GPS pilot study report

Name: Styrene

CAS No.: 100-42-5

August 2009

Showa Highpolymer Co., Ltd.

1. Preface

2. Legal Notice

2.1. Disclaimer

2.2. Antitrust and Competition Compliance

3. Background

4. ICCA Global Product Strategy (GPS) approach

5. Prioritization of substances for GPS risk assessment

Selected: Styrene

Rationale:

(i) The substance is of social concern. The substance is classified by IARC as Group 2B (possible carcinogenic).

(ii) There is high degree of concern over exposure because styrene is manufactured in large quantities (more than 1,000 tons annually) and consumed in large quantities and has therefore been designated as a high production volume (HPV) chemical by the OECD.

6. General guidance to tiered risk characterization

7. GPS Risk characterization process

7.1. Gathering Hazard and Exposure Information

7.1.1. Chemical Definition—Identification of Chemical/Application

Cases of exposure to styrene may be classified into 5 categories including (i) manufacturing styrene, (ii) formulating using styrene, (iii) molding the formulator, (iv) consumer's uses, and (v) disposal. In this report, the risk assessment was carried out for copolymer resins of unsaturated polyester with styrene, using a case of polystyrene synthesis in our company's plant as an example of occupational exposure and the case where styrene is used as a floor paint as an example of exposure to consumers.

Actual status of occupational exposure

Styrene monomer is used as a diluting agent or a monomer for polymerization during a synthesis of unsaturated polyester resins. During this process, there seems to be low worker exposure because closed reaction vessels and a local exhaust ventilation system are furnished and all workers wear protective equipments (a gas mask, goggles, long-sleeved clothes, etc.).

Actual status of consumer exposure

Floor paints are used as corrosion-proofing, antifouling and wear-resistance coating on floors inside warehouses, etc. Workers may be exposed to the vapor of the styrene during painting the floors because the paints are polymerized and hardened on-site. . However, the consumer exposure is considered to be very low at any site where styrene is likely to be encountered by consumers. The most of the styrene is polymerized, and residual monomers vaporize in the atmosphere. This sort of floor is normally only used for business purposes, and t is not assumed that consumers will be walking about on it in bare feet.

The influence on the environment, especially with regard to water pollution, etc., is considered to be small because of the high level of the efficiency of the sewage-treatment plant operation.

7.1.2. Establishing Knowledge Base

References

(*1) Initial Risk Evaluation of Chemical Substances: Styrene. National Institute of Technology and Evaluation, Japan, August 2007

(*2) Integrated Risk Information System List of IRIS Substances: Styrene

(*3) European Union Risk Assessment Report, Styrene. Part. 1-environment, Final 2002, UK

(*4) European Union Risk Assessment Report, Styrene. Draft edition, June 2008, UK

(*5) Risk Assessment Report on Styrene. Scientific Committee on Health and Environmental Risks; May 2006

(*6) Annex XV Transitional Dossier, Styrene UK Competent Authority, November 2008

Legislative Restriction

Legislative information was gathered by searching the Chemical Risk Information Platform provided by the National Institute of Technology and Evaluation, Japan.

7.2. How to conduct the risk characterization

7.2.1. Hazard Evaluation

Hazard was evaluated by examining the documents cited in 7.1.2. Read-across and QSAR analyses were not performed.

7.2.2. Exposure Evaluation

Exposure was evaluated using ECETOC-TRA (the European Centre for Ecotoxicology and Toxicology of Chemicals—Targeted Risk Assessment), as recommended by the Japan Chemical Industry Association.

Input data were obtained by calculation based on the data from sources mentioned in 7.1.2. The calculation details are described in the appendix ECETOC TARGETED RISK ASSESSMENT MODEL.

7.2.3. Is Information Sufficient to Complete a Risk Characterization?

The risk characterization carried out using ECETOC-TRA demonstrated that the risk of the present occupational conditions is controlled and can specify the use conditions which can control the risk of consumer and environmental exposure. Existing information is determined to be sufficient to complete a risk characterization in accordance with the flow described in the chapter 9.7 of the risk assessment guidance.

7.2.4. Decision Point

.See the chapter 9.7 in this document for the detail on the determination

7.2.5. Documentation of the risk assessment

7.2.5.1. Company or value chain internal use

Relevant information has already been distributed as a MSDS.

7.2.5.2. Elements of a product stewardship summary document for the public

Relevant information has already been distributed as a MSDS.

8. Applying Appropriate Risk Management

Various risks can be adequately avoided by the appropriate selection of systems and protective equipments.

Risk assessment reports will be published on a homepage, etc. or distributed to customers, together with MSDSs, as appropriate.

Thus, neither limiting the uses or the markets nor qualification nor training customers are necessary at the present time.

9. Annex 1

9.1. GPS "Base Set of Information"

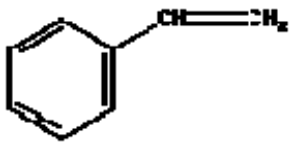
9.1.1. Standard Parameters to be evaluated for every substance

9.1.1.1. Chemical Identity and use

CAS No.: 100-42-5

Name: Styrene

Structural Formula:



Use Pattern: SU12. Manufacture of plastics products, including compounding and conversion (rationale for selecting this Sector of Use: meeting the business requirements of our company)

Source of Exposure: Three categories were considered: occupational (manufacture), consumers (use) and the environment (plant effluent).

9.1.1.2. Physical-Chemical Properties

Physical State:	Liquid	(*3)
Melting Point:	−30.6°C	(*3)
Boiling Point:	145–146°C	(*3)
Relative Density:	0.906 g/cm^3 at 20°C	(*3)
Vapor Pressure:	667 Pa at 20°C	(*3)
Partition Co-efficient:	2.95 (logKow)	(*1)
Water Solubility:	300 mg/L at 20°C	(*3)
Ignition Temperature (Flammability):	490°C	(*3)

9.1.1.3. Environmental Fate

Aerobic biodegradability: readily biodegradable (*1, p. 7)

9.1.1.4. Environmental Toxicology

Acute toxicity (fish): 96-hour LC_{50} *fathead minnows,* Flow-through: 4.02 mg/L

Reason for selection: Data associated with the highest degree of risk was selected. (*1, p. 21)

9.1.1.5. Mammalian Toxicology (significant exposure)

Skin toxicity, the most significant exposure route was extrapolated from inhalation toxicity.

LC_{50} in rats after inhalational exposure: 2800 ppm (4 hours) (*1, p. 38, Table 8-2).

Human toxicity has been evaluated by ECETOC-TRA (*7, See Appendix.)

9.1.2. Tiered information requirements depending on the hazard / exposure

9.1.2.1. Tiered toxicological data requirements

The exposure for workers seems to be low using closed reaction vessels, a local exhaust ventilation and wear protective equipments (a gas mask, goggles, long-sleeved clothes, etc.). The exposure for consumers also seems to be very low because most of the styrene monomers are polymerized, almost all of the residual monomers vaporize into the atmosphere and because this sort of floor (a typical use) is normally only used for business purposes and consumers are unlikely to walk barefoot.

Therefore, Tier 2 (low-level exposure) was selected.

Tier 1	Tier 2	Tier 3	Tier 4
Minimal exposure or hazard potential Minimal requirement irritation (Eye / Skin) in case of accidental exposure	**Low exposure Or hazard potential** Irritation (Eye / Skin)	**Medium exposure Or hazard potential** Irritation (Eye / Skin)	**High exposure Or hazard potential** Irritation (Eye / Skin)
	Mutagenicity e.g. Ames test (only if deemed necessary due to chemical structure)	Mutagenicity (e.g. Ames)	Mutagenicity (e.g. Ames, mammalian cell in vitro, micronucleus)
	Sensitization (only if deemed necessary due to chemical structure)	Sensitization (only if deemed necessary due to chemical structure)	Sensitization
		28-days sub acute toxicity data	28-days sub acute toxicity data Reproduction and developmental toxicity screening tests (421 or 422)

9.1.2.2. Tiered ecotoxicological data requirement

Tier 1	Tier 2	Tier 3	Tier 4
Minimal exposure or hazard potential In case of accidental exposure relevant ecotoxicological data is needed	**Low exposure Or hazard potential**	**Medium exposure Or hazard potential** Acute Toxicity to Daphnia	**High exposure Or hazard potential** Acute Toxicity to Daphnia
		Acute Toxicity to Algae	Acute Toxicity to Algae Chronic Toxicity (fish or daphnia) within limitations of the chemical properties

Tier 2 was selected because of only a low effect on the environment as follows:

LC_{50} in fathead minnows after 24 hours: 12 mg/L

LC_{50} in fathead minnows after 96 hours: 10 mg/L (*3, p. 57)

9.1.3. Alternative source of information to fulfill the Information

An evaluation was performed using information corresponding to Klimisch Code 1 or 2. Alternative information sources such as read-across analysis, a category approach, QSAR analysis, *in vitro* methods, a WoE (weight of evidence) approach, etc. were not necessary...

9.1.4. Adaptations to the tiered information requirements

Adaptation was not needed.

9.2. Sorting Criteria

9.2.1. How to attribute a substance to a certain Tier (1-4)

9.2.1.1. Toxicological sorting criteria

(i)

Hazard	Tier 1	Tier 2	Tier 3	Tier 4
Level	Minimum	Low	Medium	High
Flammability	Flashpoint >200°F	100°F < F.P. < 200°	20°F < F.P. < 100°	Flashpoint < 20°F

Flashpoint: 31°C = 87.8 F (*3, p. 10)

(ii)

Reactivity	Essentially nonreactive	Unstable at elevated temp and pressure (nonviolently with H20)	Normally unstable, detonation possible, violently with water	Ready detonation or explosive decomp. at normal temp/pressure

The rate constant for the atmospheric reaction between styrene and OH radicals is 5.8 × 10^{-11} cm^3/molecule/second (25°C, measured value). The half-life calculated supposing that hydroxyl radical concentration of 5 × 10^5 to 1 × 10^6 molecules/cm^3 is 4 to 7 hours. Styrene does not have any chemical binding liable to be hydrolyzed in water. Therefore, styrene is not considered very reactive (*1: p. 6 SRC: AopWin, 2003).

(iii)

Acute Tox (skin / oral / inhalation)	oLD50 >2000 mg/kg or dLD50 >2000 mg/kg or LC50 >20 mg/l	oLD50<300 mg/kg or dLD50<1000 mg/kg LC50 <10 mg/l	oLD50<50 mg/kg or dD50<200 mg/kg or LC50 <2 mg/l	oLD50<5 mg/kg or dLD50<50 mg/kg or LC50 <0,5 mg/l

Oral LD_{50} (oLD_{50}) for an acute toxicity study in rats is 5,000 mg/kg (*4, p. 97)

No data available for dermal LD_{50} (dLD_{50}).

Inhalational LC_{50} (4 hours) in rats is 2,770 ppm = 11.80 mg/L (*4, p. 95)

The criteria given for inhalation are considered to be misprints.

(iv)

Eye/Skin irritation	Nonirritating	Mild Irritant	Irritant	Corrosive
Sensitization	No sensitizer	Weak sensitizer	Moderate sensitizer	Strong sensitizer or GHS Cat 1
Mutagenicity / Carcinogenicity	Not carcinogenic in humans or no mutagen	Not likely carcinogenic in humans or no mutagen	Probable carcinogenic or suspected mutagen or GHS Cat 2	Likely carcinogenic or positive mutagen or GHS Cat 1A-B

Irritation:

Animal skin = moderate irritant

Animal eye = irritant

Human eye = strong irritant (*4, pp.101-104)

Styrene is not corrosive but it is irritating (*1, p. 38).

Sensitization:

Styrene has no significant potential to cause this effect (*4). .

Mutagenicity:

Styrene has shown positive reactions in *in vitro* reverse mutation tests, chromosomal aberration tests, sister chromatid exchange tests, etc. *In vivo*, the substance has shown positive reactions in micronucleus tests, DNA strand break assays and

unscheduled DNA synthesis tests. Based on these results, styrene is considered to be a genotoxic substance. (*1, p. 48)

Carcinogenicity:

No data available. However, the substance has been classified into Group 2B (Possibly carcinogenic to humans) by the IARC (*1, p. 56).

(v)

Eye/Skin irritation	Nonirritating	Mild Irritant	Irritant	Corrosive
Sensitization	No sensitizer	Weak sensitizer	Moderate sensitizer	Strong sensitizer or GHS Cat 1
Mutagenicity / Carcinogenicity	Not carcinogenic in humans or no mutagen	Not likely carcinogenic in humans or no mutagen	Probable carcinogenic or suspected mutagen or GHS Cat 2	Likely carcinogenic or positive mutagen or GHS Cat 1A-B

Repeated dose toxicity:

No data was available for a 28-day repeated-dose study.

A NOAEL of 100 mg/kg/day from a 60-day study in rats was substituted. (*1 p. 39, p. 42)

Reproductive/developmental toxicity:

NOEL in an oral 3-generation study in rats: 125 ppm = 10.5 mg/kg/day (*1, p. 46)

Based on the above results, styrene can be assigned to Tier 3 for human toxicity.

9.2.1.2. Ecotoxicological sorting criteria

Hazard Level	Tier 1 Minimum	Tier 2 Low	Tier 3 Medium	Tier 4 High
Eco GHS classification	None	Acute category 3 or chronic category 3	Acute category 2 or chronic category 2	Acute category 1 or chronic category 1 or M-factor < 10
Eco Acute toxicity	LC50 >100 mg/l	LC50 10-100 mg/l	LC50 1-10 mg/l	LC50 <1 mg/l

LC_{50} in *fathead minnows* after 96 hours = 4.02 mg/L (*3: p. 57)

The acute aqueous toxicity classification is classified into Tier 2 since $1 < LC_{50} < 10$.

Chronic aqueous toxicity is not applicable because log Kow is not 4 or higher (although the acute aqueous toxicity classification is classified into Tier 2).

Therefore, the ecotoxicological classification of styrene is classified into Tier 3.

Exposure	Tier 1	Tier 2	Tier 3	Tier 4
Level	Minimum	Low	Medium	High
Description	Closed processes	Industrial operations Risk control: dedicated equipment. technical, organizational and PPE	Professional use (e.g. craftsmen); Risk control: PPE and organizational	Consumer use (exposure assumed) Risk control: Product design, use instructions
E.g. REACH PROC (Process Categories)	PROC 1-3	PROC 4-7, 9, 12,14,	PROC 8,10, 11, 13, 15, 17-19, 22, 23	PROC 16, 20, 21, 24, 25

Process category 5 (PROC5: blending and denaturation in the batch production of drugs) has been selected and the substance has been classified into Tier 2.

Exposure	Category 1	Category 2	Category 3	Category 4
Level	Minimum	Low	Medium	High
Description	Industrial operations – Emission control: closed / tightly controlled systems	Industrial operations - Emission control: technical (end of pipe) and organizational	Professional/ Consumer Use Emission of substances: Not intended, e.g.: adhesives sealants, coatings	Professional/ Consumer Use Emission of substances: Intentional e.g.: personal care, cleaning, agrochemical
REACH – ERC (Environmental Release Classes)	ERC 1,6a-d,7	ERC 2,3,4,5,	ERC8c,8f,9a,9b,10a,11a	ERC8a,8b,8d, 8e,10b,11b

Styrene is classified into Category 1 because ERC 2 (Formulation of preparations) has been selected.

9.3. Hazard Identification (Human health / Environment)

9.3.1. Physico-chemical properties

Physicochemical properties are described in 9.1.1.2.

9.3.1.1. Ignition temperature (Flammability)

9.3.1.2. Boiling point

9.3.1.3. Vapor pressure

9.3.1.4. Water solubility

9.3.1.5. Partition coefficient

Criterion	PBT criteria	vPvB-criteria
P	Half-life > 60 d in marine water or > 40 d in freshwater or half-life > 180 d in marine sediment or > 120 d in freshwater sediment *Or not readily or inherently biodegradable* *Or predicted biodegradability in a time frame of weeks-months*	Half-life > 60 d in marine- or freshwater or >180 d in marine or freshwater sediment *Or not readily or inherently biodegradable* *Or predicted biodegradability in a time frame of weeks-months*
B	BCF > 2,000 *Or log Kow >4.5*	BCF > 5,000 *Or log Kow >5*

It is assumed that styrene discharged into the atmosphere remains mainly in the atmosphere, that styrene discharged into water remains mainly in the water, and that styrene discharged into the soil remains mainly in the soil. Styrene discharged into environmental water is considered to be eliminated from the water by volatilization into the atmosphere and through biodegradation. Styrene bound to soil particles, etc. sinks to the bottom but is likely to be eliminated by anaerobic biodegradation. (*1: P.7 and 8)

Moreover, log Kow = 2.95, BCF = 37 (*1: p. 8).

Therefore, it is unlikely that styrene will become concentrated in any aquatic creatures; therefore, is not applicable to any of the above classifications.

9.3.2. Endpoint-specific guidance

9.3.2.1. Human Health Hazard Potential

9.3.2.2. Tier 1: Minimal hazard potential

9.3.2.2.1. Acute toxicity

	Tier 1	Tier 2	Tier 3	Tier 4
Oral (mg/kg)	>2000	<300	<50	<5
Dermal (mg/kg)	>2000	<1000	<200	<50
Gases (ppm)	5000	2500	500	100
Vapors (mg/l)	20	10	2	0,5
Dusts and Mists (mg/l)	0.05	0.5	1.0	5

Oral: LD_{50} in rats = 5000 mg/kg (*1: P. 38) (*4: P. 97)

Dermal: No data available (*1: P. 38) (*4: P. 97)

Gases: LC_{50} in rats (2 hours) = 4930 ppm (*1: P. 38) (*4: P. 96)

Vapor: LC_{50} in rats and guinea pigs (4 hours) = 2770 ppm = 11.8 mg/L (*4: P. 95)

Dust/mist: No data available

Based on the above data, styrene can be classified into Tier 2.

9.3.2.2.2. (Eye / Skin) Irritation

9.3.2.2.3. Corrosion

A 4-week skin irritation study in rabbits reported blisters on the skin and loss of fur (*1: p. 39)

9.3.2.3. Tier 2: Low hazard potential

9.3.2.3.1. Genotoxicity

Styrene has shown positive reactions in reverse mutation tests, chromosomal aberration tests, sister chromatid exchange tests, etc.

In vivo, the substance has shown positive reactions in micronucleus tests, DNA strand break assays and unscheduled DNA synthesis tests. Based on these results, styrene can be considered genotoxic. (*1: p. 48)

9.3.2.3.2. Skin sensitization (in case of structural alert)

No data available (*1: p. 39)

9.3.2.4. Tier 3: Medium hazard potential

9.3.2.4.1. Repeated dose toxicity (e.g. a 28-days study)

No data is available concerning any 28-day repeated-dose study.

NOAEL in rats after 60 days: 100 mg/kg/day (*1: p. 39 and p. 42)

9.3.2.5. Tier 4: High hazard potential

9.3.2.5.1. Reproductive and developmental toxicity

In inhalational exposure studies in mice and hamsters, increased embryonic/fetal death rates and skeletal anomalies have been reported. However, fetal death or teratogenicity has not been reported in any oral or inhalational studies in rats, even when dams were exposed to the test substance at a dose large enough to affect body weight. In a 3-generation proliferation study, no reproductive toxicity associated with the administration of styrene was observed and the NOAEL was found to be 250 ppm. (*1: p. 44 to 47)

9.3.3. Environmental Hazard Potential

9.3.3.1. Tier 1: Minimal hazard potential

9.3.3.1.1. Degradation/biodegradation

Percentage degradation of styrene in a wastewater treatment plant (estimated by EUSES)

Specific biodegradability: 58.3%

Aerobic biodegradability: 31.4%

Biodegradation in seawater: 7.2%

Non-biological changes: 3.1% (*3: p. 41)

Therefore, styrene can be considered readily biodegradable.

9.3.3.2. Tier 2-3: Low to medium hazard potential

9.3.3.2.1. Aquatic toxicity (algae, daphnia, fish)

(*1: pp. 18 to 20, *3: pp. 56 to 62)

Algae

EC50 in *Selenastrum capricornutum* after 72 to 96 hours was 0.72 to 1.4 mg/L in terms of biomass calculation, and 4.9 to 6.3 mg/L in terms of growth rate. (*1: p. 18)

Daphnia

The lowest toxicity value in studies taking into account volatilization was an EC50 (Immobilization, 48 hours) of 4.7 mg/L for *Daphia magna*. No report has been made concerning long term toxicity. (*1 p. 19)

Fish

The lowest toxicity value in studies under flow-through conditions and taking into account volatilization is and LC50 was 4.02 mg/L (mean measured concentration) for *fathead minnows.* (*1 p. 20)

9.3.3.3. Tier 4: High hazard potential

9.3.3.3.1. Chronic toxicity (daphnia, fish)

Daphnia: No report has been made concerning long-term toxicity.

Algae: The EC10 acting an indicator in a long-term study was 0.13 mg/L (biomass method). This was similar to the NOEC. (*1: p. 18)

Fish: No data available

9.4. Dose-Response Assessment

9.4.1. Metabolism and Pharmacokinetics

9.4.2. Potency

9.4.3. NOAEL / LOAEL approach

9.4.4. MOS approach

Calculation was impossible because the amount of exposure was unknown.

9.5. Exposure assessment

9.5.1. General Use Pattern

9.5.1.1. Use categories

No sector of use is mentioned in the guidance material provided. If a sector of use specific to an exposure assessment tool is applied, this must be clearly stated. Moreover, the range of uses included as examples does not provide sufficient choice and none are applicable.

Here, the SU12 (Manufacture of plastics products) sector (ECETOC-TRA) was used.

9.5.1.1.1. Isolated intermediate used/stored off site

9.5.1.1.2. Substance that is included into or onto a matrix

9.5.1.1.3. Non-dispersive use – Professional (industry point-sources)

9.5.1.1.4. Wide dispersive use

9.5.2. Considerations and uncertainties

9.5.3. General exposure assessment guidance

9.5.4. Occupational exposure estimation assessment

9.5.4.1. Measurements

9.5.4.2. Modeling approaches

9.5.4.3. Inhalation

9.5.4.4. Dermal

9.5.4.5. Oral

9.5.5. Consumer exposure estimation

9.5.5.1. Inhalation

9.5.5.2. Dermal, two options:

9.5.5.3. Oral, two options:

9.5.6. Environmental exposure assessment

9.5.7. Generic Supply Chain Exposure Assessment

9.5.7.1. Information on the safe use of substances in the supply chain

9.5.8. Exposure Assessment

9.5.8.1. Tools

ECETOC-TRA was used as the initial step evaluation tool.

9.5.8.2. Functioning of the Tier-One Tools preferred by industry: stop

9.5.9. Industry Input to exposure assessment

See (Annex: ECETOC TARGETED RISK ASSESSMENT MODEL Supplement).

9.5.10. Downstream User Activities

Upgrading of the ERC classification, which is highly versatile, by the Synthetic Resin Industry Association, is anticipated.

9.5.11. Industry Strategy

Establishment of a detailed risk assessment is anticipated at the meeting of the Synthetic Resin Industry Association.

9.5.12. Generic Environmental Exposure Assessment

ERC2: Production of Preparation has been selected as the most appropriate category.

9.5.13. Exposure assessment as input to risk characterization

In this assessment, a PEC-derived model was not used because it was possible to simply extract PEC values from available references. (*7 See Annex.)

9.5.14. Exposure assessment in defining conditions of safe use

Risks were evaluated using an evaluation tool (ECETOC-TRA).

A risk is considered to be under control if the annual production is less than 90 tons.

At present, it is likely that an adequate level of risk control can be achieved even if annual production exceeds 90 tons, provided that adequate effluent treatment facilities are available and wastewater is fully controlled.(*7 See Annex.)

9.5.15. Environmental risk assessment with base set information:

Environmental risks were assessed using the essential items entered in ECETOC-TRA (yellow parts of the sheet). (*7 See Annex.)

9.5.16. Environmental modeling tools

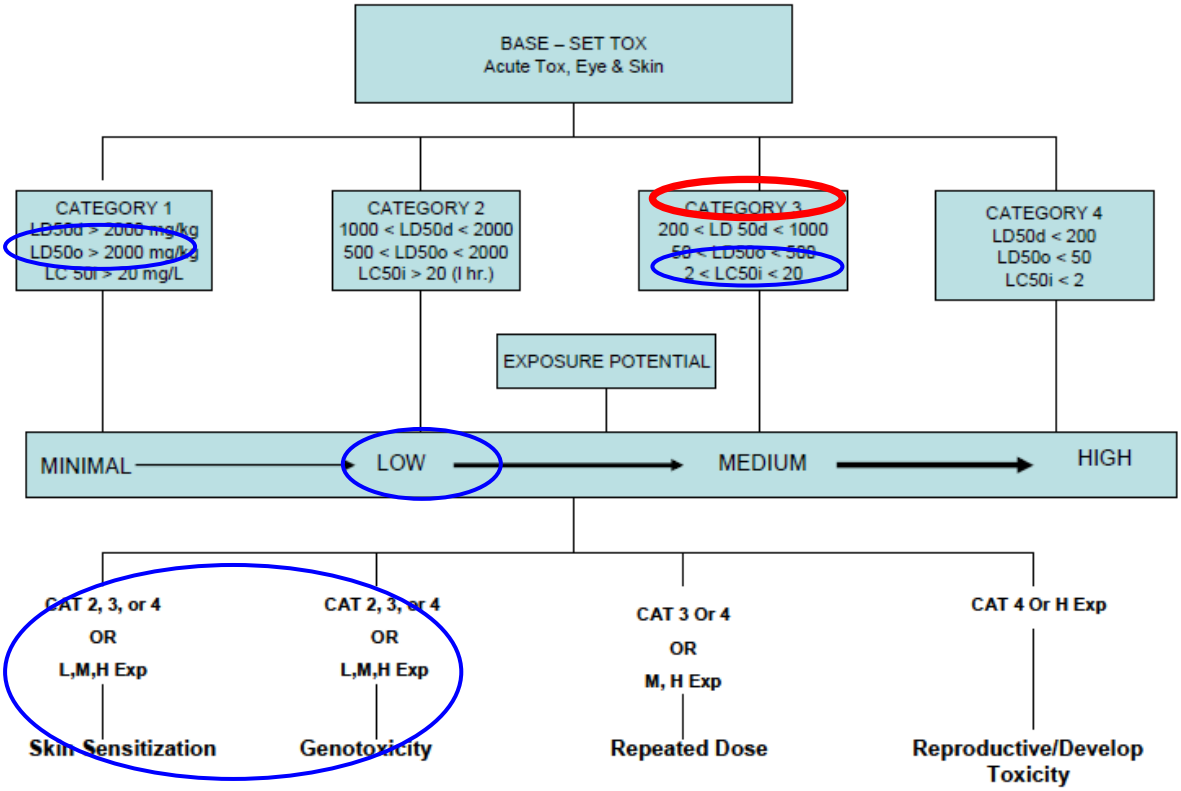
No environmental modeling tool was used because existing data, such as that found in the initial risk assessment reports, etc., was cited.

9.6. Risk characterization

9.6.1. Conclusion in situations where no LOAEL has been identified

Not applicable (because the LOAEL has been specified).

9.7. Triggers for additional data requirements



Rationale:

There was no obvious skin irritability after a single exposure but the substance acted as an irritant when exposures were repeated (*4: p. 104).

NOAEC for irritation (eye): 216 ppm/1 hr, no irritability

100 ppm/7 hrs, slightly irritating (*4: pp. 102 and 103)

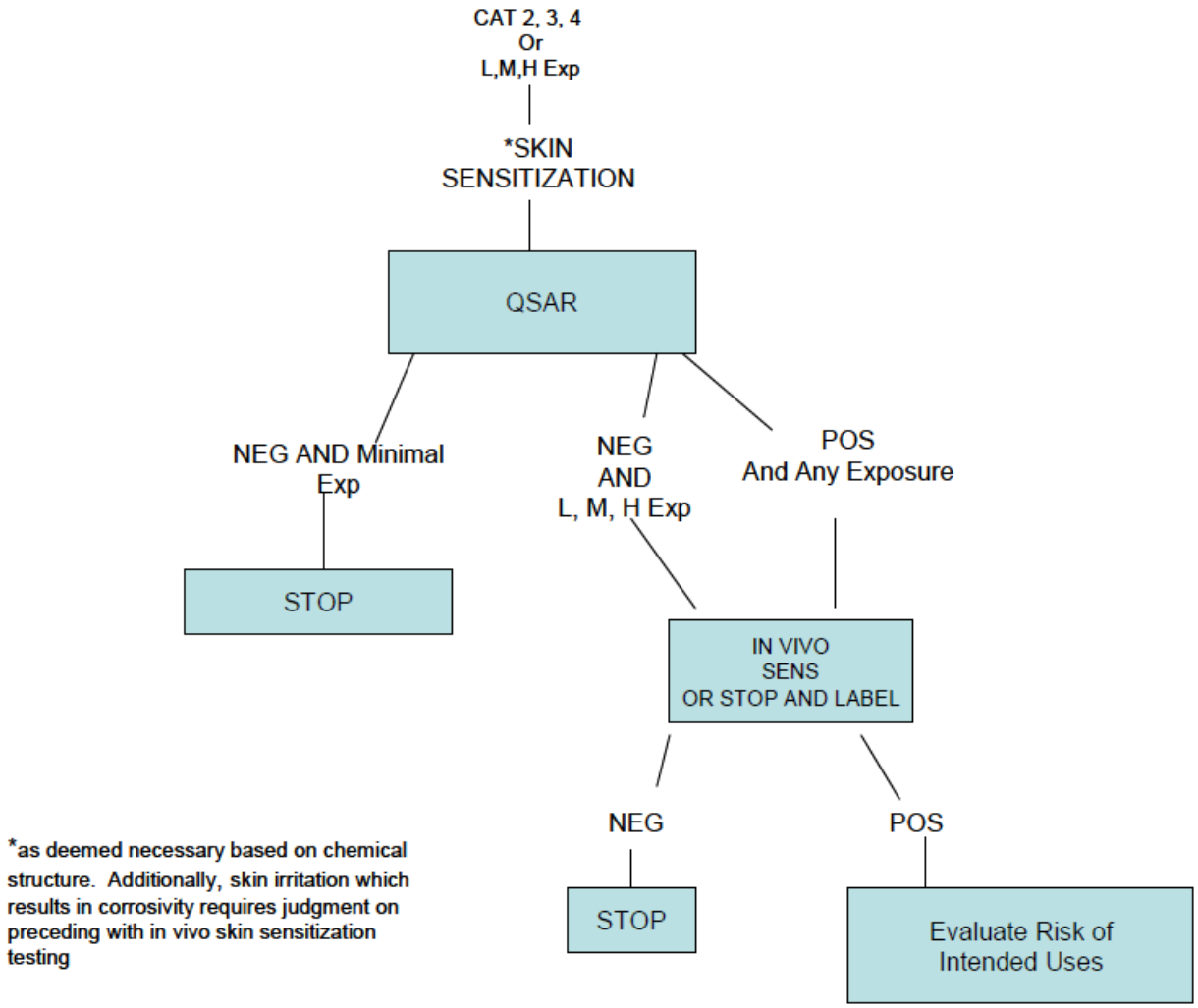
NOAEC (skin): No data available

oLD_{50} = 5000 mg/kg (*4: p. 97), iLC_{50} = 11.8 mg/L (*4: p. 95)

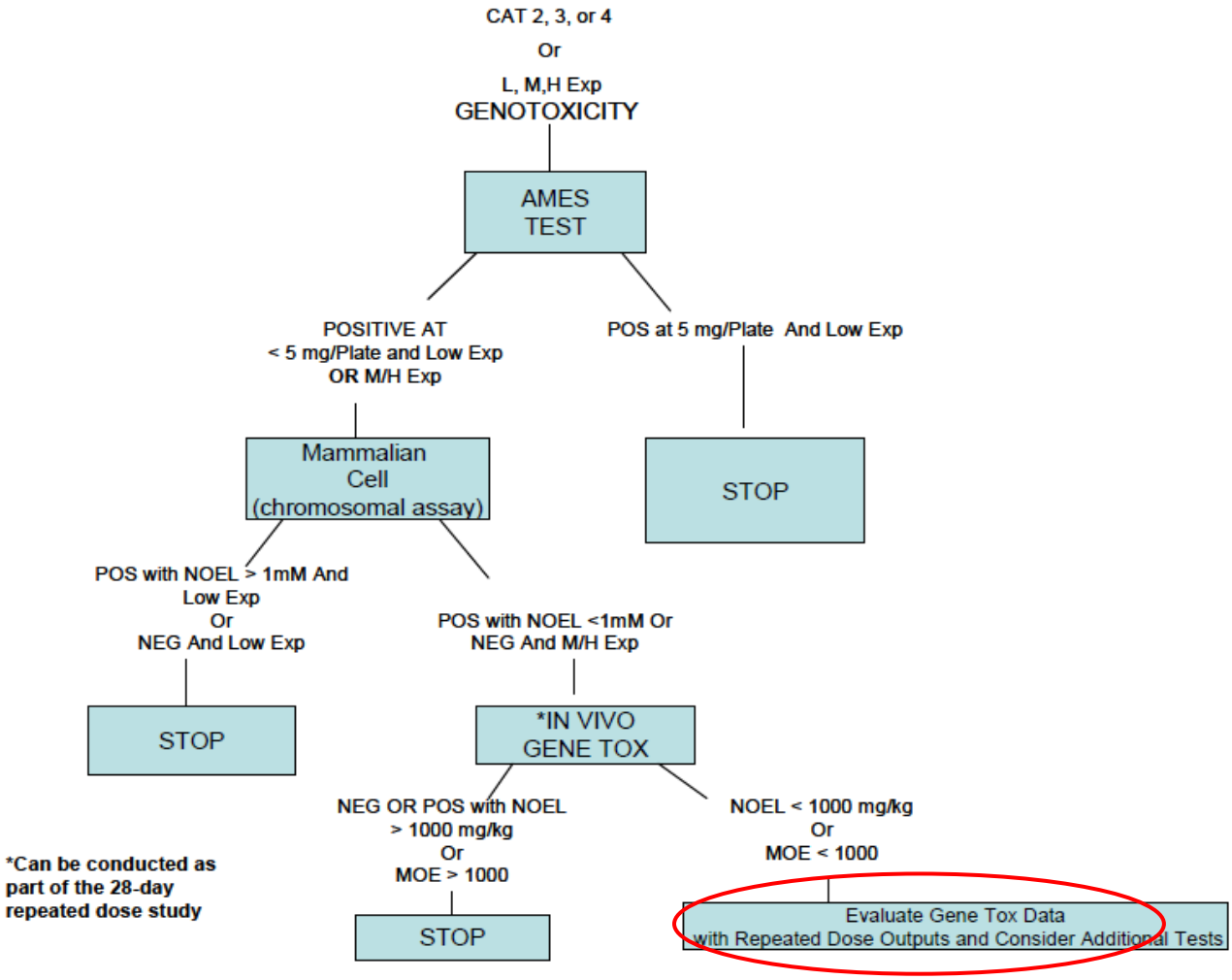
Therefore, styrene can be classified into category 3.

If the exposure potential is assumed to be low, additional data on skin sensitization and genotoxicity will be required.

No data on skin sensitization was found in the initial risk evaluation reports, etc.



The company cannot evaluate these parameters because DEREK (Deductive Estimation of Risk from Existing Knowledge, Lhasa Limited, UK), which can be used as a QSAR tool for the evaluation items concerned, is not available.



Rationale

In vitro

(i) Reverse mutation test: The plate method using *Salmonella typhimurium*, 52 μg/mL < 5 mg (*1: p. 49)

(ii) Chromosomal aberration test (CHL cells): 250 μg/mL < 1 mM (*1: p. 49)

In vivo

(iii) NOEL = 21 mg/kg, MOE = 700 (*1: p. 59)

Based on the above results, it can be seen that further evaluation of genotoxicity and carcinogenicity is required, taking repeated dose administration and additional studies into consideration.

With regard to carcinogenicity, the incidence of lung adenoma/cancer increased in a

78-week oral study in mice, although the relationship between the amount of exposure and the increase in the incidence of tumors was not clear when background data was also taken into consideration. An increase in the incidence of lung tumors was observed in a study in which styrene was administered transplacentally in female pregnant mice and orally in their neonates, from weaning through to 16 weeks, but this increase was not observed in rats and, therefore, the presence or absence of carcinogenicity cannot be clearly determined.

An increase in the incidence of breast tumors was observed in a 52-week inhalational exposure study in rats, indicating a relationship between exposure to styrene and the occurrence of breast tumors, but details regarding the methodology and the data are unavailable and the relationship with spontaneous tumors is also unclear.

The carcinogenicity of styrene cannot, therefore, be determined on the basis of the above results obtained from animal experimentation. The IARC has classified styrene into Group 2B (Possibly carcinogenic to humans) on the basis of its mechanism of action with regard to genotoxicity and the observation of chromosomal aberrations in humans, although there is still only limited evidence available for carcinogenesis in experimental animals. (*1: p. 58)

Styrene has shown a positive reaction in an *in vitro* genotoxicity study. Both negative and positive reactions were observed *in vivo* while a positive reaction was observed for DNA damage. Based on these results, it can be concluded that styrene is genotoxic. (*4: p. 218)

9.8. Examples of Possible Risk Management Actions to Consider

A. Chemical substance

1 **Manufacturing specifications:** Product specificities (as a preparation) are shown in the MSDS.

2 **Product hazard classification**: The hazard classification is stated on the product and in the MSDS, in accordance with various relevant laws and regulations.

3 **(Material) Safety Data Sheets**: Preparation has been completed in accordance with the GHS

4 **Classification and packaging labels**: GHS has been adopted.

B. R&D

1 **Sourcing of alternative raw materials**. There is no need to obtain alternative materials at present because risks are not predicted, provided that the prescribed conditions are met.

2 **Changes to product physical form to reduce exposure potential**: Not needed (for the same reasons given above).

C. Purchase

1 **Supplier materials contracts:** A delivery specification has been exchanged with the supplier.

2 **Switching suppliers**. No needs to change suppliers as risks are predicted, at present.

D. Manufacturing

1 **Legislation and operating permits**: Controllable using the current in-house rules

2 **Engineering control:** The manufacturing formulation and process sheet are highly controlled.

3 **Personal protective devices:** Wearing of protective devices is compulsory in accordance with in-house rules.

E. Contractors

1 **Toll-manufacturing contracts**: No applicable example

2 **Audits:** No applicable example

F. Marketing

1 **Voluntary restrictions on applications and uses.** In accordance with the policy of voluntary restrictions by industry groups.

G. Sales

1 **Customer assistance:** To be provided, as necessary.

2 **Assessment of customer's safe handling of chemicals.:** To be conducted, as necessary

3 **Provision of advice, possibly equipment:** To be provided, as necessary.

4 **Halt sales:** To be decided on the basis of the purpose of use, construction conditions, etc.

H. Distributors

1 **Product stewardship agreements**: Education and training, as well as the provision of yellow cards.

2 **Distributor training:** To be conducted, as necessary.

3 Assessment and Audits: To be conducted, as necessary.

I. Recycling and disposal

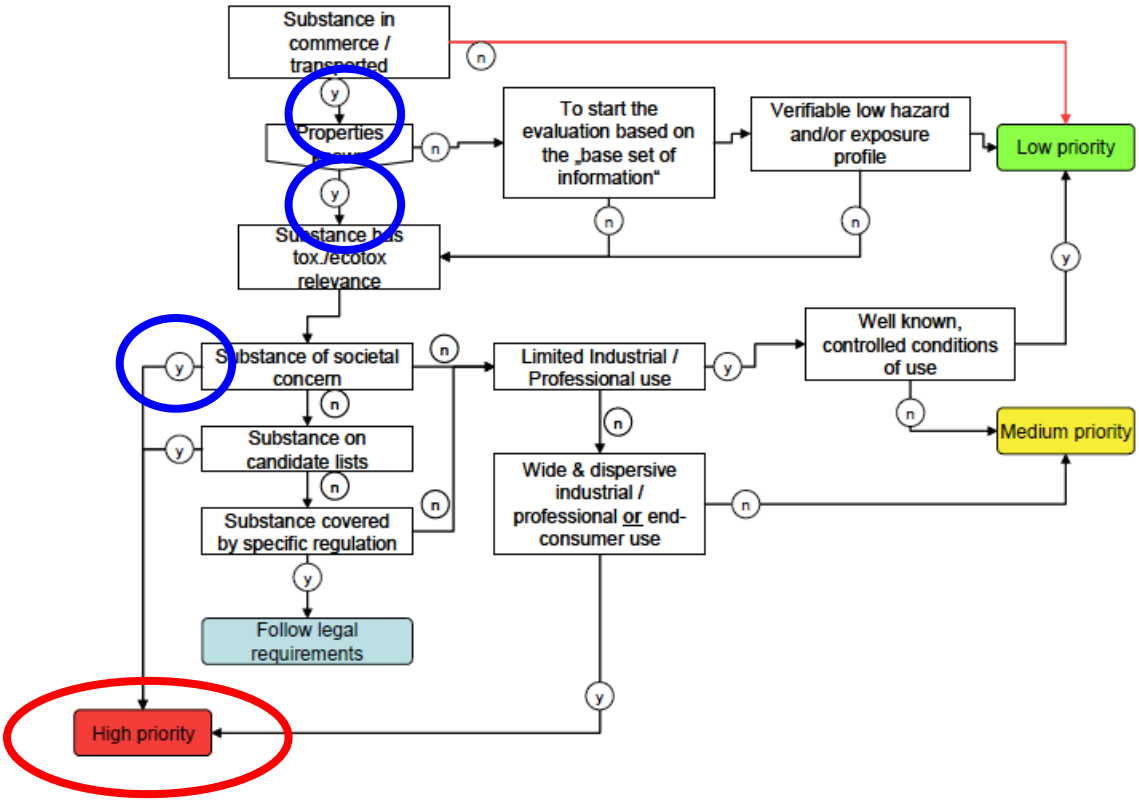
1 **Feasibility of recycling or reusing used and unused product or packaging**: Feasible.

2 **Labels, safety data sheets and other relevant guidance contain adequate disposal information:** Preparation completed.

3 **Expertise available to advice on product & packaging disposal:** To be dealt with by the sales representatives and researchers.

J. Transportation

9.9. Process of Setting Priorities for CSA



9.10. Frequently Asked Questions on ICCA Implementation of the Global Product Strategy (GPS)

9.10.1. GPS Background

9.10.2. GPS & Responsible Care®

9.10.3. GPS & Other Programs (REACH, HPV)

9.10.4. Product Stewardship Summaries

9.10.5. Information Resources