Phenyloxirane and its isomers: Human health tier II assessment

01 September 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Oxirane, phenyl-	96-09-3
Oxirane, phenyl-, (R)-	20780-53-4
Oxirane, phenyl-, (S)-	20780-54-5

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to

human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group consists of phenyloxirane (CAS No. 96-09-3) and its stereoisomers [(S)-phenyloxirane (CAS No. 20780-54-5) and (R)-phenyloxirane (CAS No. 20780-53-4)]. The chemicals in this group have similar molecular formula, molecular weight and physicochemical properties. Phenyloxirane (CAS No. 96-09-3) may also refer to the racemic mixture composed of the (S)- (CAS No. 20780-54-5) and the (R)- (CAS No. 20780-53-4) isomers; therefore, it is expected that these chemicals have a similar toxicological profile and would qualify to be assessed as a group.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers;
- Galleria Chemica;
- the International Agency for Research on Cancer (IARC);

- the National Toxicology Program (NTP), Report on Carcinogens; and
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemicals have reported commercial uses as reactive plasticisers or diluents in epoxy resin systems.

The chemicals have reported site-limited uses as intermediates in the production of styrene glycol and its derivatives.

Restrictions

Australian

These chemicals are listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP)—in Schedule 5 (SUSMP, 2015) under '*Epoxy resins, liquid*'.

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2015).

International

Phenyloxirane is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’).

Existing Worker Health and Safety Controls

Hazard Classification

Phenyloxirane (CAS No. 96-09-3) is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Carc. Cat. 2; R45 (carcinogenicity);
- Xi; R36 (irritation);
- Xn; R21 (acute toxicity)

Exposure Standards

Australian

No specific exposure standards are available for any chemicals in this group.

International

No specific exposure standards are available for any chemicals in this group.

Health Hazard Information

Toxicokinetics

Limited information indicates that phenyloxirane is absorbed through ingestion, inhalation, and skin application (NTP, 2002). Phenyloxirane is the initial metabolite of absorbed styrene which is then further metabolised through glutathione conjugation or styrene glycol formation. Phenyloxirane is primarily excreted through the urine as either the mandelic acid or phenylglyoxylic acid metabolites (NTP, 2008). It was reported that epoxide hydrolase—the enzyme that metabolises phenyloxirane through hydrolysis—favours the S-enantiomer compared to the R-enantiomer while glutathione S-transferase—the enzyme that is responsible for glutathione conjugation—favours the R-enantiomer compared to the S-enantiomer (IARC, 1994).

Acute Toxicity

Oral

The chemicals in this group are expected to have low acute oral toxicity. It was reported that the median lethal dose (LD50) of phenyloxirane in rats was in the range of 3000 to 4290 mg/kg bw (IARC, 1985).

Dermal

Phenyloxirane is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in the Hazardous Substances Information System (HSIS) (Safe Work Australia). Although the available information only reports the LD50 values, in the absence of more comprehensive information, these values are consistent with the current classification. The health hazard classification for phenyl oxirane also applies to the (S)- and (R)- isomers.

It was reported that the LD50 values of phenyloxirane in rabbits were 930–1184 mg/kg bw (IARC, 1985). In an experiment conducted in four male New Zealand White rabbits, a single occlusive application of phenyloxirane caused deaths within 14 days. The LD50 value was determined to be 1060 mg/kg bw. No other study details were provided (REACH).

Inhalation

Limited information is available for the acute inhalation of phenyloxirane. It was reported that exposure to phenyloxirane at a concentration of 4900 mg/m^3 for four hours caused deaths in 2/6 rats (IARC, 1985).

Corrosion / Irritation

Skin Irritation

No data are available.

Eye Irritation

Phenyloxirane is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The health hazard classification for phenyl oxirane also applies to the (S)- and (R)- isomers. The available data support this

classification.

It was reported that application of 1% solution of phenyloxirane onto rabbit eyes caused corneal injury (IARC, 1985). In an experiment conducted on three Japanese White rabbits, application of 0.1 mL of phenyloxirane into the conjunctival sac of the left eye caused corneal irritation which persisted for more than 24 hours. The effects were reversed within 21 days after the treatment. Phenyloxirane was classified as a moderate to severe eye irritant (REACH).

Observation in humans

It was reported that acute exposure to phenyloxirane caused skin and eye irritation in humans (IARC, 1985).

Sensitisation

Skin Sensitisation

Based on observation in humans, and observation for related epoxy compounds (HSDB), the chemicals in this group are considered to be skin sensitisers, and will warrant classification as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (Xi; R43) in the HSIS (Safe Work Australia).

All the chemicals in this group have functional groups that present alerts for skin sensitisation based on their molecular structures as profiled by the OECD Quantitative Structure–Activity Relationship (QSAR) Toolbox v3.2.

Observation in humans

It was reported that acute exposure to phenyloxirane caused skin sensitisation in humans. It was also reported that, based on experience, individuals who have become hypersensitive may develop severe reactions upon contact with the vapour and the liquid form of phenyloxirane (IARC, 1985; HSDB).

Repeated Dose Toxicity

Oral

In an experiment conducted in Fischer 344 (F344) rats (10 animals/sex/dose), phenyloxirane in corn oil was administered by gavage at doses of 0, 180, 360, 750, 1500 or 3000 mg/kg bw three times per week, for 24 weeks. Mortalities occurred in the 1500 and 3000 mg/kg bw dose groups. All the animals in the 3000 mg/kg bw dose group died by week 10 of the study while 20 % of the females and 30 % of the males in the 1500 mg/kg bw group died by the end of the study. Histopathological examination of the deceased animals revealed basal cell hyperplasia, hyperkeratosis of the forestomach, lesions in the liver and renal tubular epithelial degeneration or necrosis. In the lower dose groups, mild to moderate liver cell hyperplasia and renal tubular degeneration were noted. The lowest observed adverse effect level (LOAEL) was determined to be 180 mg/kg bw/d (REACH).

In another study conducted in B6C3F1 mice (10 animals/sex/dose), phenyloxirane in corn oil was administered by gavage at doses of 0, 60, 90, 300, 600 and 900 mg/kg bw, three times per week, for 20 weeks. No deaths in any dose groups were reported. Reported effects were basal cell hyperplasia, hyperkeratosis of the forestomach, and hyperplasia of the liver. The no observed adverse effect level (NOAEL) was determined to be 300 mg/kg bw/d (REACH).

Dermal

No data are available.

Inhalation

No information is available for the repeat inhalation toxicity of phenyloxirane. However, in a reproductive toxicity study, widespread mortality was observed in rats exposed to vapours of phenyloxirane at 300 ppm (equivalent to 1470 mg/m^3) (see **Reproductive and Developmental Toxicity** section).

Genotoxicity

In vitro

Phenyloxirane tested positive for genotoxic effects in the following tests:

- Bacterial mutation assays conducted in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1530, TA1535, and TA1537; in *Escherichia coli* strain WP2urA; and in *Klebsiella pneumoniae,* all assays without metabolic activation (IARC, 1994; NTP, 2002);
- gene conversion assay in *Saccharomyces cerevisiae* without metabolic activation (NTP, 2002);
- forward mutations at the hypoxanthine phosphoribosyl transferase (hrpt) locus in Chinese hamster lung V79 cells without metabolic activation (NTP, 2002); and
- chromosomal aberrations, sister chromatid exchanges, and DNA single-strand breaks in human lymphocytes (NTP, 2002);

In vivo

Phenyloxirane tested positive for genotoxic effects in the following tests:

- increased frequencies of gene conversion in *S. cerevisiae* and forward mutations in *Schizosaccharomyces pombe* in host-mediated assays (NTP, 2002);
- induction of sex-linked recessive lethal mutations in *Drosophila melanogaster* (IARC, 1994); and
- increased incidences of chromosomal aberrations in bone marrow cells of gavage-treated CD-1 mice (NTP, 2002).

However, phenyloxirane gave negative results in the following tests (NTP, 2002):

- no increased incidences of chromosomal aberrations in bone marrow cells of vapour-exposed male Chinese hamsters;
- absence of induced dominant lethal mutations or translocations in meiotic germ cells of male BALB/c mice; and
- no increase in micronuclei frequency in bone marrow cells of BALB/c mice and Chinese hamsters.

Although genotoxic effects were demonstrated when phenyloxirane was tested *in vitro*, the overall weight of evidence for genotoxicity from the *in vivo* studies is not strong.

Carcinogenicity

Phenyloxirane is classified as hazardous—Category 2 carcinogenic substance—with the risk phrase ‘May cause cancer’ (T; R45) in the HSIS (Safe Work Australia). The health hazard classification for phenyl oxirane also applies to the (S)- and (R)-isomers. The available data support this classification.

The IARC has classified phenyloxirane, under the chemical name 'styrene-7,8-oxide' (CAS No 96-09-3), as 'probably carcinogenic to humans' (Group 2A) (IARC, 1994).

In an experiment conducted in B6C3F1 mice (53 animals/sex/dose), phenyloxirane in corn oil was administered daily by gastric intubation at doses of 0, 375, or 750 mg/kg bw/d three times a week for 104 weeks. Significant increases in the incidences of squamous cell carcinoma of the forestomach, squamous cell papillomas, carcinomas, and hepatocellular tumours were

observed in all dosed groups (IARC, 1994). Similar effects in the forestomach were observed in studies conducted in Sprague Dawley (SD) and F344/N rats (IARC, 1994).

In a prenatal and postnatal exposure study in BDIV rats, phenyloxirane in olive oil was administered by gavage to pregnant rats at a dose of 200 mg/kg bw on gestation day (GD) 17. The offspring received 96 oral doses of phenyloxirane at doses of 100-150 mg/kg bw once a week from four weeks of age until week 120. Compared to the control group, offspring in all dosed groups showed increased incidence of forestomach tumours. Hyperplasia, dysplasia, and hyperkeratosis of the forestomach were also observed in the dosed group (IARC, 1994).

Phenyloxirane was also reported cause liver tumours in male mice (NTP, 2002).

Reproductive and Developmental Toxicity

One reproductive toxicity study is available for phenyloxirane (IARC, 1994). Wistar rats (at least 31 animals in six groups) were exposed to vapours of phenyloxirane at concentrations of 0, 100 or 300 ppm (equivalent to 0, 490, or 1470 mg/m^3) for seven hours per day during either a three week pregestational period (five days/week) up to GD 19 or on GD 1–19 only. Widespread mortality was observed in all dose groups. All the animals in the 300 ppm group died after the first day of exposure and were excluded from the study. Reduced maternal weight gain, increased preimplantation loss, reduced foetal weights and lengths, and increased incidences of retarded ossification of the sternebrae and occipital bones were observed in the 100 ppm group. In the same study, New Zealand White rabbits were exposed to phenyloxirane vapours at doses of 0, 15, or 50 ppm (equivalent to 0, 74, or 245 mg/m^3), seven hours per day on GD 1–24. Increased mortality in the highest dose group (50 ppm) was observed (19 out of 24 animals) compared with the low dose group (4 out of 24 animals) and controls (1 out of 23 animals). There were no effects on the proportion of animals pregnant at term, no effects on foetal weights, nor any marked preimplantation loss. However, there was an increase in postimplantation loss (0.25, 0.93, and 1.5 resorptions per litter in the control, 15 and 50 ppm groups, respectively).

In a prenatal and postnatal carcinogenicity study in BDIV rats, no developmental effects were noted for phenyloxirane (see **Carcinogenicity** section).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity), systemic acute effects (acute toxicity from skin exposure) and local effects (skin sensitisation). The chemicals can also cause eye irritation.

Public Risk Characterisation

Given the uses identified for the chemicals in this group and the reactivity of the oxirane moiety, it is unlikely that the public will be exposed. Although the public could come into contact with articles and/or coated surfaces containing phenyloxirane, it is expected that phenyloxirane will be bound within the article and/or coated surfaces and therefore will not be bioavailable. Therefore, the chemicals in this group is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

Given the critical systemic long-term, systemic acute and local health effects, the chemicals in this group could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

NICNAS Recommendation

Assessment of these chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2015).

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as below. The existing and recommended classification for phenyloxirane (CAS No. 96-09-3) is also expected to be applied to the individual isomers that are included in this assessment. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful in contact with skin (Xn; R21)*	Harmful in contact with skin - Cat. 4 (H312)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;

- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

References

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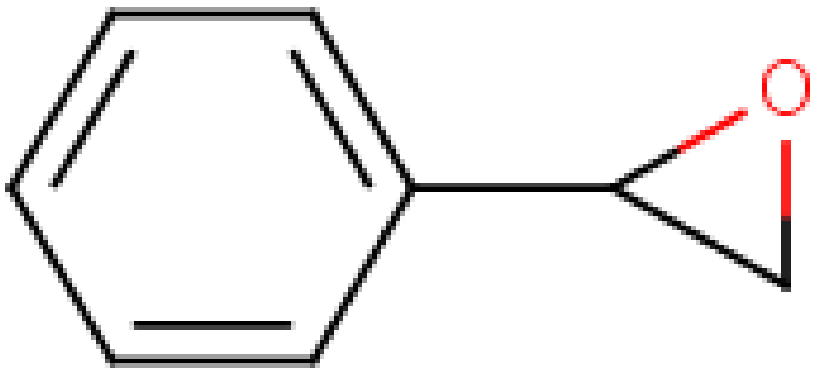
Safe Work Australia. Hazardous Substances Information System (HSIS). Accessed June 2015 at **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**

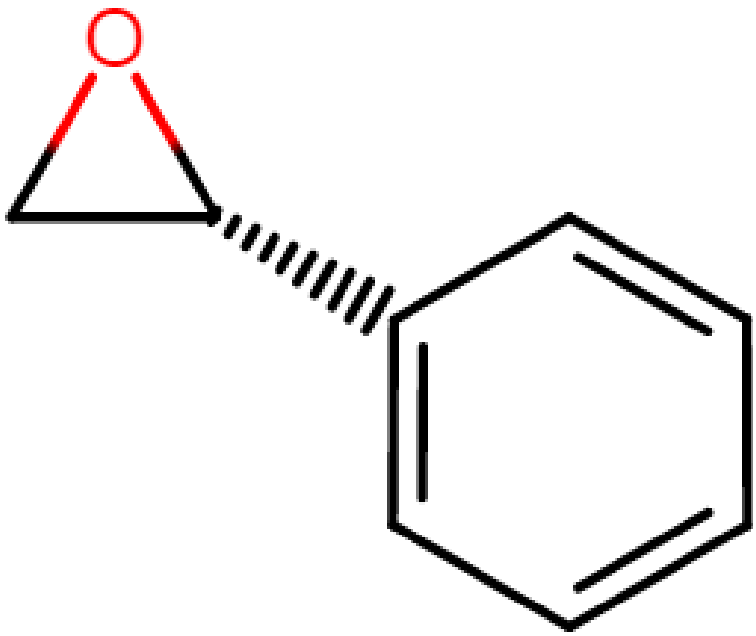
The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2015. Accessed June 2015 at **http://www.comlaw.gov.au/Details/F2015L00128**

Last Update 01 September 2015

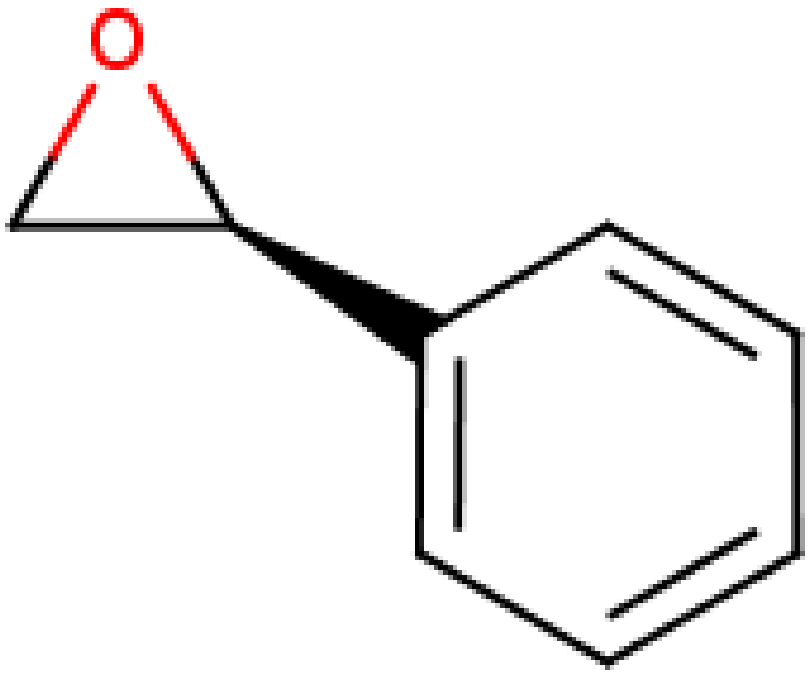
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Oxirane, phenyl-** Styrene oxide Styrene-7,8-oxide
CAS Number	96-09-3
Structural Formula	
Molecular Formula	C8H8O

Molecular Weight	120.15

Chemical Name in the Inventory and Synonyms	**Oxirane, phenyl-, (R)-** Benzene, (epoxyethyl)-, (R)-(+)- Phenylethylene oxide, (R)- Styrene oxide, (+)-
CAS Number	20780-53-4
Structural Formula	
Molecular Formula	C8H8O
Molecular Weight	120.15

Chemical Name in the Inventory and Synonyms	**Oxirane, phenyl-, (S)-** Benzene, (epoxyethyl)-, (S)- Phenyloxirane, (S)-(-)- Styrene oxide, (-)-
CAS Number	20780-54-5
Structural Formula	

	
Molecular Formula	C8H8O
Molecular Weight	120.15

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