16.47
sperm morphology
normal, %
99.4+/-0.68 99.8+/-0.32 99.6+/-0.62 98.87+/-1.17
normally shaped head separated from flagellum, %
0.5+/-0.64 0.1+/-0.30 0.4+/-0.61 0.8+/-0.77
head absent with normal flagellum, %
0.0+/-0.13 0.1+/-0.18 0.1+/-0.18 0.3+/-0.56

Mean+/-S.D.
No values were significantly different from control group, p<0.05.

There were no treatment-related effects noted on reproductive organ weights of male or female rats gavaged with ERL-4221 for 90 days. Mean absolute prostate weight was slightly decreased in the 5 mg/kg/day group which was not considered to be treatment-related.

There were no treatment-related microscopic findings noted on reproductive organs of male or female rats. All microscopic findings were consistent with normal background lesions in clinically normal rats of the strain and age used in this study and were considered to be spontaneous and/or incidental in nature and unrelated to test material administration.

Reliability : (1) valid without restriction
1A

06.08.2003 (20)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	gestation days 6-19
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	0, 5, 25, 125 and 500 mg/kg/day (based on epoxy equivalent weight)
Control group	:	yes, concurrent vehicle
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	2003
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 25 bred female rats were orally administered 0, 5, 25, 125 or 500 mg/kg/day based on epoxy equivalent weight of ERL-4221 on gestation days 6-19. These dosages corresponded to 0, 5.4, 27, 135 and 541 mg/kg/day of ERL-4221, respectively. The control group received the vehicle, Mazola corn oil. Clinical observations, body weights and feed consumption were recorded at appropriate intervals. On gestation day 20, all females were euthanized for a scheduled laparohysterectomy. The uteri and ovaries were examined and the number of fetuses, early and late absorptions, total implantations and corpora lutea were recorded. Gravid

uterine weights were recorded, and net body weights and net body weight changes were calculated. The liver and kidneys of each female were weighed. The fetuses were weighed, sexed, examined for external, visceral and skeletal malformations and developmental variations.

Result : All females survived to the scheduled necropsy. The clinical condition of the animals in the test article-treated groups was not adversely affected by ERL-4221. No test material-related maternal or fetal effects were observed in the 5 and 25 mg/kg/day groups. No test material-related fetal malformations were observed at any dose level; no test material-related developmental variations were noted in the 5, 25 and 125 mg/kg/day groups. Intrauterine growth and survival in the 125 mg/kg/day group were unaffected by test material administration.

Test material-related effects noted in the 125 mg/kg/day group consisted of:
- Transient, initial mean body weight losses and reduced feed consumption (some statistically significant). These observations were not considered to be adverse due to the rapid amelioration of the effects.
- Macroscopic findings in the kidney (one female with depressed areas grossly visible) in conjunction with increased mean kidney weight (statistically significant).

Test material-related effects noted in the 500 mg/kg/day group and consisted of:
- Mean maternal body weight losses and reduced body weight gain and feed consumption (occasionally statistically significant).
- Increased macroscopic findings in the kidney (two females with drepressed area grossly visible) in conjunction with increased mean kidney weight (statistically significant).
- Reduced mean fetal body weight (statistically significant).
- Increased skeletal developmental variations (reduced mean litter proportion of cervical centrum #1 ossified (statistically significant) and increased mean litter proportions of unossified sternebrae (not statistically significant).

Based on the results of this study, the no-observed-adverse-effect-level (NOAEL) for maternal toxicity was 25 mg/kg/day following oral administration. For prenatal developmental toxicity the NOAEL was considered to be 125 mg/kg/day.

Reliability : (1) valid without restriction
1A

06.08.2003 (29)

Species : rat
Sex :
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : days 6-19 of gestation
Frequency of treatment : daily
Duration of test :
Doses : 0, 50, 100, 250, 500 and 750 mg/kg (based on epoxy equivalent weight)
Control group : yes, concurrent vehicle
Method : other: probe study for definitive OECD 414 study
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : Groups of eight bred Sprague Dawley rats were dosed via oral gavage on gestation days 6-19. Target dosage levels were 0, 50, 100, 250, 500 and 750 mg/kg/day of epoxy equivalent weighted ERL-4221. These dose

levels corresponded to 0, 54, 108, 270, 541 and 811 mg/kg/day of actual ERL-4221, respectively. The control group received the vehicle, Mazola corn oil. Clinical observations, body weights and feed consumption were recorded. On gestation day 20, all females were euthanized for a scheduled laparohysterectomy. The uteri and ovaries were examined and the number of fetuses, early and late absorptions, total implantations and corpora lutea were recorded. Gravid uterine weights were recorded, and net body weights and net body weight changes were calculated. The liver and kidneys of each female were weighed. The fetuses were weighed, sexed, examined for external malformations and developmental variations and discarded.

Result : All maternal animals survived to the scheduled laparohysterectomy on gestation day 20. No test article-related clinical findings were observed.

Mean body weight gains were reduced in the 500 and 750 mg/kg/day groups during gestation days 6-9, 12-20 and when the overall treatment period (gestation day 6-20) was evaluated. Mean body weights (gestation days 11-20), gravide uterine weights, net body weights and net body weight gains in these dose groups were also reduced. Feed consumption in the 500 and 750 mg/kg/day group was slightly reduced during gestation days 6-9 and 12-20. Feed consumption in the 50, 100 and 250 mg/kg/day groups was not affected by the test article.

No test article-related macroscopic changes or effects on liver and kidney weights were noted at the scheduled necropsy on gestation day 20.

Mean fetal weights were reduced in the 500 and 750 mg/kg/day groups.

No external malformations or developmental variations were observed in fetuses at any dose level.

In conclusion, maternal toxicity was expressed at dose levels of 500 and 750 mg/kg/day by effects on body weights and feed consumption. Prenatal developmental toxicity was expressed by reduced fetal body weight at dose levels of 500 and 750 mg/kg/day. No maternal or prenatal developmental toxicity was expressed at dose levels of 50, 100 or 250 mg/kg/day. Based on this data, dose levels of 5, 25, 125 and 500 epoxy equivalent weight were used for the definitive study.

Reliability : (2) valid with restrictions
2E

06.08.2003 (30)

5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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(4) Macnab, J.I. (2000). Cycloaliphatic epoxide resin ERL-4221: Determination of vapor pressure. Unpublished UCC report 63-10.

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7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT