BUREAU FOR CHEMICAL SUBSTANCES

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Furfuryl alcohol

EC No 202-626-1

CAS No 98-00-0

Evaluating Member State(s): Poland

Dated: 23 July 2018

Template Version 2.1
March 2015

Evaluating Member State Competent Authority

MSCA name: Bureau for Chemical Substances
Dowborczykow 30/34 Str.
90 – 019 Lodz,
Tel: + 48 42 25 38 440
Fax: + 48 42 25 38 440
Email: evaluation@chemikalia.gov.pl

Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a Decision to request further information was issued on: 20 May 2015. Based on the follow-up assessment of the new information the substance evaluation is concluded.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Furfuryl alcohol was originally selected for substance evaluation in order to clarify concerns about:

- CMR
- Consumer use
- High (aggregated) tonnage
- Wide dispersive use

During the evaluation also additional other concerns were identified:

- skin sensitisation
- local toxicity via the inhalation route.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Substance is already listed in Annex VI of the CLP Regulation (Index no: 603-018-00-2).

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	x
Harmonised Classification and Labelling	x
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

The results of two LLNA studies presented by the Registrant indicate that furfuryl alcohol meets the criteria for classification in accordance with Regulation (EC) No 1272/2008 on

classification, labelling and packaging of substances and mixtures (CLP) as a skin sensitiser.

The eMSCA considers that the importance of the results of two independent LLNA studies cannot be ignored, despite differences in the severity of the effects in both of these studies. Based on the existing data the substance meets the criteria for classification as skin sensitiser. Therefore the eMSCA concludes that there is no need for additional information on the endpoint skin sensitisation.

The available information suggests that based on two LLNA studies furfuryl alcohol should be classified as moderate skin sensitiser (cut-off of EC 3 is > 2). The way forward is to propose harmonised classification as Skin Sensitiser Sub-category 1B.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable.

5.2. Other actions

The eMSCA revised Derived No Effect Level (DNEL) for workers for acute and/or long-term local effects via inhalation exposure to furfuryl alcohol.

The exposure scenarios with revised Risk Characterisation Ratios (RCRs) above 1 are summarised in section 7.13 Risk characterisation.

The eMSCA recommends the Registrant(s) of furfuryl alcohol to revise the DNELs for workers for acute and/or long-term local effects via inhalation exposure to furfuryl alcohol and, consequently, to revise the Chemical Safety Assessment.

As the available information suggests that furfuryl alcohol should be classified as moderate skin sensitiser, eMSCA recommends that registrants(s) updates its chemical safety assessments and verifies whether current RMMs/OCs are sufficient to cover also this type of adverse effect. Exposures should be controlled for the inhalation and the dermal route of exposure.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 3

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
CLP Annex VI	2019	Poland

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Furfuryl alcohol was originally selected for substance evaluation in order to clarify concerns about:

- CMR
- Consumer use
- High (aggregated) tonnage
- Wide dispersive use

During the evaluation, the eMSCA noted additional concerns regarding skin sensitisation and local toxicity via the inhalation route of exposure. It was concluded that there is a need for harmonised classification and labelling as a skin sensitiser.

Table 4

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
CMR	Concerns not confirmed.
Consumer use	No consumer-related uses
Exposure of workers	With eMSCA's revised DNEL for inhalation, there are risks of inhalation long-term and acute local effects to workers.
Classification and labelling	The current classification is supported. Additional classification as Skin Sensitiser Cat. 1B is proposed to be considered.

7.2. Procedure

The updated Community rolling action plan (CoRAP) was published on the ECHA website on 20 March 2013.

First substance evaluation: 2013

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of Poland has initiated substance evaluation for furfuryl alcohol, CAS No 98-00-0 (EC No 202-626-1).

The evaluation was first based on the data contained in the IUCLID dataset that was compiled on March 2013 including CSRs from the lead registrant and other registrants. Until October 2013 updates of the dossiers were taken into account if applicable.

The evaluation of furfuryl alcohol was targeted at human health endpoints and focused on the grounds for concern that were included in the justification document for the inclusion of the substance in the CoRAP. In addition to these initial concerns, additional concerns on skin sensitisation and local toxicity via the inhalation route of exposure were also identified during the evaluation. On 29th of July 2013 the informally requested information was provided by the lead registrant along with an additional report from the monitoring study conducted by the lead registrant in order to determine the level of worker exposure during specific activities. This report was submitted on 8th of November 2013 and also taken into account for evaluation.

The eMSCA analysed registrations submitted by the registrants and other relevant and available information (aggregated IUCLID dossier, Chemical Safety Report and Worker Exposure Monitoring Report – November 2013). Additionally, the eMSCA conducted a literature search to gather all relevant new data on the concerned endpoints.

The eMSCA considered that further information was required to clarify the above mentioned concern. Therefore, a draft decision pursuant to Article 46(1) of the REACH Regulation was submitted to ECHA on 20 March 2014.

Comments from the registrants and several proposals for amendment to the draft decision were received from other MSCAs. The eMSCA reviewed the proposals for amendment received and did not amend the draft decision.

On 15 December 2014 ECHA referred the draft decision to the Member State Committee.

By 5 January 2015, in accordance to Article 51(5), the Registrant(s) provided comments on the proposed amendments. The Member State Committee took into account the comments of the Registrant(s) made on the proposals for amendment.

The Member State Committee, after discussion in its meeting on 3-5 February 2015, amended the information required (Section II) by removing the original information request for a 28-day repeated dose toxicity study. Furthermore, it amended information required (Section II) by adding a request for an In Vivo Mammalian Alkaline Comet Assay.

The Member State Committee reached an unanimous agreement on the draft decision as modified at the meeting on 5 February 2015.

On 20 May 2015 ECHA sent the final decision to the registrants. An In Vivo Mammalian Alkaline Comet Assay (OECD test guideline 489) in mice, oral route, with examination of stomach, kidney and liver was required.

On 24 May 2016 the Registrant submitted to ECHA an update of the registration dossier containing the information required.

Follow up evaluation: 2016-2017

This new information has been assessed by the eMSCA. Based on the outcome of the In Vivo Mammalian Alkaline Comet Assay, the eMSCA has concluded that the new information submitted by the registrants clarifies the concerns.

7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Furfuryl alcohol
EC number:	202-626-1
CAS number:	98-00-0
Index number in Annex VI of the CLP Regulation:	603-018-00-2
Molecular formula:	C5H6O2
Molecular weight range:	98.0999
Synonyms:	Furfurol 2-furan carbinol 2-furanmethanol 2-furyl carbinol 2-hydroxymethyl furaan 2-hydroxymethyl furan (2-Furyl)-methanol FA Furfural Alcohol Furyl Alcohol

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:

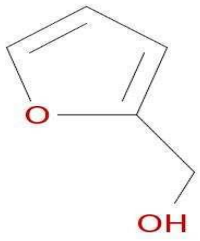

Table 6

Constituent			
Constituents	**Typical concentration**	**Concentration range**	**Remarks**
Furfuryl alcohol EC no.: 202-626-1	[redacted]% (w/w)	>=97.0 - <=100.0% (w/w)	

Table 7

Impurity			
Constituents	**Typical concentration**	**Concentration range**	**Remarks**
Unknown	< [redacted]% (w/w)		There are no impurities with a concentration >=1% w/w

7.4. Physico-chemical properties

Table 8

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	53 Pa at 20 °C
Water solubility	Furfuryl alcohol is miscible with water.
Partition coefficient n-octanol/water (Log Kow)	A log Kow value of 0.3 has been determined in a recent, GLP study (Unpublished study report, 2010) and this value is used for the CSA.
Flammability	not applicable
Explosive properties	Furfuryl alcohol is non-explosive.
Oxidising properties	not applicable
Granulometry	not applicable
Stability in organic solvents and identity of relevant degradation products	not applicable
Dissociation constant	9.55
Viscosity	The viscosity of furfuryl alcohol is 4.62 mPa s at 25 deg C
Flash point	The closed cup value of 65°C is taken as key.
Self ignition temperature/Autoflammability	The auto-ignition temperature of furfuryl alcohol is concluded to be 490°C.
Surface tension	The surface tension of furfuryl alcohol is concluded to be 38 mN/m at 25 deg C.

7.5. Manufacture and uses

7.5.1. Quantities

Table 9

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☒ 10,000-50,000 t
☒ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

This substance is used by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

Table 10

USES	Use(s)
Uses as intermediate	Intermediates
Formulation	polymers, laboratory chemicals and coating products
Uses at industrial sites	polymers and laboratory chemicals, chemicals and plastic products
Uses by professional workers	coating products
Consumer Uses	-
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 11

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
603-018-00-2	furfuryl alcohol	202-626-1	98-00-0	Acute Tox. 4* Acute Tox. 4* Eye Irrit. 2 Acute Tox. 3* STOT SE 3 Carc. 2 STOT RE 2*	H302 H312 H319 H331 H335 H351 H373**		

7.6.2. Self-classification

Self-classification notifications for furfuryl alcohol (EC 202-626-1) are available in the C&L Inventory:

https:/echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/71434

In the following table the additional notified classification for furfuryl alcohol is given (dating of August 2017).

Table 12

Classification	
Hazard Class and Category Codes	**Hazard Statement Codes**
Acute Tox. 3	H301
Acute Tox. 4	H302
Acute Tox. 3	H311
Acute Tox. 4	H312
Skin Irrit. 2	H315
Eye Irrit. 2	H319
Acute Tox. 2	H330
Acute Tox. 2	H331
Acute Tox. 4	H332
STOT SE 3	H335 (eyes, central nervous system, lungs)
Muta. 2	H341
Carc. 2	H351
STOT SE 3	H335, H370
STOT RE 2	H373 (liver, respiratory system)
Aquatic Chronic 3	H412

7.7. Environmental fate properties

This evaluation was targeted to human health concerns and did not consider environmental fate properties.

7.8. Environmental hazard assessment

This evaluation was targeted to human health concerns and did not consider environmental hazards.

7.9. Human Health hazard assessment

7.9.1. Read-across hypothesis

Data from furfural (CAS 98-01-1) toxicity studies have been included in the assessment of furfuryl alcohol. According to the EFSA Journal (2004) furfural and furfuryl alcohol are interconverted in the gut, with oxidation of furfuryl alcohol to furfural and conversion back to furfuryl alcohol mediated by enteric bacteria (EFSA, 2004). The studies with laboratory animals have been demonstrated that both furfural and furfuryl alcohol were well absorbed after oral exposure.

Concerning systemic toxicity, it is therefore considered appropriate to read across to studies with furfural (e. g. for repeat dose oral, reproductive and developmental endpoints).

Endpoints of furfuryl alcohol toxicity that are associated with direct contact-mediated effects (e.g. eye, skin, and respiratory tract irritation) cannot be extrapolated from furfural data due to the difference in physical-chemical properties.

7.9.2. Toxicokinetics

The metabolism and kinetics of furfuryl alcohol have already been reviewed by JECFA (2001) and considered in the EFSA (2004) opinion on furfural, although there is no EU RAR for furfuryl alcohol. Some relevant data from updated literature review has been attached by the Registrant(s).

According to the data presented by the Registrant(s), the toxicokinetics (absorption, metabolism, distribution and elimination) of furfuryl alcohol has been determined in rats and mouse. Studies in humans are also provided.

Non human data

There are three studies in animals with furfuryl alcohol for toxicokinetics (supporting studies with experimental results, reliability 2).

In the first study, the toxicokinetics of furfuryl alcohol and furfural were determined in rats following oral administration. In the second in vitro study the metabolism of furfuryl alcohol in male rat and mouse olfactory and respiratory epithelium was compared. In the next study the metabolism and excretion of furfural was determined in rats and mice.

Nomeir et al, (1992) demonstrated the comparative metabolism and disposition of furfural and furfuryl alcohol after oral dosing. Rats were dosed with approximately 0.127, 1.15 and 12.5 mg/kg bw furfural or 0.275, 2.75 and 27.5 mg/kg bw furfuryl alcohol. For both furfural and furfuryl alcohol, at least 86% to 89% was absorbed from the gastro-intestinal tract, as indicated by the excretion of radioactivity in urine and in the expired air. Furfural and furfuryl alcohol were extensively metabolised, and the major route of excretion in rats was via urine (~85% of the dose), whereas 2-4% of the dose was excreted in the faeces. About 7% of the dose was recovered as $^{14}CO2$ from the expired air in rats dosed 12.5 mg/kg bw furfural. Both furfural and furfuryl alcohol showed similar patterns of tissue distribution with highest levels of radioactivity in liver and kidney, and lowest levels in the brain. Tissue concentrations were proportional to the dose.

Identification of radioactivity in the urine demonstrated that no unchanged furfural or furfuryl alcohol was excreted in the urine. The major urinary metabolite was furoylglycine (73-80% of the applied dose), with furanacrylic acid (3-8% of the dose) and furoic acid (1-6% of the dose) as minor metabolites following exposure to either furfural or furfuryl alcohol.

It is of note that similar oxidative metabolism for furfuryl alcohol and furfural has been reported from in vitro studies of rodent nasal tissue (Unnamed report, 2005), however it was unclear what contribution this makes relative to metabolism in the liver.

Human data

There are two human toxicokinetic studies (supporting studies, reliability 2). One study was conducted with furfuryl alcohol and the second with furfural.

Consistent with the findings in animal studies, similar toxicokinetic processes occur in humans exposed to furfural with the overall biological half-life following inhalation exposure estimated at 2-2.5 hours (Flek & Sedivec, 1978).

Percentage absorption

Based on the observations on excretion of radioactive metabolites after oral absorption in rats, it can be concluded that furfuryl alcohol will be absorbed almost completely in the gastro-intestinal tract. For risk assessment purposes the oral absorption of furfuryl alcohol is set at 90%, in accordance with the proposed absorption value for furfural (EU RAR, 2008), with comparable oral absorption in rats and humans.

Based on the observations of similar absorption, metabolism, excretion and distribution of furfural and furfuryl alcohol after oral absorption and in the absence of additional data, for risk assessment purposes the proposed dermal and inhalation absorption are the same as those proposed for furfural i. e. 100% for both. For inhalation, this is based on information on excretion of radioactive metabolites and lung retention after inhalation of furfural vapour in humans and is in accordance with the RAR for furfural (EU RAR, 2008). For the dermal route, exposure of humans to furfural vapour or to furfural liquid resulted in significant dermal uptake and for risk assessment purposes dermal absorption is proposed at 100% (in accordance with the EU RAR (2008) for furfural).

Summary of key information on bioaccumulation potential

Furfuryl alcohol is rapidly and extensively oxidized to furfural which in turn is converted by oxidative metabolism to furoic acid and excreted in urine as a conjugate with glycine. At high dose levels, the glycine conjugation pathway may saturate and the direct excretion of furoic acid increases. The glycine conjugation pathway involves the intermediate formation of furoyl CoA which is proposed to be interconverted to furanacryloyl CoA followed by excretion as furanacryloylglycine. Consistent with this database in animals, similar toxicokinetic processes occur in humans exposed to furfural with the overall biological half-life following inhalation exposure estimated at 2-2.5 hours.

eMSCA agrees with Registrant's conclusion, that for the purposes of risk assessment percentage absorption via the oral route is proposed to be 90% and for absorption via dermal and inhalation routes, 100%.

7.9.3. Acute toxicity and Corrosion/Irritation

The acute toxicity of furfuryl alcohol has already been assessed and summarized by, for examples: US NIOSH (1979); JECFA (2001) and INRS (2010).

Oral

In rats, reported acute oral LD_{50} values range from 132 – 275 mg/kg bw (Woods & Seevers, 1954; Unnamed report, 1949). The only signs of toxicity observed in the rat were convulsions and respiratory paralysis preceding death at lethal doses (INRS, 2010). Available data for mice do not conflict with these values (NIOSH, 1979; INRS, 2010).
Since furfuryl alcohol rapidly and extensively metabolises to furfural, for systemic endpoints it is also relevant to consider the toxicity of furfural. This has been evaluated and reported in the EC Risk Assessment Report for furfural (2-furaldehyde) (EC RAR, 2008) with the acute oral LD_{50} concluded to be in essentially the same range and warranting classification under CLP.

Inhalation
In a GLP compliant study (Unpublished study report, 2005) the LC_{50} for inhalation was found to be in the range of 820 to 2070 mg/m3. At 2070 mg/m^3, 8 out of 10 animals died during exposure and the surviving male and female animals were killed immediately after exposure for humane reasons. There were no mortalities following exposure to 510 or 820 mg/m^3 furfuryl alcohol. Slightly decreased breathing rate was noted during exposure to 510 and 820 mg/m^3 and sniffing and/or nasal encrustations were seen at 820 mg/m^3 on the second day of the 14-day observation period in most animals. There were no other significant clinical observations and all animals at these two doses survived to scheduled termination. At necropsy, treatment-related macroscopic changes in the animals exposed to 2070 mg/m^3 included red or dark red discoloured lungs, foam in the trachea and haemorrhagic or foamy discharge from the nose and mouth or foamy discharge from the nose. There were no macroscopic abnormalities at necropsy in the other groups.

Other supporting studies report 4 hour LC_{50} values of 950 mg/m^3 (Unnamed report, 1958) and 880 mg/m^3 (Terrill et al, 1989).

Dermal
Limited data is available. After acute dermal exposure to furfuryl alcohol, the rabbit appears to be more susceptible than the rat. The LD_{50} has been reported to be in the range of 400 to 657 mg/kg (NIOSH, 2004; Woods & Seevers, 1954).

Considering the available data, the acute oral LD_{50} in the rat lies in the range of 132-275 mg/kg. The acute dermal LD_{50} lies in the range of 400 to 657 mg/kg bw.
The inhalation LC_{50}, derived from a GLP study, lies between 820 - 2070 mg/m^3. There were no mortalities at <=820 mg/m^3 and the overall NOAEC for systemic effects is concluded to be 510 mg/m^3. Other supporting data indicate LC_{50} values of 880 and 950 mg/m^3.

According to Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation), furfuryl alcohol, classification should be at minimum:
- Category 4 for oral exposure (H302),
- Category 4 for dermal exposure (H312),
- Category 3 for inhalation exposure (H331).

The Registrant has proposed a stricter self-classification for furfuryl alcohol in comparison with harmonised classification according to the Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation). In the opinion of registrant furfuryl alcohol warrants classification under Category 3 for acute exposure via the oral and dermal routes (as Toxic if swallowed H301 and Toxic in contact with skin H311). In relation to acute inhalation exposure, furfuryl alcohol warrants classification in Category 2 as fatal if inhaled H330.

Skin irritation

Animal data

Evaluation of the data presented in the registration dossier shows that no guideline study is available for furfuryl alcohol. Some limited data are available as reviewed by US NIOSH (1979). The study reported by Unnamed author (1974) used acetone as a solvent. Acetone itself causes skin dryness and cracking after repeated exposure and therefore no conclusion regarding skin irritation potential of furfuryl alcohol can be made. As discussed in the sensitisation endpoint summary, there was evidence of skin irritation in the LLNA studies reported by Unnamed author 2012 and Unnamed author, 2004. Lead registrant proposed that furfuryl alcohol should be considered as a skin irritant under CLP.

Human data

eMSCA noticed that there is very little human data in relation to skin irritation. Lack of evidence of skin irritation in the workplace is reported by Apol (1973). Dermatitis was reported in 2 of 15 workers who had skin contact with acid-resistant cement containing furfuryl alcohol (Unnamed author, 1965), but the effects may have occured due to other components of the cement and there was no other reports linking furfuryl alcohol to dermatitis.

Eye irritation

Animal data

From the process of evaluation it is concluded that for furfuryl alcohol eye irritating effects are reported (as reviewed by NIOSH, 1979). Although information is limited (all Klimisch 4), evaluation of the data shows that furfuryl alcohol is considered to have eye irritating properties.

Human data

OSHA concluded that the irritation experienced by the foundry workers was due to the furfuryl alcohol rather than exposure to formaldehyde. Subsequent information suggested that the threshold for eye irritation arising from exposure to furfuryl alcohol is between 100 and 122 mg/m3. NIOSH (1979) reviewed a study in which no effects were observed at concentrations of 44 mg/m3 and severe eye irritation was reported at 64.5 mg/m3 in workers exposed to furfuryl alcohol during core preparation. In another study 28 workers reported airway symptoms (cough, nose, throat) and eye irritation. Time-weighted exposure levels were 7 mg/m3 with peak values of more than 40 mg/m3 (Ahman et al. 1991).

Furfuryl alcohol is irritating to eyes, leading to classification with H319 according to CLP (Regulation (EC) No 1272/2008).

Respiratory irritation

Signs of respiratory tract (specifically nasal) irritation were seen in rats after repeated exposure and based on these observations furfuryl alcohol is classified for respiratory irritation.

Animal data

Several animal studies on respiratory irritation have been evaluated. Evaluation of the data shows that furfuryl alcohol is considered to have respiratory irritating properties.

In the acute inhalation toxicity study, effects included respiratory tract irritation (Unnamed author, 2005). In repeated dose inhalation toxicity studies with furfuryl alcohol, irritating effects were reported.

In the 16-day carcinogenicity dose range-finding mouse and rat studies with furfuryl alcohol (NTP, 1999), at the lower doses of 16, 31, 63 and 125 ppm, all exposed rats exhibited acute and/or suppurative inflammation, necrosis, regeneration and squamous cell metaplasia of the respiratory epithelium and necrosis and degeneration of the olfactory epithelium. The respiratory changes can be considered an adaptive response to irritation, with increasing severity with increasing dose. In contrast to rats, at the same dosages not all exposed mice were affected and there was lower incidence and severity of respiratory and olfactory changes. At the lowest dose of 16 ppm in the mouse, the changes were only minimal.

After chronic exposure, extensive non-neoplastic alterations in the respiratory and olfactory epithelia and hyperplastic Bowman's glands were observed in both species. A small increase in the incidence of nasal epithelial tumours was reported in male rats at the top dose of 32 ppm, but not in female rats or in mice (NTP, 1999). Sustained extensive chronic damage was necessary for tumour development and the NTP (1999) study report notes that the hyperplasia and squamous cell metaplasia in the rat represent conversion of highly specialised nasal tissue into more resistant types of epithelium, representing an adaptive response to chronic irritation.

Based on these observations, furfuryl alcohol is considered to have respiratory irritating properties.

Human data

Several human studies on respiratory irritation has been evaluated.

In relation to respiratory irritation, in one study (Ahman et al., 1991) the results indicated an acute restrictiveness induced by exposure to furan resin sand and was most likely induced by furfuryl alcohol in combination with dust and formaldehyde or other chemicals, but the underlying mechanism was unclear. Chronic impairment of lung function was not reported. In another study (Unnamend study, 1985) onset of symptoms in relation to exposure to various fumes and vapours suggested that both irritant and hypersensitivity mechanisms were present.

In conclusion, from these studies it appears that furfuryl alcohol in combination with dust and formaldehyde or other chemicals, or exposure to various fumes and vapour might cause slight irritation and or acute restrictiveness of the lungs. However, a direct correlation with furfuryl alcohol exposure levels could not be clearly established since, in these studies, humans were exposed to mixtures and/or reactions products and not to furfuryl alcohol alone.

In European countries, a national OEL of 5 or 2 ppm has been established for exposure to furfuryl alcohol in the workplace. In repeated dose inhalation toxicity studies in rats, local effects on the nasal epithelium have been reported that warrant classification of furfuryl alcohol under CLP as "may cause respiratory irritation" (H335). However, no significant nasal irritation has been reported by workers exposed to furfural alcohol despite its extensive use over the last 60 years or more. To confirm this, a statement from one production plant is available: "no nasal irritation has been reported in workers exposed to furfuryl alcohol in a plant which could be attributed to furfuryl acohol". Overall it seems likely that furfuryl alcohol is irritating to the respiratory tract, eyes and skin.

Although furfuryl alcohol is not classified as irritating to the skin under Annex VI of CLP, the Registrant self-classifies it as “irritating to the skin”, H315 based on limited evidence, including information from the dermal sensitisation studies.

Furfuryl alcohol is irritating to eyes, leading to harmonised classification H319 according to CLP (Regulation (EC) No 1272/2008). Irritating effects were shown in the respiratory system (nasal tissue) of rats after repeated exposure. Based on these observations furfuryl alcohol is also classified with H335 according to CLP.

7.9.4. Sensitisation

Skin sensitisation

The results of two LLNA studies indicate that furfuryl alcohol meets the criteria for classification as a skin sensitiser in accordance with Regulation (EC) No 1272/2008 (CLP).

Non-human

The registrant has provided the results of two local lymph node assays (LLNA) for furfuryl alcohol. Studies have been carried out in accordance with Regulation (EC) 440/2008 (method B.42 / OECD 429 Skin sensitisation: local lymph nodes assay).

The first LLNA (Unnamed author, 2004) tested CBA/J mice, as recommended in the OECD TG 429. Test material ST 16 C 03 (furfuryl alcohol, purity 98.5%) was tested with 5 concentrations (1%, 5%, 10%, 20% and 40%) using 4:1 acetone: olive oil (AOO) as the vehicle. A positive control, isoeugenol (a known skin sensitiser), was tested concurrently (0.5%, 1% and 5% in AOO). Control animals were treated with AOO alone.

The LLNA was conducted in compliance with GLP using a standard procedure. There was an induction of draining lymph node cell proliferation by furfuryl alcohol that was dose-related. The data are consistent with a positive response in the LLNA, insofar as at 3 test concentrations (10%, 20% and 40%) stimulation indices of 3 or greater were recorded (8.8, 9.2 and 21.0, respectively). In the same animals increases in ear thickness associated with exposure to furfuryl alcohol were less than 3% (compared to 2.9% with vehicle control). The interpretation is that the changes in lymph node cell proliferative activity observed with the higher test concentrations of furfuryl alcohol were not to be attributable to elicitation of a strong skin irritant response at the point of contact. Using the LLNA data the investigators derived an EC3 value of 4.63% resulting in Cat 1B according to CLP criteria.

In the same study responses observed with isoeugenol, a positive control, were as expected. That is, a clear positive response (SI = 18.3) was observed with 5% of the chemical. The response to isoeugenol in this study translates into an EC3 value of 0.75%.

This is not dissimilar to a previously reported EC3 value for isoeugenol of 1.8% (Gerberick et al., 2004).

The second LLNA study (Unnamed author, 2012), was performed on the Balb/c mice strain. Furfuryl alcohol (10%, 20%, 50% and 75%) was applied using acetone as a vehicle (purity of the test material not reported). A dose-related increase in lymph node cell proliferation was observed. The SI values were 1.3, 2.9, 4.3 and 5.9 at 10%, 20%, 50% and 75%, respectively. Statistically significant increases in proliferative activity were recorded with 50% and 75% furfuryl alcohol, concentrations that induced positive responses (SI values of 3 or greater). Only at concentration of 75% furfuryl alcohol caused significant skin irritation, measured as a function of induced increases in ear thickness.

In this case the EC3 value was 25.6% which causes classification in Cat. 1B according to CLP criteria.

The important difference in the effective concentration of furfuryl alcohol between two studies described in the registration dossier was noted.

In the first study (2004) the proliferation of cells in local lymph node were observed following application of 10%, 20% and 40% of the substance. In the second one (Franco, 2012) such effect occurred after application of 50% and 75 % of furfuryl alcohol.

There seems to be a problem of reproducibility of results in terms of potency of sensitisation, which is much higher in the first study (2004). The skin irritation contribution was in both LLNAs monitored by measurements of ear thickness and considered not significant, however it is not known whether such measurements are sufficient to exclude the contribution of direct skin irritation to proliferation of lymph node cells.

Human

In the view of the eMSCA the epidemiological data presented by the Registrant (U. S. National Institute for Occupation Safety and Health, 1979) are unsuitable to dismiss the classification of the registered substance. Furthermore, the CLP guidance states that "Positive effects seen in either humans or animals for skin sensitisation will normally justify classification. Evidence from animal studies on skin sensitisation is usually more reliable than evidence from human exposure, although adequate reliable and respresentative human data are usually more relevant. In cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to decide on the classification on a case-by-case basis. Negative human data should not normally negate positive findings in animal studies (CLP Annex I, 3.4.2.2.4.2)." Hence, the lack of positive response in humans is not acceptable to disregard the clear positive findings in the two LLNA studies.

Conclusion:

The eMSCA considers that the importance of the results of the two independent LLNA studies cannot be ignored, despite differences in the severity of the effects in both of these studies. In the first study the correct mouse strain was used and the purity of the test material was reported. In the second study, the mouse strain used was not the recommended strain and no information on the test material purity was reported. Therefore, due to these differences in the tests performed, the reason for the differences

in the severity of the effects cannot be concluded. However, based on both studies the substance meets the CLP criteria for classification as skin sensitiser Cat 1B.

The registrant states in his summary on skin sensitisation that "There have been suggestions that certain classes of chemical are associated with false positive reactions in the LLNA (Unnamed study, 2008)." However, the cited publication discusses the possibility that fatty acid type substances may cause false positive results in LLNA. The registered substance is not a fatty acid type substance. Moreover, the Registrant does not make the case why this substance would yield false positive results in this specific assay.

In the opinion of the eMSCA harmonised classification should be proposed, since the registrants do not self-classify the substance.

Therefore the eMSCA concludes that there is no need for additional information on the endpoint skin sensitisation. The available information suggests that based on two LLNA studies furfuryl alcohol should be classified as a moderate skin sensitiser i.e. Cat 1B according to CLP criteria (cut-off of EC3 is > 2). The way forward is to propose harmonised classification.

Respiratory sensitisation

There is little information available regarding the respiratory sensitisation potential of furfuryl alcohol. There are no structural alerts that suggest that furfuryl alcohol has respiratory sensitising potential. Nor does it share structural homology with classes of chemicals (acid anhydrides, diisocyanates, piperazine, chloroplatinate salts) that are known to be associated with respiratory allergy and occupational asthma.

Non-human

The Lead registrant presented only one study concerning allergenic potential and increased respiratory response as a result of inhalation exposure and inhalation exposure preceded by dermal exposure (Unnamed study, 2012). The eMSCA considers, however, that the reported mechanism is mostly based on the activity of methacholine (MCH) as cholinergic receptor agonist.

No established protocol has been adopted so far for efficient identification of respiratory sensitisers. However, in accordance with the Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a (Endpoint specific guidance), the only solution is to characterise the likelihood of sensitisation through the LLNA test or other tests used to measure the potential skin sensitisation. They are designed to test skin allergies, but there is evidence that chemical respiratory allergens trigger positive responses in these assays.

Human

No studies concerning exposure exclusively to furfuryl alcohol have been presented by the Registrant, but only to the furfuryl alcohol mixture with other reaction products, including sulfuric acid and butanol.

Conclusion

On the basis of the information provided it cannot be determined conclusively whether furfuryl alcohol exhibits respiratory sensitisation properties or not.

7.9.5. Repeated dose toxicity

Subchronic inhalation toxicity studies with furfuryl alcohol in rats and mice and a subchronic dietary toxicity study in rats with the proximate metabolite, furfural, are available.

Oral

Based on comparable absorption, distribution, metabolism and excretion of furfural and furfuryl alcohol it is appropriate to consider data for the proximate metabolite; furfural, for systemic toxicity. The toxicity of furfural was reviewed and a final Risk Assessment Report published by the EU in 2008 (EU RAR, 2008). The key study identified for oral toxicity was a 13 week feeding study in rats (Jonker, 2000a,b). No new studies have been identified and there are no newly published studies on the oral toxicity of furfuryl alcohol.

In a 13-week oral toxicity study rats were exposed to the proximate metabolite, furfural, via their feed. Haematological differences and minor microscopic liver changes were seen in males at 82 and 160 mg/kg bw/day. In females minor clinical chemistry changes were seen at 170 mg/kg bw/day (Jonker, 2000a, b). There is reference to an unpublished 13-week oral toxicity study with furfuryl alcohol in NTP (1999). In this study mild hepatic and renal effects were reported at 75, 150 and 300 mg/kg/day with a NOAEL of 38 mg/kg bw/day. The overall oral NOAEL is from the Jonker (2000a, b) study and is 53 mg/kg bw/day.

Inhalation

The National Toxicology Program (NTP) has reported inhalation studies in rats and mice undertaken over 16 days, 14 weeks and 2 years with furfuryl alcohol (NTP, 1999). In all three experiments, animals were exposed for 6 hours/day, 5 days/week.

In the 16 day study, rats exposed to 1020 mg/m3 (6 hours per day, 5 days per week) all died within the first two days of exposure. One rat exposed to 510 mg/m3, died on day 5 and the other rats exposed to 510 mg/m3 showed reduced weight gain. Male, but not female rats, also showed reduced weight gain at 127 mg/m3 and 257 mg/m3. Both male and female rats showed dyspnoea, hypoactivity and nasal and oculardischarge at exposures above 257 mg/m3 and all the exposed animals developed lesions in the nasal respiratory epithelium and olfactory epithelium. Similar effects were seen in mice but one of the exposed animals developed lesions in the nasal respiratory and/or olfactory epithelium. The lowest observed adverse effects level (LOAEC) in both species was 127 mg/m3, but the no observed adverse effects level (NOAEC) was not established.

In the key 14-week (5 days/week, 6 hours/day) inhalation toxicity studies in rats and mice the only evidence of systemic toxicity induced by furfuryl alcohol was lower body weight gain in female rats at 32 ppm (128 mg/m3), the highest dose tested (NTP, 1999). However, local changes were observed in the nasal passages of both sexes in both species at all concentrations tested. The findings indicate that furfuryl alcohol causes significant irritation and tissue damage. The reported LOAEC for local effects was 2 ppm (equivalent to 8 mg/m^3). According to registrant the NOAEC for systemic effects was 16 ppm (equivalent to 64 mg/m^3) in the rat and 32 ppm (equivalent to 128 mg/m^3) in the mouse.

According to cited report, in the 14 week study, a reduction in body weight gain was seen in female rats exposed to 131 mg/m3 and in mice, the heart weights of the 131 mg/m3

males were significantly reduced. A dose-related increase in the severity of lesions of the respiratory and olfactory epithelium was observed in both species. The LOAEC in both species was 8 mg/m3, but the NOAEL was not established.

In the 2 year study, animals were exposed 6 hours per day, 5 days per week to 0, 8, 16 or 131 mg/m3. Male rats exposed to 131 mg/m3 showed reduced body weights and all died by week 99 of the study. An increased incidence of non-neoplastic histological changes of the nose was observed in rats at all exposure concentrations. Neoplastic changes in the nose and in the kidneys were also observed. Renal toxicity was also observed and rats exposed to 131 mg/m3 showed parathyroid gland hyperplasia and fibrous osteodystrophy arising from renal toxicity. In mice, the mean body weights of all exposed females were reduced during the second year of the study. Female mice exposed to 131 mg/m3 developed focal corneal opacities. Male mice showed kidney damage that increased in severity with increasing concentration. The most sensitive endpoint was hyperplasia of the lateral wall of the nose in male and female rats. The dose-response-curve is very steep and therefore it is not possible to estimate a benchmark dose. The LOAEC in both species was 8 mg/m3 (2 ppm), but the NOAEC was not established.

A much earlier study undertaken by Savolainen and Pfaffli (1983) exposed rats for 6 hours/day, 5 days/week to fufuryl alcohol vapour concentrations of 100, 200 and 400 mg/m3. All the exposed animals showed reduced weight gains and changes in enzyme activity in the brain. The authors concluded that furfuryl alcohol may cause significant mitochondrial effects in the brain that lead to glial cell degeneration and initiation of demyelination.

In an unpublished study cited by NIOSH (1979), rats and mice exposed for 6 hours/day for 6 weeks to 77.5 mg/m3 furfuryl alcohol showed moderate pulmonary congestion, but no significant signs of toxicity and no evidence of eye irritation (Comstock and Oberst, 1952).

The results of the present studies demonstrate that furfuryl alcohol is an obvious nasal irritant in both rats and mice. However, it is unknown if the primary irritant is the parent alcohol or a metabolite. At vapor concentrations similar to those used in the present study, simple aliphatic alcohols such as methanol and ethanol are essentially nontoxic to the nose (Andrews et al.,1987; Poon et al., 1994). By contrast, their respective aldehydes, formaldehyde and acetaldehyde, are nasal toxicants and nasal carcinogens (Swenberg et al., 1980; Appelman et al., 1982; Woutersen et al., 1984; Monticello et al., 1996). Furfural, the aldehyde, is the major metabolite of furfuryl alcohol. In the only inhalation study of furfural in which the nose was examined histologically, Syrian golden hamsters were exposed to 0, 20, 115, or 552 ppm furfural, 6 hours per day,5 days per week for 13 weeks (Feron et al., 1979). In this study, the nose was the only target organ; 20 ppm was the no-observable-effect level, while 115 and 552 ppm caused atrophy and hyperplasia of the olfactory epithelium but were without effect on the respiratory epithelium. These results indicate that furfural is considerably less toxic to the nose than furfuryl alcohol.

Exposure of male and female rats and male mice to furfuryl alcohol was associated with increased incidences of nonneoplastic lesions of the nose and increased severities of nephropathy. Exposure of female mice to furfuryl alcohol was associated with increased incidences of nonneoplastic lesions of the nose and corneal degeneration.

Following repeated oral or inhalation exposure there was no evidence of significant target organ toxicity at dose level below regulatory thresholds and no classification is warranted for this end-point. The local effects (due to respiratory (nasal tissue) irritation) are covered by the respective classification (STOT-SE H335).

However, furfuryl alcohol has been classified as STOT-RE 2, H373*("May cause damage through prolonged or repeated exposure") and this classification will be applied, even though it is considered not to be warranted after assessment of the available data.

However repeated dose toxicity was not a specific target for the substance evaluation, it was noted that results of inhalation studies in rats and mice suggested that repeated exposure to 8 mg/m3 (2 ppm) of furfuryl alcohol caused nasal lesions arising from respiratory irritation (NTP, 1999) and NOAEC has not been established.

7.9.6. Mutagenicity

The genotoxic potential of furfuryl alcohol has already been assessed and reported in an EFSA review (2011). Some additional relevant data from updated literature review has been attached by lead registrant along with the key studies from EFSA review.

According to the data presented by lead registrant furfuryl alcohol has been examined for mutagenicity both in vitro and in vivo in a range of recognized core assay types, and also in a number of non-standard genotoxicity assays of limited relevance for a weight of evidence assessment of genotoxic activity.

In vitro

The Registrant has provided a number of in vitro studies with furfuryl alcohol for gene mutation using the Ames test (4 key studies, 5 supporting studies, 6 studies with experimental result for weight of evidence).

Based on the results of in vitro studies, furfuryl alcohol proved to be non-genotoxic for this endpoint in standard tester strains, but genotoxic in a Salmonella strain modified to have enhanced sulphotransferase activity. DNA adducts were found in the DNA from such modified bacteria.

There is conflicting evidence for clastogenic activity from in vitro mammalian cell assays, but with some positive results recorded. These have been of limited reproducibility however, and the effects seen were sometimes small.

It can be concluded that there is some limited evidence for cytogenetic activity in vitro.

In vivo

The lead registrant has provided several in vivo studies with furfuryl alcohol for gene mutation (2 key studies, 1 supporting studies, 3 studies with experimental result for weight of evidence). There is evidence from a robust evaluation in mice showing negative results in the bone marrow for the endpoints of micronucleus, chromosomal aberration and SCE induction. A positive result for chromosomal aberrations was from a study using two animals per group, and is considered insufficient to alter a conclusion of no clastogenic activity in vivo. A study by Unnamed author (2011) reported DNA adducts formed in liver, kidney and lung tissue, but not in colonic mucosa from mice exposed for 28 days to furfuryl alcohol.

It is concluded that the available data are sufficient to indicate that furfuryl alcohol has no significant mutagenic activity in the conventional assays examined. Modification of

Salmonella to enhance sulphotransferase activity, however, resulted in DNA adducts and a mutagenic response in vitro. This suggests that a mutagenic response can result from metabolism of furfuryl alcohol by this enzyme. Investigation of mice dosed with furfuryl alcohol resulted in the same DNA adducts being detected in some but not all of the tissues examined, and at low levels. The significance of this DNA binding (an indicator assay for genotoxicity) is not clear, although furfuryl alcohol was not mutagenic in two studies for mutagenicity in the bone marrow.

Additionally, more recently a (Q)SAR model for assessment of chemical genotoxicity was developed (Unnamed study, 2012). This model was optimized for application to industrial chemicals using three commercially available (Q)SAR systems: Derek for Windows and MultiCase, which are used widely by regulatory agencies, and ADMEWorks. For validation of this (Q)SAR combination approach for mutagenicity prediction about 2000 flavor chemicals, including furfuryl alcohol, were tested. A positive result was not returned for furfuryl alcohol.

Furfuryl alcohol has been examined for mutagenicity both in vitro and in vivo in a range of recognised core assay types, and also in a number of non-standard genotoxicity assays of limited relevance for a weight of evidence assessment of genotoxic activity.

During the consultation with MSCAs, a proposal for amendment (PfA) was submitted to investigate concern for genotoxicity raised by positive results obtained on modified Salmonella typhimurium strains, in accordance with testing strategy proposed by MSCA. The Registrant(s) submitted comments to the PfA pointing out the results on modified Salmonella TA100 strain may be of value from mechanistic perspective but that positive results from these tests should not outweigh the results of negative findings of other data from established assays. It was discussed that most standard in vitro assays for gene mutation were negative for furfuryl alcohol. However, two modified Salmonella test strains show positive results. Unnamed author (2011) studied mutagenicity using two different TA100-derived strains expressing human SULT1A1. As a result, mutagenicity increased in a dose-dependent manner up to more than 4-fold the solvent control value. According to the authors, the results of this study indicate that furfuryl alcohol is metabolically converted to an electrophile metabolite reacting with DNA. In addition, two recent scientific studies have pointed to bioactivation of furfuryl alcohol by the enzyme sulfotransferase (Unnamed author, 2014a4; Unnamed author, 2014b5). Hence, there was a non-resolved concern for genotoxicity.

Following the substance evaluation decision to clarify the concern for genotoxicity, an In Vivo Mammalian Alkaline Comet Assay (OECD test guideline 489) was conducted according to GLP with furfuryl alcohol in mice (Furfuryl Alcohol: CD1 Mouse In Vivo Comet Test, 2016).

This study was designed to assess the potential of furfuryl alcohol (FA) to induce DNA strand breaks in the glandular stomach, liver and kidney of male CD1 mice. Animals were treated oraly via gavage with FA twice to dose levels of 93.8, 187.5 and 375 mg/kg/day, the second dose being administered approximately 24 hours after the first dose and 3 hours before sacrifice. The study presents reliable data on furfuryl alcohol genotoxicity testing in the in vivo comet assay according to OECD TG 489. The results confirm no genotoxic effect of FA in the glandular stomach, liver or kidney tissues of the CD-1 mice exposed orally to doses up to a maximum tolerated dose of 375 mg/kg/day.

It is concluded that there is limited evidence for genotoxicity of furfuryl alcohol in vitro.

It is concluded that the available data is sufficient to indicate that furfuryl alcohol has no significant genotoxic activity and does not warrant classification under CLP.

This conclusion is supported by the position reached by the Technical Committee on C&L of dangerous substances (European Chemicals Bureau, ECBI/90/06 Rev. 8) which agreed not to classify furfuryl alcohol for genotoxicity. The EFSA (2011) also concludes on a lack of concern for genotoxicity.

So the initial concern for genotoxicity was not confirmed in this substance evaluation.

7.9.7. Carcinogenicity

Lead registrant submitted two-year inhalation carcinogenicity studies with furfuryl alcohol, as well as rat and mouse oral (gavage) carcinogenicity studies with the proximate metabolite, furfural.

Inhalation

In the two year rat inhalation study with furfuryl alcohol (NTP, 1999) all male rats at 32 ppm died by week 99. There were no exposure related clinical findings and mean body weights of 32 ppm males were reduced. Increased severity of nephropathy was noted in both males and females at 32 ppm. Local toxicity including non-neoplastic lesions in nasal tissue was noted at all dose levels (LOAEC 2 ppm, equivalent to 8 mg/m3). Neoplastic effects in males included an increased incidence of adenoma, carcinoma or squamous cell carcinomas in nasal tissue at 32 ppm, and of renal tubule adenoma at 32 ppm. In females, no clear neoplastic effects were seen. The NOAEC for systemic toxicity was 8 ppm (32 mg/m3).

In the mouse inhalation (6 hours per day, 5 days per week) carcinogenicity study with furfuryl alcohol there was an increased incidence of renal tubule neoplasms at 32 ppm. There was no evidence of carcinogenic activity of furfuryl alcohol in females. Exposure of mice to furfuryl alcohol was associated with increased incidences of non-neoplastic lesions of the nose at 2, 8 or 32 ppm in both sexes, increased severities of nephropathy at 32 ppm in males and corneal degeneration at 32 ppm in females. The reported LOAEC for local toxicity was 2 ppm (8 mg/m3) and the NOAEC for systemic toxicity was 8 ppm (32 mg/m3).

The 'adversity' of the furfuryl alcohol induced pathological changes in the nose in both rats and mice in the NTP study are considered below using the criteria described by ECETOC (ECETOC, 2002).

In rats some changes, in particular a low incidence of combined malignant tumours in males at the high dose (128 mg/m3) are clearly adverse. In contrast, at the low dose (8 mg/m3) most of the nasal changes observed at the high (effect) dose have either a zero incidence (hyperplasia of glands, squamous metaplasia of respiratory epithelium, adenoma and carcinoma of respiratory epithelium) or an incidence and severity similar to that in the unexposed control group (suppurative inflammation, lateral wall squamous metaplasia, hyperplasia / fibrosis of olfactory epithelium). The exceptions to the above are hyperplasia of the lateral wall, atrophy and metaplasia of olfactory epithelium, and hyperplasia of respiratory epithelium where the incidences at 8 mg/m3 were statistically significantly increased compared to the control rats. Although the incidences were increased, the severity was similar to the controls. Atrophy of olfactory epithelium with metaplasia to a respiratory type epithelium is a common defensive (adaptive) response to inhaled irritants. The only neoplastic diagnosis at 8 mg/m3 was an adenoma of the

lateral wall in a male rat. Although the historical control incidence of this tumour type is not recorded in the report, the absence of similar tumours in the 16 and 128 mg/m3 groups indicates that this is an incidental finding and the tumour is not related to furfuryl alcohol exposure.

In mice, the nasal findings are similar to those in rats. Lesions considered to be adverse e. g. necrosis of respiratory epithelium, are not present in the 8 mg/m^3 group. There are no neoplastic findings at any dose level. Treatment related findings at 8 mg/m^3 e. g. metaplasia of olfactory epithelium, hyaline degeneration of respiratory epithelium are of minimal severity.

In summary, in both sexes of rats and mice, there are some changes in the nasal epithelium which are statistically significantly increased compared to the corresponding controls and are treatment related. However the nature and severity of the treatment related changes indicates that they were not adverse, but rather adaptive changes that were considered not toxicologically relevant. The furfuryl alcohol study report notes that the hyperplasia and squamous metaplasia represent conversion of highly specialised nasal tissue into a more resistant type of epithelium, representing an adaptive response to chronic irritation (NTP, 1999). In addition to the type of lesion, the limited severity of the changes (ECETOC, 2002) is a very important consideration in reaching the conclusion that they are non-adverse.

All the treatment related changes at 8 mg/m^3 were consistently in the minimal/slight range of severity i. e. below a threshold of concern when compared with controls.

It is concluded that the treatment related nasal tissue findings in both rats and mice exposed to 8 mg furfuryl alcohol/m^3 were of minor severity and considered to be adaptive in nature.

Oral

Oral carcinogenicity studies with furfural in rats and mice (NTP, 1990) showed some evidence of carcinogenic activity for male rats, based on the occurrence of uncommon cholangiocarcinomas in two animals and bile duct dysplasia with fibrosis in two other animals at the high dose of 60 mg/kg bw/day. In mice there was an increased incidence of hepatocellular adenoma at the highest dose (175 mg/kg bw/day). These carcinomas were associated with hepatotoxicity (chronic inflammation and pigmentation) which was also seen at 100 mg/kg bw/day.

Conclusion

The presented studies provide limited evidence of carcinogenicity at dose levels associated with systemic toxicity and only in tissues which exhibit significant tissue damage (i. e. nose and kidney for furfuryl alcohol, liver for furfural). The kidney tumours seen in the inhalation studies were at an incidence similar to the overall background range and are considered likely to have arisen as an exacerbation of the common rodent specific age-related phenomenon of chronic progressive nephropathy and thus not to be relevant to human risk assessment. As tumours were associated with tissue damage and there is no evidence of genotoxicity it may be concluded that the tumours are induced by a non-genotoxic mechanism. This interpretation is supported by the final Risk Assessment Report on Furfural published by the EU in 2008 (EU RAR, 2008) which concluded "Therefore, it is assumed that the observed liver tumours were induced via some mechanism involving liver toxicity, and that at levels at which no liver toxicity is induced, tumours will not arise. Hence, as starting point for the risk characterisation for

carcinogenicity the oral NOAEL for liver toxicity by the relevant route of administration is taken". Therefore, the oral NOAEL of 53 mg/kg bw/day from the dietary repeated dose toxicity study (Jonker, 2000a, b) is used as the starting point for both oral and inhalation DNEL determination.

In summary, two-year inhalation carcinogenicity studies with furfuryl alcohol are available, as well as rat and mouse oral (gavage) carcinogenicity studies with furfural, the proximate metabolite. These provide limited evidence of carcinogenicity at dose levels associated with systemic toxicity and only in tissues which exhibit significant tissue damage (i. e. nose and kidney for furfuryl alcohol, liver for furfural). As tumours were associated with tissue damage and furfuryl alcohol is assessed to be not genotoxic, it may be concluded that the tumours are induced by a non-genotoxic mechanism. The reported LOAEC for nasal tissue non-neoplastic lesions was 2 ppm (8 mg/m^3), however the changes at this concentration may be viewed as adaptive and non-adverse.

The classification for carcinogenicity laid down in Annex VI of CLP (Regulation (EC) No 1272/2008) is Carc. 2. Although limited evidence of carcinogenicity was seen as an increase in the incidence of tumours at toxic dose levels and associated with tissue damage a classification of Carc. 2, H351 "Suspected of causing cancer" is considered appropriate based on the available data.

Therefore, the initial concern regarding carcinogenic potential of furfuryl alcohol was clarified.

7.9.8. Toxicity to reproduction (effects on fertility and developmental toxicity)

Effects on fertility

There are no fertility or reproduction studies available for furfuryl alcohol or for furfural. From the evaluation of estrus cyclicity and sperm analysis conducted as part of 14 week repeated dose inhalation studies with furfuryl alcohol, there is no indication of any adverse effect in rats or in mice that would impair reproductive performance.

Developmental toxicity

The eMSCA agrees with the lead registrant that based on comparable absorption, distribution, metabolism and excretion of furfural and furfuryl alcohol it is considered appropriate to consider data for the proximate metabolite, furfural, for systemic toxicity.

The available OECD Guideline 414 developmental toxicity study in rats used the oral (gavage) route of administration for furfural (Nemec, 1997). This key study was described in the Risk Assessment Report of 2-Furaldehyde (Furfural) published as a final version by the EU in 2008.

Mated female rats were dosed with 0, 50, 100 or 150 mg/kg bw/day furfural from days 6 to 15 of gestation. The highest dose level of 150 mg/kg bw/day produced maternal lethality and was unsuitable for the evaluation of developmental toxicity. The maternal NOAEL was considered to be less than 50 mg/kg bw/day, based on clinical observations (exophthalmia) at all dose levels. The developmental NOAEL was considered to be 100 mg/kg bw/day, the highest dose level that could be evaluated; no teratogenicity was observed at this dose level.

In summary, there is no available developmental toxicity study of furfuryl alcohol. A developmental toxicity study in rats is available for furfural (proximate metabolite). On the basis of this study, neither furfural nor furfuryl alcohol are considered to have the potential to cause developmental or teratogenic effects at dose levels below a maternally lethal dose.

Toxicity to reproduction: other studies

For female rats and mice, at approximately 18 weeks of age and following 12 weeks repeated exposure to furfuryl alcohol at vapour concentrations of up to 32 ppm, vaginal samples were collected for up to 12 consecutive days prior to the end of the study. The period of exposure to furfuryl alcohol was consistent with the pre-mating period for a reproduction study and the animals were of a similar age. The vaginal samples were evaluated for the relative frequency of estrous stages and for estrous cycle length and the stage of estrous cycle was determined (diestrus, proestrus, estrus or metestrus).

For male rats and mice, at approximately 18 weeks of age and following 14 weeks repeated exposure to furfuryl at concentrations of up to 32 ppm, sperm samples were collected at the end of the study. The period of exposure to furfuryl alcohol was slightly longer than required for the pre-mating period for a reproduction study and the animals were of an equivalent age for mating. The samples were evaluated for sperm count and motility and the left cauda epididymis, left epididymis, and left testis were weighed.

There was no effect of furfuryl alcohol on estrous cyclicity or on sperm parameters in rats or mice at exposure concentrations of up to 32 ppm (equivalent to 128 mg/m3).

In summary, two 14 week studies have been conducted, one in mice and one in rats, to investigate the effects of repeated exposure to furfuryl alcohol by inhalation. These studies were conducted as preliminaries to two year studies and included evaluation of vaginal cytology and sperm analysis. No treatment-related effects on estrous cyclicity, sperm number or motility were detected and no potential for impaired reproductive performance indicated.

Exposure to furfuryl alcohol by inhalation for 14 weeks caused no adverse effect on sperm count or motility or on estrous cyclicity in rats or in mice. Although there are no reproduction data available to confirm the lack of effect, the existing data indicate that furfuryl alcohol is not a reproductive toxicant. The assessment of developmental toxicity in rats exposed to furfural by oral gavage confirmed a lack of effect on the foetus in the presence of maternal toxicity. These data provide adequate information from which to assess the potential of furfuryl alcohol to induce reproductive or developmental effects and to conclude that classification under the CLP is not warranted.

7.9.9. Hazard assessment of physico-chemical properties

Human health hazard assessment of physico-chemical properties were not part of the evaluation by the eMSCA.

7.9.10. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

According to Section R.8.4 of the REACH Guidance in Information Requirements and Chemical Safety Assessment (ECHA, 2012), DNEL for the leading health effect needs to

be derived for every relevant human population and every relevant route, duration and frequency of exposure, if feasible.

DNEL Systemic effects long-term exposure

The systemic NOAEL of 53 mg/kg bw/d was estimated in sub-chronic oral studies in the rats.

The registrant converted the rat oral NOAEL (mg/kg bw/d) into a human inhalation NOAEC (mg/m^3) after adjusting for differences in uptake between the two routes of exposure (TGD, Appendix R.8-2, Example B.3) on the basis of the formula:

NOAECinhalation = NOAELoral x [1/sRVrat] x [ABSoral-rat/ABSinhal-human] x [sRVhuman/wRV]

Standard respiratory volume (sRV) for rats for 8 hours was calculated by the registrant from TGD Table R.8-17 values. Mean male/female sRV was calculated: 1.43 L/min/kg bw = 0.343 m^3/kg bw for 8 hours. The eMSCA notes, that TGD Table R.8-17 contains default values for dose calculation in lifetime studies. Systemic NOAEL for long-term exposure was obtained in sub-chronic study (13 weeks). According to TGD R.8.4.2 default values from table R. 8-2 should be used in order to convert NOAEL from animal study into NOAEC for human. According to the table R.8-17 default sRV in rats is 0.38 m3/kg bw. The same value is used in figure 8.3 and example R.8-2 of TGD. Taking into account this value the NOAEC for workers is 84 mg/m^3. Thus the eMSCA considers that, using overall assessment factor of 3, DNEL for systemic effect followed by long-term exposure is 28 mg/m^3.

DNEL systemic effects – acute

The registrant has derived DNEL systemic effects – acute based on acute inhalation toxicity study in rats (LC_{50} key study – Unnamed author, 2005). According to information provided by the registrant three groups of 5 male and 5 female rats were exposed for a single period of four hours to a test atmosphere containing vapour of furfuryl alcohol at measured concentrations 510, 820 or 2070 mg/m3. Slightly decreased breathing rate was noted during exposure to 510 and 820 mg/m^3 and sniffing and/or nasal encrustations were seen at 820 mg/m^3 on the second day of the 14-day observation period in most animals. There were no other significant clinical observations and all animals at these two doses survived to scheduled termination.

The registrant considered NOAEC = 510 mg/m^3 as systemic NOAEC for derivation of DNEL for acute systemic effects but did not provide information on critical effect for which NOAEC was established. **The eMSCA notes that none of above mentioned effects can be considered as systemic effect.**

The eMSCA concludes that it is not possible to establish NOAEC for systemic effect based on provided information from this study. The registrant was asked for clarification. The registrant provided information that the effects seen at NOAEC were largely local effects (breathing rate decrease, slight) and a reduced bodyweight gain in the first week post-dose (one individual animal lost weight), which recovered in the second week post dose. The eMSCA recommends that information on reduced body weight gain should be included in the dossier.

DNEL local effects – long term

The lead registrant has derived inhalation DNEL long term local effect based on 14 week inhalation study in rats and mice. LOAEC (local effects): 8 mg/m3 was established based on nasal lesions (inflammatory, degenerative and proliferative lesions of respiratory, transitional and olfactory epithelium) at lowest dose tested. The registrant stated that the treatment related nasal tissue findings in both rats and mice exposed to 8 mg furfuryl alcohol/m3 were of minor severity and considered to be adaptive in nature and 8 mg/m3 may be regarded as a 'NOAEC' for assessment of a DNEL.

The eMSCA notes that toxicity was evident in both the olfactory and respiratory epithelium even at the 8 mg/m3 exposure concentration. Therefore, the NOAEC for chronic exposure is probably significantly less than 8 mg/m3.

The registrant assumed assessment factor 1 for dose response and endpoint specific/severity issues. The eMSCA does not agree with the registrant that established LOAEC may be regarded as NOAEC. Thus the eMSCA considers that AF of 2 should be applied for LOAEC to NOAEC extrapolation and inhalation DNEL long term for local effect should be 4 mg/m3.

Since the registrant concluded that the long-term local effect DNEL will be protective for acute effects, DNEL local effect – acute have to be the same. The eMSCA recommends the Registrant of furfuryl alcohol to use the DNEL local effect – acute as proposed by the eMSCA and consequently, revise the Chemical Safety Assessment.

7.9.11. Conclusions of the human health hazard assessment and related classification and labelling

The assessment of the eMSCA supports the existing harmonised classification of furfuryl alcohol as:

- Acute toxicity category 4, Harmful if swallowed (Acute Tox. 4*) – H302
- Acute toxicity category 4, Harmful in contact with skin (Acute Tox. 4*) – H312
- Eye Irritation category 2, Causes serious eye irritation (Eye Irrit. 2) – H319
- Acute toxicity category 4, Toxic if inhaled (Acute Tox. 3*) – H331
- Specific target organ toxicity after single exposure category 3, May cause respiratory irritation(STOT SE 3) (Respiratory) – H335
- Carc. 2 Suspected of causing cancer (inhalation) – H351
- Specific target organ toxicity after repeated exposure category 2, May cause damage to organs (Respiratory - nasal tissue) through prolonged or repeated exposure (inhalation)(STOT RE 2*) (Respiratory) – H373

Furfuryl alcohol has been selected for substance evaluation due to human health as potentially CMR.

The analysis of the available information indicates that the current CLP classification as Carc.2 is appropriate.

Based on the available data it is concluded that furfuryl alcohol is not genotoxic and does not induce reproductive or developmental effects. Thus, the initial concern for genotoxicity and reprotoxicity was not confirmed in the course of substance evaluation.

During the evaluation the additional concern as a skin sensitiser was identified.

The results of two LLNA studies presented by the Registrant indicate that furfuryl alcohol meets the criteria for classification in accordance with CLP as a skin sensitiser. The way forward is to propose harmonised classification as skin sensitiser sub-category 1B.

7.10. Assessment of endocrine disrupting (ED) properties

Endocrine disrupting properties were not part of the evaluation by the eMSCA.

7.11. PBT and VPVB assessment

PBT and vPvB assessment was not part of the evaluation by the eMSCA.

7.12. Exposure assessment

For the 8 exposure scenarios developed by the Registran(s) the relative contributing scenarios for controlling human exposure have been developed where appropriate:

ES1 - Manufacture - Manufacturing of the substance in a closed continuous process

ES2 - Formulation - Manufacturing of blends/formulations

ES3 - Use at industrial site - Manufacturing of polymers

ES4 - Use at industrial site - Manufacturing of moulds using formulations containing the substance

ES5 - Use at industrial site - Manufacturing of refractories, abrasive wheels, friction (brake pads, clutch facing), carbon impregnation using formulations containing the substance

ES6 - Use at industrial site - Wood impregnation/modification

ES7 - Use at industrial site - Use of Furfuryl Alcohol as Paint Stripper

ES8 - Use by professional worker - Professional end-use of acid resistant coatings

In the eMSCA's opinion the Registrant(s) have adequately described the operational conditions and the risk management measures for all the scenarios.

7.12.1. Human health

Occupational exposure to furfuryl alcohol may occur through inhalation and dermal contact in industries where it is produced, formulated or used. Oral exposure is assumed to be prevented by good hygiene practices. The production and further process of furfuryl alcohol takes place in closed system(s). The substance is mainly used by workers as an intermediate of other substances in closed installations. There is no EU defined occupational exposure limit(s). In the majority of the EU countries an exposure value of 20 mg/m^3 for 8h-TWA (eg. Sweden, Denmark, Czech Republic) is established or even higher (40 mg/m^3 in France, 41 mg/m^3 Germany) with the exception of Finland where OEL is set to 8 mg/m^3 .

7.12.1.1. Worker

Eight exposure scenarios are described for workers: two of them are related to manufacture and formulation, five correspond to end-use in industrial settings and one to professional enduse.

Exposure assessment is considered to be acceptable by the eMSCA. However, results of the monitoring study conducted by the registrant "Workers Exposure Monitoring Report Furfuryl Alcohol (CAS 98-00-0)" should also be included in the updated registration dossier.

7.12.1.2. Consumer

Exposure assessment is not applicable as there are no consumer-related uses for the substance.

7.12.2. Environment

Not relevant for this evaluation.

7.13. Risk characterisation

The registrants declare the safe use of furfuryl alcohol. The eMSCA believes that there are reasons for concern that need to be addressed.

For quantitative risk characterization of furfuryl alcohol, exposure data from inhalation exposure were compared with the local long-term and local acute inhalation DNELs derived by eMSCA. The exposure assessment was made based on the estimations given in the CSRs.

As a consequence of the lower DNELs for long-term and acute local effect, RCR>1 were obtained for the following exposure scenarios:

Table 13

ES	WCS	Exposure [mg/m3]	DNEL [mg/m3]	Type of DNEL	RCR
1	6	4.087	4	local - long term	**1.02**
2	2, 3, 4	4.905	4	local - acute	**1.22**
	5, 6 ,7 ,8 ,11, 12	5.722	4	local - acute	**1.43**
	10	4.087	4	local - acute	**1.02**
3	2, 3	4.905	4	local - acute	**1.22**
	4, 6, 11	5.722	4	local - acute	**1.43**

	5	4.087	4	local - acute	**1.02**
	8	5.8	4	local - acute	**1.45**
4	1	4.905	4	local - acute	**1.22**
	2, 3, 5, 6, 7, 9	5.722	4	local - acute	**1.43**
5	8, 10	5.722	4	local - acute	**1.43**
	9	6.54	4	local - acute	**1.64**
6	1	5.722	4	local - acute	**1.43**
	2	4.087	4	local - acute	**1.02**
	3	4.905	4	local - acute	**1.22**

Using DNEL of 28 mg/m^3 for systemic effect followed by long-term inhalation exposure, as proposed by the eMSCA, RCR for all exposure scenarios were higher, but still below 1.

The eMSCA recommends the Registrant(s) of furfuryl alcohol to revise the DNELs for workers for acute and/or long-term local effects via inhalation exposure to furfuryl alcohol and, consequently, to revise the Chemical Safety Assessment.

Furthermore, as the available information suggests that furfuryl alcohol should be classified as skin sens Cat. 1B, eMSCA recommends that registrants(s) updates its Chemical Safety Assessments and verifies whether current risk management measures and operational conditions are sufficient to cover also this type of adverse effect. Exposures should be controlled for the inhalation and the dermal route of exposure.

7.14. References

Apol, A. (1973). Health Hazard Evaluation Toxicity Determination Report No. 73-116-85. Western Foundry, Tigard, OR.

ECETOC, 2002

Flek, J., Šedivec, V.: The absorption, metabolism and excretion of furfural in man. Int. Arch. Occup. Environ. Health. 41, 159–168.

IARC (1995) Furfural. In: International Agency for Research into Cancer. Dry cleaning, some chlorinated solvents and other industrial chemicals. Lyon.: IARC. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 63): 409-429.
INRS (2010), 2-Furaldéhyde, Fiche toxicologique n°40.

Jonker D (2000a) Dose-range finding study (14-day) with micro-encapsulated fufural in F344 rats. Unpublished TNO report V98.1173, TNO Zeist, The Netherlands.

Jonker D (2000b) Amendment 1 to the TNO-report V99.520: Sub-chronic (13 week) oral toxicity study in rats with micro-encapsulated furfural. Unplublished TNO report V99.520, TNO Zeist, The Netherlands.

Muijser H (2001) A sub-acute (28-day) inhalation toxicity study with furfural in rats. TNO report V2874, TNO Zeist, The Netherlands.

NTP (National Toxicology Program) (1990). Toxicology and Carcinogenesis studies of furfural (CAS No. 98-01-1) in Fischer 344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program Technical Report Series No.382. Research Triangle Park, North Carolina.

NTP (1999). Toxicology and Carcinogenesis Studies of Furfuryl Alcohol (CAS No. 98-00-0) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). North Carolina: National Toxicology Program. (NTP Technical Report Series 482; NIH Publication No. 99-3972).

Registration dossier for furfuryl alcohol: European Chemicals Agency http://echa.europa.eu/

Risk Assessment Report of 2-Furaldehyde (Furfural) published as a final version by the EU in 2008

REACH Guidance in Information Requirements and Chemical Safety Assessment (ECHA, 2012)

Scientific Opinion on Flavouring Group Evaluation 66, Revision 1 (FGE.66Rev1): Consideration of Furfuryl Alcohol and Related Flavouring Substances Evaluated by JECFA (55th meeting) EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), European Food Safety Authority (EFSA), Parma, Italy

Terrill JB (1987) Acute inhalation toxicity study in the rat with furfural. Hazleton Laboratories America, Inc. , Vienna, Virginia, HLA study No. 468-104.

Woods A and Seevers MH (1955) Toxicity of furfural. University of Michigan Medical School Ann Arbor, Department of Pharmacology.

7.15. Abbreviations

C&L - Classification and labelling
CLP – Classification, Labelling and Packaging
CoRAP – Community Rolling Action Plan
CSR – Chemical Safety Report
DMEL - Derived Minimal Effect Level
DNEL – Derived No Effect Level
ECETOC - European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA – European Chemical Agency
EC3 - the concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation
EFSA – European Food Safety Agency

ES – Exposure Scenario
EU – European Union
eMSCA – Evaluating Member State
EPA – Environmental Protection Agency
GPL – Good Laboratory Practice
INRS – Reference body for occupational risk prevention in France
JECFA - The Joint FAO/WHO Expert Committee on Food Additives
LD – Lethal Dose
LC – Lethal Concentration
LLNA - Local lymph node assay
LOAEL – Lowest Adverse Observed Effect Level
LOAEC - Lowest Adverse Observed Effect Concentration
MSCA – Member State Competent Authority
NIOSH - The National Institute for Occupational Safety and Health
NOAEC - No Observed Adverse Effect Concentration
NOAEL – No Observed Adverse Effect Level
NTP - National Toxicology Program
OC – Operational Conditions
PBT – Persistent, Bioaccumulative, Toxic
(Q)SAR - Quantitative structure–activity relationship
RAR – Risk Assessment Report
RCR – Risk Characterisation Ratio
RMM - Risk Management Measures
SVHC – Substance of Very High Concern
TG – Technical Guidance
TWA -Time-weighted average
WCS – Working contributing scenario
vPvB – very Persistent, very Bioaccumulative