RISK ASSESSMENT

2-FURALDEHYDE

(Furfural)

CAS-No.: 98-01-1

EINECS-No.: 202-627-7

Final report, February 2008

FINAL APPROVED VERSION

Rapporteur for the risk evaluation of furfural is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report is the rapporteur.

The scientific work on this report has been prepared by the Netherlands Organization for Applied Scientific Research (TNO) and the National Institute of Public Health and the Environment (RIVM), by order of the rapporteur.

Contact point:
Chemical Substances Bureau
P.O. Box 1
3720 BA Bilthoven
The Netherlands

CONTENTS

Appendix 1: EUSES
Appendix 2: Reliability index
Appendix 3: Establishment of the minimal MOSs used for occupational risk characterisation
Appendix 4: HEDSET

0 OVERALL CONCLUSIONS/RESULTS OF THE RISK ASSESSMENT

CAS No. 98-01-1

EINECS No. 202-627-7

IUPAC Name furfural

Environment:

(X) i) There is need for further information and/or testing

(X) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

(X) iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

Conclusion i) is reached because:

- The PEC soil exceeds the PNEC soil in the scenarios 'formulation for manufacturing refractories Va, Vb' and 'use as intermediate in pesticide manufacture VI'. The terrestrial PNEC is derived through the equilibrium partitioning method and there is therefore scope to refine this PNEC through testing. However, no testing is proposed for the terrestrial compartment since for these scenarios also conclusion iii is drawn for the local aquatic compartment. The development of risk reduction measures for the aquatic compartment should take account of the conclusions for the terrestrial compartment for these three scenarios.

Conclusion iii) is reached because:

- The PEC water exceeds the $PNEC_{surface\ water}$ in the scenarios 'formulation chemical tracer in mineral oil and fuel industry IVb', 'formulation for manufacturing refractories Va, Vb' and 'use as intermediate in pesticide manufacture VI'. As no further refinement of the PECs and PNECs is possible, there is a need for limiting the risks.

For all remaining scenarios a conclusion ii is drawn for the environment.

Risks of 2-furaldehyde as a result of emissions by the pulp and paper industry (unintentional source):

The PEC_{STP} and the $PEC_{surface\ water}$ exceed the corresponding PNECs in the 'pulp and paper industry, scenario VII' (unintentional source). For the refinement of this scenario site-specific measured effluent or surface water concentrations are needed. Additionally, measured data from other pulp and paper industries in the EU are needed to refine this scenario. Since this considers an unintentional source beyond the scope of this EU risk assessment, there will be no follow-up of this scenario in the context of Regulation 793/93/EC.

Human health

Workers:

(X) iii) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion (iii) is reached because:

- systemic effects and local effects on respiratory tract cannot be excluded after repeated inhalation exposure in all scenarios;
- systemic effects cannot be excluded after repeated dermal exposure in scenarios 1 'production – cleaning and maintenance';
- carcinogenic effects cannot be excluded after repeated dermal and inhalation exposure in all scenarios; and
- developmental effects due to repeated dermal and inhalation exposure cannot be excluded in scenario 1 'production – cleaning and maintenance'.

It might be possible that in some workplaces adequate worker protection measures are already being applied.

Consumers:

(X) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human via the environment:

(X) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Combined exposure:

(X) iii) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

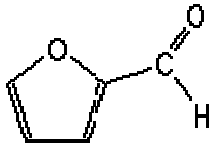
The risk characterisation for combined exposure is completely driven by the risk characterisation for the occupational settings.

Risks arising from physico-chemical properties:

(X) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS-No.	98-01-1
EINECS-No.	202-627-7
IUPAC name	furfural
Synonyms	2-formylfuran, fural, furan-2-aldehyd, furfuraldehyd, furfurol, 2-furaldehyde, artificial ant oil, furale, 2-furancarboxaldehyde, furaldehyde, 2-furyl-methanal, 2-furfural, furfurole, pyromucic aldehyde, furale, 2-furanaldehyde, 2-furancarbonal, "-furole, furole, furfurane carboxylic aldehyde, 2-furylaldehyde,artificial oil of ants, furan-2-carbaldehyde, 2-formylfuran
Molecular formula	$C_5H_4O_2$
Structural formula	
Molecular weight	96.08

Purity/impurities, additives

Purity	:	> 98% w/w
Impurity	:	$\leq$ 0.6% 5-methylfurfural (CAS-No. 620-02-0; EINECS-No. 210-622-6)
Additives	:	none

Physico-chemical properties

A list of the physico-chemical properties of furfural is provided in Table 1.1.

Table 1.1 Overview of physico-chemical properties of furfural

Property	Result	Comments
Physical state	oily liquid	
Melting point	-36.5 - -39ºC	*
Boiling point	162ºC at 1013 hPa	*
Relative density	1.154-1.156 g/cm^3 at 25ºC 1.1594-1.16 g/cm^3 at 20ºC	*
Vapour pressure	1.33-1.73 hPa at 18.5ºC	*
Surface tension	43.5 mN/m at 20ºC 40.7 - 41.1 mN/m at 29.9ºC	*
Water solubility	83 g/l at 20ºC	*
Partition-coefficient **- n-octanol/water (log)**	0.41	**
Granulometry	not applicable	
Flammability	non-flammable	***
Flash point	61.7ºC (closed cup)	*
Auto flammability temperature	315-393ºC	*
Explosive properties	not explosive	***/****
Oxidizing properties	not oxidizing	****
Conversion factors	1 ppm = 3.93 mg/m^3 1 mg/m^3 = 0.254 ppm	Calculated
Odour threshold	0.25 - 1.0 mg/m^3	*

* No test report was available. At least one independent source. No methods are specified.
** No test report was available. Based on QSAR (Hansch, 1995)
*** At elevated temperatures, a risk for fire exist. However, according to EG-guidelines, no classification as flammable is applicable. Depending on the temperature, the risk for fire may change into a risk for explosion at more elevated temperatures.
**** Property is based on theoretical and structural considerations.

These data are mainly derived from Company A (1980), Verschueren (1983), Merck (1983), Sax (1989), and Patty (1981). For an extended description, see HEDSET (2007)

and DECOS (1996).

Conclusion

All relevant physico-chemical data were provided. They were not substantiated with test reports. However, all data are considered sufficiently reliable to fulfil the Annex VIIA requirements.

Classification

Classification according to Annex I

Classification (30th ATP)		:Carc. Cat. 3; R40 T; R23/25 Xn; R21 Xi; R36/37/38
R-phrases	:	21-23/25-36/37/38-40
S-phrases	:	(1/2-)26-36/37-45

Note:

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION AND IMPORT

Furfural is assumed to be produced in the EU countries Spain and Austria (HEDSET, 1997), and to be imported by several other EU countries: see Table 2.1.. Figures on export are also included in Table 2.1 (data provided by TFC, 2003). Furfural is imported from the United States, Dominican Republic, China, South-Africa, Thailand, Indonesia and Korea (HEDSET, 1997). The world operating capacity of furfural is estimated to be greater than 240,000 tonnes per year (CEH, 1994).

Table 2.1 Production, Import & Export of furfural in the EU.

Company	**Location**	**Production, Import & Export (t/y)**
	Production	
Furfural Espanol	Spain	3000
Lenzing	Lenzing, Austria	4000 [1]
	Import	
Internat. Furan Chemicals BV	Rotterdam, The Netherlands	31000 [2]
Illovo	-	1400
Indorama and others	-	750
Slovenia	-	1200
Traders	-	low
	Export	
Furfural Espanol	Spain	500
Lenzing	Lenzing, Austria	500

[1]) 1000 tons is converted to furfuryl alcohol; [2]) 28800 tons is converted to furfuryl alcohol.

The net input (production plus import minus export) is calculated to be about 10550 tons/year. The net input of 10550 tons/year, i.e. the EU tonnage level that is available for further industrial use, has been calculated from the data in Table 2.1 after subtraction of the amount that is used at the production or import site as an intermediate in the production of furfuryl alcohol.

2.1.1 Production process

Furfural is produced industrially mainly from pentosan polysaccharides (xylan, arabinan), that are natural substances in non food residues and food crops. Mainly corncobs (primary source), cottonseed hulls, rice hulls, oat hulls, bagasse and bark of wood are used (Kirk-Othmer, 1984). In batch or continuous digestors the pentosans are hydrolysed to pentoses and, subsequently, the pentoses are cyclodehydrated to furfural. In all processes, raw material is charged to the digestor and treated with strong inorganic acid. High pressure steam is introduced through the mass and, after attaining operating temperature, furfural is steam distilled (Kirk-Othmer, 1984; HSDB, 1998).

Other occurrences:

As an unintentional source furfural is a major contamination from the sulfite pulping processes used in pulp and paper industry, where it originates from pentoses in the wood and is formed during the waste treatment in the evaporator (Gregg et al., 1997; DECOS, 1995; Rivard and Grohmann, 1991; Vinogradova et al., 1968). Furfural may also be released to the environment via the smoke from burning wood. Furfural as a natural volatile compound is identified in many foods as fruits and fruit juices, vegetables, beverages (wine), bread and bread products and in several essential oil of plants (e.g. the pinaceae family, cajenne, trifolium, ambrette, angelica, ceylon cinnamon, lavender, tobacco, etc.). Furfural is formed in trace amounts in a number of dietary sources. As a thermal/chemical degradation by-product it is also formed in the treatment of hemicellulosis feedstocks and in the refuse of chemical and fuel production.

2.2 USE PATTERN

According to TFC (2000) about 75% of the production of furfural is used for the production of furan derivates. The remaining part is mainly used as a selective solvent (13.5%). The total distribution of the industrial use of furfural in the EU is presented in Tables 2.2. and 2.3, these use volumes are used in the exposure scenarios in section 3.1.2. For the UK a different use pattern is present, where approximately 40 % is used in the production of resins, abrasive wheels and refractories. The rest is used in the refining of lubrication oils (IPCS, 2000).

Table 2.2 The industrial use of furfural in the EU (IFC, 1999; letter TFC, 21-2-2000).

Use	**Use volume (t/y)**	**Percentage of total use**
Production furan derivates	32,500	75%
Use as an extraction solvent (refineries)	5850	13.5%
Manufacturing refractories	2200	5%
Manufacturing pesticides	1500	3.5%
Use as an chemical tracer in gas-oil (refineries)	1000	2%
Use unknown (Netherlands)	375	1%

Worldwide furfural has the following use patterns (TFC, 1980; HSDB, 1996; Gomez-Arroyo and Souza, 1985):

1. manufacture of derivates (furan and tetrahydrofuran types); mainly for the manufacture of furfuryl alcohol, tetrahydrofurfuryl alcohol and polytetramethylene ether glycols
2. a chemical intermediate in manufacture of furor, hexamethylene diamene and pyromucic acid (application restricted to laboratory)
3. extractive distillation of C4 and C5 hydrocarbons for the manufacture of synthetic rubber; especially for butadiene and isoprene (2-methyl-1,3-butadiene)
4. selective solvent for separating saturated compounds in petroleum lubricating oil, gas oil, and diesel fuel, with the purpose to increase their stability under operation conditions and to improve the viscosity index
5. solvent and processing aid for the separation of anthracene from coal and coal products (out of date application)
6. reactive solvent and wetting agent in the manufacture of abrasive wheels and break linings and refractories
7. reactive solvent for phenolic-Novolak and furfuryl alcohol resins
8. flavour component in a range of food, including beef, soya sauce, roasted nuts, fried bacon, nectarines, baked potatoes, clove oil, preserved mangoes, rum, roasted coffee and blue cheese.

9. as a weed killer, fungicide, insecticide, germicide and nematicide
10. decolorization agent for wood resin
11. ingredient in dyes, polymers and resins, especially of the phenol-aldehyde types (used *e.g.* varnishes) (out of date application)
12. fragrances in soap, detergents, lotions, cream and perfume
13. as reagent in analytic chemistry
14. vulcanisation accelerator
15. solvent for nitrated cotton, cellulose acetate and gums
16. in road construction and metal refining
17. as a component of a gas oil marker (GOM X). One litre of GOM X contains 50 g furfural

Table 2.3 below shows the industrial and use categories of furfural for the European market.

Table 2.3 The industrial and use categories of furfural

Industrial Category	**IC no.**	**Use category**	**UC no.**
Chemical industry: basic chemicals	2	Solvents	48
Chemical industry: chemicals used in synthesis	3	Binders	2
		Intermediates	33
		Activators (chemical processes); Adhesion promotors; Polymerization additives	43
		Solvents	48
Mineral oil and fuel industry	9	Fuel additives	28
		Solvents	48
		Viscosity adjusters	52
Engineering Industry	16	Surface active agent - wetting agents	50
		Others (refractories)	55/0

3 ENVIRONMENT

3.1 EXPOSURE ASSESSMENT

3.1.1 General

Furfural may be released to the environment during its manufacture, formulation, or use in commercial products. Other releases may occur from natural or unintentional sources (see section 2.1.1). General characteristics of furfural which are relevant for the environmental exposure assessment are discussed in the following subsections.

a) Degradation

In the handbook of Howard (1993) a review is given of the different environmental degradation routes of furfural; several articles are available dealing with the aerobic and anaerobic degradation of furfural. In addition, Verschueren (1983) provides some data on BOD- and COD-tests.

A summary of the various abiotic and biotic degradation routes of furfural is presented below.

Hydrolysis

Furfural is not expected to hydrolyse under environmental conditions (Lyman et al., 1990).

Photodegradation

The stability of furfural in the atmosphere is limited by the rapid vapour-phase reactions with hydroxyl radicals. The half-life for this reaction is estimated to be 0.44 days. Nighttime destruction of furfural by nitrate radicals may be an important process in urban areas. Direct photochemical degradation is expected to occur, however, data on this process are not available (Howard, 1993). The half-life of 0.44 days is used in the risk assessment.

Biodegradation

The available aerobic and anaerobic biodegradation test results for furfural are summarized in Table 3.1 and Table 3.2, respectively. Validity of the tests has been

checked by reviewing the original references where available. The total set of data is regarded sufficient to draw conclusions upon the degradation potential of furfural.

Aerobic degradation tests (Table 3.1). In test no.9 for ready biodegradability (modified MITI) 93.5% degradation of furfural is found (Kawasaki, 1980). In flow-through bioreactor tests (no. 3, 4, and 5) with acclimated activated sludge inoculum, biodegradation is observed at concentrations of furfural up to 1000 mg/l (Rowe and Tullos, 1980; Pitter, 1976). When unadapted activated sludge is used biodegradation starts after a lag phase of 4-7 days (test no. 6) (Rowe and Tullos, 1980). In the river die-away tests (no. 7 and 8) with fully acclimated microorganisms, 100% degradation occurred within 3 days or 5-12 days at a furfural concentrations of 1 mg/l and 25 mg/l, respectively (Ettinger et al., 1954). In a BOD5-test (no. 1) 77% degradation is observed (Verschueren, 1983).

From the overall results of these studies it can be concluded that furfural is readily biodegradable. This conclusion is supported by a QSAR (BIODEG) result (Rorije et al., 1997)

Anaerobic degradation tests (Table 3.2). In test no.1 complete anaerobic biodegradation is measured within 30 days in an acclimated system with 580 mg furfural/l as measured by the production of methane and CO_2. Also 2320 mg furfural/l is degraded for 99% in an acclimated system in 32 days (no.3). No biodegradation is observed in the anaerobic test no. 2 with unacclimated microorganisms, suggesting that furfural is toxic to the microorganisms or merely inactivated them (Benjamin et al., 1984).

Rivard & Grohmann (1991) reported that furfural, added to a continuously stirred tank reactor with adapted sludge cultures, produced 80% of the theoretically expected biogas. Intermediates in this process include furfuryl alcohol, furoic acid and acetic acid, before final conversion to methane and CO_2.

At concentrations higher than 1000 mg/l furfural inhibits growth and metabolic activity of unadapted anaerobic cultures. However, acclimation was found to increase the capacity of anaerobic sludges to degrade the compound (Gregg et al., 1997).

Table 3.1 Biodegradation test results for 2-furaldehyde (aerobic).

No.	Type of test	Detection	Result	Day	Method	conc. TS	R.I[#]	conc. inoc.	Reference
1	BOD5-test	O2 uptake	0.77 g O2/g subst.	5	unknown	2-20 mg/l	4a		Verschueren, 1983
2	COD-test	O2 uptake	1.66 g O2/g subst.		unknown		4a		Verschueren, 1983
3	adapted activated sludge	elimination rate TS	98% degradation		flow-through bioreactor	300 mg/l	2a		Rowe & Tullos, 1980
4	adapted activated sludge	elimination rate TS	degradation occurred		flow-through bioreactor	1000 mg/l	2a		Rowe & Tullos, 1980
5	adapted activated sludge	elimination rate TS	96.3% degradation	< 5	flow-through bioreactor	200 mg/l	2a		Pitter, 1976
6	Unacclimated inoculum	elimination rate TS	degradation occurred	(a)	static bioreactor		2a		Rowe & Tullos, 1980
7	Simulation test	DOC decrease	100% degradation	3	river die-away	1 mg/l	2a	(b)	Ettinger et al., 1954
8	Simulation test	DOC decrease	100%	5-12	river die-away	25 mg/l	2a	(b) (c)	Ettinger et al., 1954
9	ready test	BOD, O2 uptake	93.5% degradation	28	MITI-test	unknown	2a	unknown	Kawasaki, 1980
10	sewage sludge	THOD	46% degradation	5	unknown	1.7-20 mg/kg	2a	unknown	Heukelekian and Rand, 1955
11	sewage sludge	THOD	17% degradation	5	unknown	440 mg/kg	2a	unknown	Heukelekian and Rand, 1955

#: Reliability Index and usefulness of information in HEDSET (See Appendix 2)
a: there was a lag period of 4-7 days
b: rate of degradation is dependent upon the degree of acclimation
c: fully acclimated inoculum

Table 3.2 Biodegradation test results for 2-furaldehyde (anaerobic).

No.	Type of test	Detection	Result	Day	Method	conc. TS	R.I	conc. inoc.	Reference
1	methane fermentation	gas production	100% degradation	30	unknown	580 mg/l	2a	unknown (a)	Benjamin et al., 1984
2	methane fermentation	gas production	no degradation	30	unknown	1160 mg/l	2a	unknown (b)	Benjamin et al., 1984
3	methane fermentation	gas production	99% degradation	32	unknown	2320 mg/l	2a	unknown (c)	Benjamin et al., 1984
4	methane fermentation	gas production	80% degradation	-	unknown	-	2a	unknown	Rivard & Grohman, 1991

a: unacclimated inoculum
b: furfural was found to be toxic to the microorganisms or inactivated them
c: acclimated inoculum

b) Distribution

Water-Air: According to the TGD (1996) a Henry's Law constant of 0.2 Pa.m^3/mol can be calculated. This value is also used for further calculations. Howard (1993) calculated an almost similar Henry's Law constant of 0.375 Pa.m^3/mol, based on a water solubility of 86 g/l and a vapour pressure of 2.5 mm Hg at 25 deg. C (= 333 Pa). Both Henry's Law constants indicate that volatilization of furfural from surface waters may occur, although it is not expected to be a rapid process.

Soil-Water: With regard to the adsorption of furfural in a soil-water system, a K_{oc} of 17.1 has been calculated using the QSAR for non-hydrophobics and the log K_{ow} of 0.41 (Sabljic and Guesten, 1995). Lyman et al. (1982) reported calculated K_{oc}'s in the range of 1 to 40 l/kg. Based on these K_{oc} values, furfural is expected to be highly mobile in soil and may leach into groundwater. However, volatilization to the atmosphere and degradation processes may attenuate movement through soil towards groundwater.

As experimentally derived K_{oc}-values are lacking, the calculated K_{oc} of 17.1 will be used throughout the further exposure assessment of furfural. K_p-values for soil, sediment and suspended matter can subsequently be calculated by multiplying the K_{oc} with the corresponding f_{oc}-values, resulting in K_p's of 0.34 l/kg (soil), 0.86 l/kg (sediment), and 1.7 l/kg (suspended matter). It should be borne in mind, however, that the derivation of a K_p from low log K_{ow}-values is less reliable.

Soil-Air: Volatilization from soil to the atmosphere may occur, however, it is not expected to be a rapid process. Half-life values for this process are not available (Howard, 1993).

Air-Soil/Water: Besides photochemically induced degradation, vapour-phase furfural in the atmosphere is expected to be removed by wet deposition. A half-life value for this process is not reported (Howard, 1993).

The EUSES model (SimpleTreat) (Struijs, 1996) calculates the distribution of furfural in an STP, which is presented in Table 3.3.

Table 3.3 Theoretical distribution of furfural in an STP (SimpleTreat).

Compartment	**Distribution (fraction)**
Air	<0.01
Water	0.13
Sludge	<0.01
Degraded	0.87

c) Accumulation

On the basis of the high water solubility of furfural and its low Log K_{ow}, no bioaccumulation is expected. No experimental data are reported to confirm this. The EUSES model (version 1.0; based on the EU TGD, 1996) calculates a bioconcentration factor for fish (BCF_{fish}) of 1.41 l/kg and a bioconcentration factor for earthworms ($BCF_{earthworm}$) of 0.95 l/kg, according to the method of Veith et al. (1979) and the method of Connell and Markwell (1990), respectively.

The calculated BCF values for fish and earhworms will be used in the risk assessment.

3.1.2 Emission scenarios

The exposure assessment is based on the EU Technical Guidance Document (TGD, 1996) applying the European Union System for the Evaluation of Substances, EUSES version 1.0. The input data and the results of the various EUSES calculations are presented in Appendix 1. The exposure assessment relies on both generic and site-specific scenarios. Site-specific scenarios are based on actual data from industry on emission patterns etc., whereas generic scenarios are fully based on model calculations for a realistic worst case situation. Generic scenarios are used if no data were obtained from either industry or other bodies. In case of furfural almost all industries submitted site specific production or use tonnages and, in addition, some actual release data is available for the furfural production, the furan derivates production and the mineral oil and fuel industry.

The environmental exposure assessment of furfural will be based on information for the following life cycle stages:

I. Production

II. Processing of furan derivates in the chemical industry

III Processing as extraction solvent in the mineral oil and fuel industry

IV Formulation as a chemical tracer in the mineral oil and fuel industry

V Formulation for manufacturing refractories

VI Use as chemical intermediate in pesticide manufacture (processing)

The expected releases from unintentional sources:

VII. Pulping processes used in the pulp and paper industry

3.1.3 Local exposure assessment

For the life cycle stages I-VI local PEC values are calculated below for the different environmental compartments. Presented PECs already include the calculated regional concentrations as a background (see section 3.1.6 Regional exposure assessment).

I. Production

As stated in section 2.1 in the EU furfural is produced at a site in Spain and at one in Austria. The production volumes for both sites are confidential. A site specific emission value for water was available for the Spanish site. For this site no data was available for the emission to air and therefore also a generic scenario is used with the available site specific production tonnage. According to the Austrian company the emissions to air are estimated 'marginal', as production takes place in a closed system. The Austrian site further mentioned that the measured concentrations in untreated waste water and in WWTP effluent water are below the detection limit of 100 µg/l. For this site the PEC_{STP} is assumed to be equal to 100 µg/l. Table 3.4 shows the assumptions and results of the exposure calculations for both production sites in the EU.

Table 3.4 Input data and results for the local exposure assessment for the production of furfural.

Production	**Austria, site specific / generic scenario**	**Spain, site specific / generic scenario**
Scenario number	Ia	Ib
Tonnage (tonnes/y)	Conf.	Conf.
Fraction release to air (A-tables, TGD 1996)	0.001 (MC Ic)	0.001 (MC Ic)
Fraction release to waste water (A-tables, TGD 1996)	not relevant [2)]	-
Fraction of main source (B-tables, TGD 1996)	1	1
Number of emission days	300	300
Calculated local release to air (kg/d)	0 [1)]	11.7
Calculated local release to waste water (kg/d)	not relevant [2)]	0 [1)]
Size of STP (m^3/d)	not relevant [2)]	-
Dilution factor	10	-
PEC values:		
PEC STP (µg/l)	100 [3)]	0
PEC surface water, during emission period (µg/l)	10.1	0.11
PEC air (µg/m^3)	$2.1.10^{-3}$	2.67
PEC sediment (mg/kg_{wwt})	0.012	$1.27.10^{-4}$
PEC agricultural soil, avg. 30 days (mg/kg_{dwt})	$3.70.10^{-3}$	$4.73.10^{-4}$
PEC in wet fish (mg/kg)	$5.96.10^{-3}$	$1.55.10^{-4}$
PEC in worm (mg/kg)	$4.7.10^{-4}$	$2.0.10^{-3}$

1) Site specific emission value submitted by the industry.

2) Not relevant, because the concentrations in the aquatic compartments are based on a measured concentration in STP effluent.
3) Measured concentrations are below detection limit of 100 µg/l (information from industry).

II. Processing of furan derivates in the chemical industry

Site-specific emissions of a major importer are presented in Table 3.5. For this site it is known that about 90% of the imported volume of furfural is used for the production of furan derivates and that the remaining part is mainly used as a selective solvent (TFC, 1996). The total volume of this importer is used completely at his own processing site.

Table 3.6 gives the assumptions and results of the calculations for scenario II.

Table 3.5 Environmental releases (actual data) from TFC (TFC, 1996).

Industrial category	**Approximate numbers of site**	**Industrial processes which are likely to generate releases to the environment**	**releases to surface water (kg/year)**	**releases to air (kg/year)**	**releases to soil (kg/year)**
Storage	1	transfer of furfural	0	204	0
Destillation	1	recovery of furfural from a residue	0	29	0
Residue storage	1	emission from the residue tank	0	9	0
Resin making	1	reactor loading and unloading	0	70	0
TOTAL			**0**	**312**	**0**

Note: Possible release of waste: 5 ton/year. This is waste in solid form (polymerized furfural) (TFC, 1996).

Table 3.6 Input data and results for the local exposure assessment for processing in the chemical industry.

Processing in the chemical industry	**Site specific (Table 3.5)**
Scenario number	II
Tonnage (tonnes/y)	-
Industrial category	3
Use category	33
Fraction release to air (A-tables, TGD 1996)	-
Fraction release to waste water (A-tables, TGD 1996)	-
Fraction of main source (B-tables, TGD 1996)	-
Number of emission days	300
Calculated local release to air (kg/d)	1.04
Calculated local release to waste water (kg/d)	0
Size of STP (m^3/d)	-
Dilution factor	-
PEC values:	
PEC STP (µg/l)	0
PEC surface water, during emission period (µg/l)	0.11
PEC air (µg/m^3)	0.240

Processing in the chemical industry	**Site specific (Table 3.5)**
PEC sediment (mg/kg_{wwt})	$1.27.10^{-4}$
PEC agricultural soil, avg. 30 days (mg/kg_{dwt})	$5.26.10^{-5}$
PEC in wet fish (mg/kg)	$1.55.10^{-4}$
PEC in worm (mg/kg)	$2.45.10^{-5}$

Scenario II is assumed to cover both furan derivates production sites (= furfural importers) in the EU.

III Processing as extraction solvent in the mineral oil and fuel industry

The mineral oil and fuel industry uses furfural for several refining and extraction processes. In the EU about 9 larger companies and some smaller companies use furfural as an extraction solvent (see Table 3.7). For all companies a site specific processing tonnage is available. Only for two companies in the Netherlands the actual emission to air is known (Table 3.7). For calculating the PEC in surface water the generic scenario IIIc is assumed to be relevant for scenario IIIa and IIIb as well. There is no further information available about the use of furfural for refining and extraction in the mineral oil and fuel industry in the EU.

For this use category three scenarios are carried out. Two are only based on the site specific emissions to air and one aditional generic scenario is based on the largest site specific use tonnage (1000 t/y). Table 3.8 presents the assumptions and results for the exposure calculations for the above-mentioned scenarios. It is noted that for site No. 1 the submitted site specific emission to air is considerably larger than the emission calculated with the generic scenario (with values of 323 kg/d and 14.3 kg/d, respectively) while for site No.2 the submitted site specific emission to air (3.88 kg/d) is similar to the calculated value from the generic scenario).

Table 3.7 Site specific information and emissions of furfural to air in the processing as extraction solvent in the mineral oil and fuel industry (NL) (DEI, 1994; v.d. Koepel, 1998).

No.	Company	Use tonnage (tonnes/year)	Emission to air (kg/y)
1	Shell Ned. Raffinaderij B.V.; The Netherlands	375	113,001
2	Kuwait Petroleum (Q8); The Netherlands	400	1357
3	AgipPetroli; Italy	600	Unknown
4	Total Raff. Distr.; France	600	Unknown
5	Mobil; France	500	Unknown
6	Shell; France, UK and Germany	825	Unknown
7	BP Oil; UK	1000	Unknown
8	Petrogal; Portugal	250	Unknown
9	Repsol Petroleo; Spain	800	Unknown
10	Other small companies	500	Unknown

Table 3.8 Input data and results for the local exposure assessment in the processing as extraction solvent in the mineral oil and fuel industry.

Processing as extraction solvent in the mineral oil and fuel industry	Site specific: site no. 1 (see Table 3.7)	Site specific: site no. 2 (see Table 3.7)	Generic scenario: (based on largest site, no. 7)
Scenario number	IIIa	IIIb	IIIc
Local tonnage (tonnes/y)	375	400	1000
Industrial category	9	9	9
Use category	48	48	48
Fraction release to air (A-tables, TGD 1996)	-	-	5.10^{-3}
Fraction release to waste water (A-tables, TGD 1996)	-	-	5.10^{-4}
Fraction of main source (B-tables, TGD 1996)	1	1	1
Number of emission days	350	350	350
Local release to air (kg/d)	323 (site specific)	3.88 (site specific)	14.3 (calculated)
Calculated local release to waste water (kg/d)	-	-	1.43
Size of STP (m^3/d)	-	-	2000
Dilution factor	-	-	10
PEC values:			
PEC STP (µg/l)	-	-	90
PEC surface water, during emission period (µg/l)	-	-	9.1
PEC air (µg/m^3)	86.1	1.03	3.81
PEC sediment (mg/kg_{wwt})	-	-	0.0105
PEC agricultural soil, avg. 30 days (mg/kg_{dwt})	-	-	$4.01.10^{-3}$
PEC in wet fish (mg/kg)	-	-	$6.26.10^{-3}$
PEC in worm (mg/kg)	-	-	$7.07.10^{-4}$

IV Formulation as a chemical tracer in the mineral oil and fuel industry

Scenario IV is split up in two parts. Part A gives the exposure assessment for the production of furfural containing gas oil markers. Part B describes the assessment for the subsequent formulation of that marker in fuel.

A. Manufacturing of gas oil marker (formulation)

Table 3.9 presents the companies from which it is known that they are manufacturing a gas oil marker in which furfural is used. Only for one company in the Netherlands the actual emission amount to air is known. For this company a site specific scenario for the atmospheric compartment is carried out (Table 3.10). There is no information available about the use quantities in other EU countries. Therefore an additional, generic scenario is carried out with the European tonnage as starting point. The EU tonnage is divided by 10 to derive a regional tonnage (10% rule). This is justifed because the sites are more or less evenly distribution over Europe (see Table 3.9). The dosage of furfural in the end product is known for the gas oil marker GOM X. One litre of GOM X contains 50 g furfural. The generic scenario is carried out with this percentage of furfural in the end product. Table 3.10 presents the assumptions and results for the exposure calculations for the above-mentioned scenarios.

Table 3.9 Site specific information and emission of furfural to air for the manufacturing of a chemical tracer in the mineral oil and fuel industry (NL) (DEI, 1994; v.d. Koepel, 1998).

No.	Company	Tonnage (tonnes/year)	Emission to air (kg/y)
1	Morton International B.V, The Netherlands	Unknown	70
2	NDT Europa B.V., Weesp, The Nederlands	Unknown	Unknown
3	Rutgers AG, Duisburg, Germany	Unknown	Unknown
4	Brenntag Chemie, Kassel, Germany	Unknown	Unknown
5	Steiner, Rouen, France	Unknown	Unknown
6	John Hogg, Manchester, UK	Unknown	Unknown

Table 3.10 Input data and results for the local exposure for the production of a chemical tracer in the mineral oil and fuel industry.

	Site specific: site no. 1 (see Table 3.9)	**Generic (based on EU tonnage)**
Scenario number	Iva	IVb
Tonnage (tonnes/y)	Unknown	1000 (EU)
Used regional tonnage (t/y)	-	100
Industrial category	9	9
Use category	28	28
Fraction release to air (A-tables, TGD 1996)	-	0.01
Fraction release to waste water (A-tables, TGD 1996)	-	0.02
Content furfural in end product	-	50 g/l
Use level of furfural in end product (%)	-	5.8
Correction factor for tonnage for use of B-Tables	-	17.2
Used tonnage for B-tables (B-tables TGD, 1996)	-	17,200 (<100,000)
Fraction of main source (B-tables, TGD 1996)	1	1
Number of emission days	300	300
Calculated local release to air (kg/d)	0.233 (site- specific)	3.33
Calculated local release to waste water (kg/d)	-	6.66
Size of STP (m^3/d)	-	2000
Dilution factor	-	10
PEC values:		
PEC STP (µg/l)	-	420
PEC surface water, during emission period (µg/l)	-	42.1
PEC air (µg/m^3)	0.055	0.764
PEC sediment (mg/kg_{wwt})	-	0.0487
PEC agricultural soil, avg. 30 days (mg/kg_{dwt})	-	$1.57.10^{-2}$
PEC in wet fish (mg/kg)	-	0.0246
PEC in worm (mg/kg)	-	$2.0.10^{-3}$

B. Use of gas oil marker (formulation)

Table 3.11 presents the companies for which it is known that they formulate a furfural containing gas oil marker in fuels. One company in the Netherlands submitted an estimated site specific annual loss of furfural to water of 0.5%, based on an effluent concentration in water of < 5 ppm and an effluent flow of 4800 m^3/d. For this company a site specific scenario is carried out (Table 3.12). For the other companies no site specific emission values are available. An additional scenario is carried out based on the largest known processing tonnage (IVd). There is little information available about the use quantities in the EU. The four known companies (companies 1-4, Table 3.11) only represent about 3% of the total European use tonnage of 1000 t/y. Therefore a generic scenario is carried out, based on the EU tonnage corrected for the total tonnage of the four known companies. The EU tonnage is divided by 10

to derive a regional tonnage (10% rule). This is based on the assumption that there will be more use companies having approximately the same size and that they are more or less evenly distribution over Europe as the companies mentioned in Table 3.11. The dosage of gas oil markers in fuel is different for each EU country. In the Netherlands about 12.5 tonnes furfural is used per year as a marker in non road-traffic, with a dosage of 10 mg furfural per litre fuel. The generic scenario is carried out for this percentage of furfural in the end product (fuel) as information from other countries is lacking.

Table 3.12 presents the assumptions and results for the exposure calculations for the above-mentioned scenarios.

Table 3.11 Site specific information for the use of a furfural tracer in the mineral oil and fuel industry.

No.	**Company**	**Tonnage (tonnes/year)**	**Emission to waste water**	**Emission to air**
1	Shell, The Netherlands	6.25	0.5%	unknown
2	Company in Finland	7.35	unknown	unknown
3	Company in Germany	10.5	unknown	unknown
4	Company in Austria	9.5	unknown	unknown
	Total	**33.6**		

Table 3.12 Input data and results for the local exposure for the use of a chemical tracer in the mineral oil and fuel industry.

	Site specific: site no. 1 (see Table 3.11)	**Generic: (based on site no. 3 tonnage) (see Table 3.11)**	**Generic: (based on EU tonnage)**
Scenario number	IVc	IVd	IVe
Tonnage (tonnes/y)	6.25 (local)	10.5 (local)	1000 (EU) -33.6 (Table 3.11) = 966
Used regional tonnage (t/y)	-	-	96.6
Industrial category	9	9	9
Use category	28	28	28
Fraction release to air (A-tables, TGD 1996)	0.01	0.01	0.01
Fraction release to waste water (A-tables, TGD 1996)	0.005 (site-specific)	0.02	0.02
Content furfural in end product	-	-	10mg/l
Use level of furfural in end product (%)	-	-	$1.16.10^{-3}$
Correction factor for tonnage for use of B-Tables	-	-	86,200
Used tonnage for B-tables (B-tables TGD, 1996)	-	-	83,270,000 (≥ 250,000)
Fraction of main source (B-tables, TGD 1996)	1	1	0.4
Number of emission days	300	300	300
Calculated local release to air (kg/d)	0.208	0.35	1.29
Calculated local release to waste water (kg/d)	0.104	0.7	2.56

	Site specific: site no. 1 (see Table 3.11)	**Generic: (based on site no. 3 tonnage) (see Table 3.11)**	**Generic: (based on EU tonnage)**
Scenario number	IVc	IVd	IVe
Size of STP (m^3/d)	4800	2000	2000
Dilution factor	10	10	10
PEC values:			
PEC STP (µg/l)	2.73	44.1	162
PEC surface water, during emission period (µg/l)	0.383	4.52	16.3
PEC air (µg/m^3)	0.0493	0.0817	0.296
PEC sediment (mg/kg_{wwt})	$4.43.10^{-4}$	$5.22.10^{-3}$	0.0189
PEC agricultural soil, avg. 30 days (mg/kg_{dwt})	$1.20.10^{-4}$	$1.65.10^{-3}$	$6.06.10^{-3}$
PEC in wet fish (mg/kg)	$3.14.10^{-4}$	$2.72.10^{-3}$	$9.92.10^{-3}$
PEC in worm (mg/kg)	$2.29.10^{-5}$	$2.17.10^{-4}$	$8.05.10^{-4}$

V Formulation for manufacturing refractories

Furfural can be used in the production of bonded abrasive products. Furfural is used to wet the abrasive grain at the start of the production process where resin bonding is used. After the resin bonding agent is added, the wheels are pressed to size and then heat treated to cure the resin. As furfural is a reactive solvent it will also react in the curing process (Kirk-Othmer, 1984). Furfural is used at two companies in the EU for the manufacturing of refractories and (possibly) abbrasive products (Table 3.13). For both companies no actual emissions are available and therefore generic scenario are carried out for both companies, based on the local use tonnages. Table 3.14 presents the assumptions and results for the exposure calculations for this scenario.

Table 3.13 Site specific tonnages of furfural in the formulation for manufacturing refractories.

No.	**Company**	**Tonnage (tonnes/year)**
1	Vesuvius; UK	2000
2	Staverma; Germany	200

Table 3.14 Input data and results for the local exposure for the formulation for manufacturing refractories in the engeneering industry.

Formulation for manufacturing refractories in the engeneering industry	**Generic, site 1 (based on local tonnage)**	**Generic, site 2 (based on local tonnage)**
Scenario number	Va	Vb
Local tonnage (tonnes/y)	200	2000
Industrial category	16	16
Use category	55/0	55/0
Fraction release to air (A-tables, TGD 1996)	0.01	0.01
Fraction release to waste water (A-tables, TGD 1996)	0.02	3.10^{-3}
Fraction of main source (B-tables, TGD 1996)	1	1
Number of emission days	300	300
Calculated local release to air (kg/d)	6.67	66.7
Calculated local release to waste water (kg/d)	13.3	20
Size of STP (m^3/d)	2000	2000
Dilution factor	10	10
PEC values:		
PEC STP (µg/l)	841	1260
PEC surface water, during emission period (µg/l)	84.2	126
PEC air (µg/m^3)	1.53	15.2
PEC sediment (mg/kg_{wwt})	0.0972	0.146
PEC agricultural soil, avg. 30 days (mg/kg_{dwt})	0.0313	0.0493
PEC in wet fish (mg/kg)	0.0489	0.0733
PEC in worm (mg/kg)	$4.0.10^{-3}$	$6.97.10^{-3}$

VI Use as chemical intermediate in pesticide manufacture (processing)

Furfural is used at one company in the EU as a raw material in the production of pesticides. Furfural is in this process converted to mucochloric acid, a pesticide used in cotton and sugar cane production. No local emissions are available and therefore a generic scenario is carried out with the available local tonnage of 1500 t/y. Table 3.15 presents the assumptions and results for the exposure calculations for this scenario.

No pesticidal use of furfural itself is reported within the EU. However, industry is considering an application for inclusion of furfural in Annex I of Directive 91/414/EEC at a yet unconfirmed future date.

Table 3.15 Input data and results for the local exposure for the use of 2-furaldehyde as chemical intermediate in pesticide manufacture (processing) industry.

Formulation in pesticide industry	**Generic (based on local tonnage)**
Scenario number	VI
Local tonnage (tonnes/y)	1500 [1)]
Industrial category	3
Use category	33
Fraction release to air (A-tables, TGD 1996)	0.01
Fraction release to waste water (A-tables, TGD 1996)	7.10^{-3}
Fraction of main source (data available for 1 known site)	1
Number of emission days	300
Calculated local release to air (kg/d)	50
Calculated local release to waste water (kg/d)	35
Size of STP (m^3/d)	2000
Dilution factor	10
PEC values:	
PEC STP (mg/l)	2.21
PEC surface water, during emission period (µg/l)	221
PEC air (µg/m^3)	11.4
PEC sediment (mg/kg_{wwt})	0.255
PEC agricultural soil, avg. 30 days (mg/kg_{dwt})	$8.35.10^{-2}$
PEC in wet fish (mg/kg)	0.128
PEC in worm (mg/kg)	$1.1.10^{-2}$

1) In 1999 the consumption of furfural has dropped to a volume of 400 t/y.

Private use

There is no information available about the private use of fuels in which furfural is used as a gas oil marker. Most probably total combustion of furfural takes place at use. Emissions are therefore assumed to be negligible.

VII. Pulping processes used in the pulp and paper industry

As an unintentional source furfural is a major contamination from sulfite pulping processes used in the pulp and paper industry. Furfural is formed from xylan in wood during the production of sulphite pulp under acid conditions. More furfural is formed if the raw material is deciduous wood than if it is coniferous. The furfural is found in the condensed gases collected from the production (Swedish Forest Ind. Fed., 2006).

For this industrial category there are no site-specific emissions of furfural available. However, measured waste water concentrations for a UK pulp and paper factory are presented in section

3.1.4.1. This scenario is limited to the aquatic compartment. Sludge application on agricultural soil is not considered here, because site specific information (e.g. on removal in the STP) is lacking. Additionally, based on the theoretical distribution of furfural in an STP (see Table 3.3), the adsorption on STP sludge is expected to be less relevant.
Information from the Swedish Forest Industries Federation (2006) indicated that the release of organic substances (primarily furfural, methanol and acetic acid) from sulphite pulping processes is ca. 6 kg/tonne (viscose pulp) or 2 kg/tonne (paper pulp). In Sweden the production of sulphite pulp has decreased to ca. 5% of the total pulp production. In 2006 there are 4 sites in Sweden using this process and all have biological waste water treatment in which furfural is biodegraded. In some cases the evaporator condensates are de-watered and burnt at the site.

3.1.4 Measured local data in the environment

3.1.4.1 Measured local data in the aquatic compartment

There are almost no measured local aquatic concentrations available for furfural. One EU furfural production site mentioned that the concentrations in untreated waste water and in WWTP effluent water are below the detection limit of 100 µg/l.

Furfural was detected in 1 out of 204 surface water samples taken near heavily industrialised sites across the USA (detection limit 1 ppb) at a concentration of 2 pbb. Furfural was further found in 1 of 13 samples taken in the Lake Michigan basin (1977) at a concentration of 2 µg/l (HSDB, 1998).

Levels of furfural in sulphite evaporator condensate, which represents about 15% of the wastewater flow from pulp mills in the pulp, paper and board industry, have been reported to range between 10 and 1280 mg/l and between 179 and 471 mg/l (avg. 247 mg/l) (IPCS, 2000). Using the average value of 247 mg/l, a waste water concentration can be calculated of 37 mg/l using the contribution of 15% of the waste water flow. The fraction in waste water directed to effluent water in the STP is 0.13 for furfural (see Table 3.3). With that fraction the calculated concentration in effluent water is 4.7 mg/l. With the following equation (TGD,

1996) an average C_{local} in surface water of 455 µg/l can be calculated near pulp, paper and board industry.

$$Clocal_{water} = \frac{Clocal_{effluent}}{(1 + Kp_{susp} * C_{susp}) * D}$$

$Clocal_{water}$:	local concentration in water during emission episode (kg/m^3)
Kp_{susp}:	solids-water partition coefficient of suspended matter. For furfural 1.71 l/kg (see EUSES print-out)
C_{susp}:	concentration of suspended matter in river water (0.015 kg_{dwt}/m^3, TGD)
D:	dilution factor (default = 10)

With the same calculation method a concentration in STP effluent water of 24.2 mg/l and a PEC surface water of 2.36 mg/l can be calculated for the measured maximum concentration of 1,280 mg/l in the evaporator condensate.

3.1.4.2 Measured local data in the atmospheric compartment

There are no measured local atmospheric concentrations of furfural submitted or available.

3.1.4.3 Measured local data in the soil compartment

There are no measured local soil concentrations of furfural submitted or available.
Furfural has been identified in the drinking water supplies of the United States and Europe. It has been qualitatively detected in the drinking water of Ottumwa, Iowa (Howard, 1993).

3.1.5 Summary of local concentrations

Table 3.16 Summary of the local concentrations for each scenario for the different environmental compartments.

Scenario	PEC air µg/m3	PEC STP µg/l	PEC surface water µg/l	PEC sediment mg/kg_{wwt}	PEC agricultural soil mg/kg_{dwt}	PEC in fish mg/kg_{wwt}	PEC in worm mg/kg_{wwt}
Ia production site 1 (Austria)	$2.1.10^{-3}$	100	10.1	0.012	$3.70.10^{-3}$	$5.96.10^{-3}$	$4.70.10^{-4}$
Ib production site 2 (Spain)	2.67	0	0.11	$1.27.10^{-4}$	$4.72.10^{-4}$	$1.55.10^{-4}$	$2.05.10^{-3}$
II processing furan derivates chemical industry: site specific	0.240	0	0.11	$1.27.10^{-4}$	$5.26.10^{-5}$	$1.55.10^{-4}$	$2.45.10^{-5}$
IIIa processing extr. solvent min. oil & fuel ind: site specific 1 (air)	86.1	-	-	-	-	-	-
IIIb processing extr. solvent min. oil & fuel ind: site specific 2 (air)	1.03	-	-	-	-	-	-
IIIc processing extr. solvent min. oil & fuel ind: generic (largest site)	3.81	90	9.11	0.0105	$4.01.10^{-3}$	$6.26.10^{-3}$	$7.07.10^{-4}$
IVa production chem. Tracer min. oil & fuel ind: site specific air	0.0550	-	-	-	-	-	-
IVb production chem. tracer: generic EU tonnage	0.764	420	42.1	0.0487	$1.57.10^{-2}$	0.0246	$2.0.10^{-3}$
IVc use chem. tracer min. oil & fuel ind: site specific waste w.	0.0493	2.73	0.383	$4.43.10^{-4}$	$1.20.10^{-4}$	$3.14.10^{-4}$	$2.29.10^{-5}$
IVd use chem. tracer min. oil & fuel ind: generic (largest site)	0.0817	44.1	4.52	$5.22.10^{-3}$	$1.65.10^{-3}$	$2.72.10^{-3}$	$2.17.10^{-4}$
IVe use chem. tracer: generic EU tonnage	0.296	162	16.3	0.0189	$6.06.10^{-3}$	$9.92.10^{-3}$	$8.05.10^{-4}$
Va formulation for manufacturing refractories, site 1	1.53	841	84.2	0.0972	0.0313	0.0489	$4.0.10^{-4}$
Vb formulation for manufacturing refractories, site 2	15.2	1260	126	0.146	0.0493	0.0733	$6.97.10^{-3}$
VI use as intermediate in pesticide manufacture	11.4	2210	221	0.255	0.0835	0.128	$1.1.10^{-2}$
VII processing pulp, paper and board industry: Mean	n.a.	4,700	455	0.526	n.a.	0.53	-
Max.	n.a.	24,200	2,360	2.73	n.a.	2.74	-

n.a. not available
1) Measured concentration (detection limit)

3.1.6 Regional exposure assessment

As mentioned, EUSES 1.0 (according to the TGD, 1996) has been used for calculating the regional PEC values for the different environmental compartments. Emissions to air and waste water are used as input for the regional exposure assessment. Unintentional emissions (e.g. pulp/paper industry) are not taken into account for the regional exposure assessment. This is primarily because unintentional releases are beyond the scope of ESR. Furthermore, emission data are lacking for this scenario (only local monitoring data). The absence of regional monitoring data also hampers a comparison ('validation') of the calculated regional PEC.

For all scenarios, except scenario IV A and B, the regional tonnages are based on the largest local site and the remaining volume is assigned to the continental volume. For scenario IV A and B the 10% rule is used based on the European use tonnage of 1000 t/y. The used regional and continental tonnages and emissions are presented in Table 3.17. The resulting regional PEC values are presented in Table 3.18.

Table 3.17 Summary of the used regional and continental tonnages and emissions.

				Air		**Waste Water**	
	Scenario	**Tonnage Continent.**	**Tonnage Regional**	**Emission Continent.**	**Emission Regional**	**Emission Continent.**	**Emission Regional**
		(t/y)	(t/y)	(kg/d)	(kg/d)	(kg/d)	(kg/d)
I	Production EU:	conf.	conf.	95.9	95.9	28.8	28.8
II	Use furan derivates (conversion to FA)	-	-	0	1.04	0	0
III	Use extraction solvent (refineries)	4850	1000	66.4	13.7	6.64	1.37
IV	A. Manufacture of tracer	900	100	24.7	2.74	49.3	5.48
V	B. Use of tracer	900	100	24.7	2.74	49.3	5.48
V	Use refractories	200	2000	5.48	54.8	1.64	16.4
VI	Use as intermediate for pesticide manufacture	0	1500	0	41.1	0	28.8
	Use application unknown	-	-				
	Total			**217**	**212**	136	81.4
	30% to Surface water:					**41**	**24.4**
	70% to Waste water:					**95**	**57**

conf. confidential

Table 3.18 Regional PEC values.

PEC air (μg/m^3)	0.0018
PEC surface water (μg/l)	0.127
PEC sediment (mg/kg$_{wwt}$)	$1.14.10^{-4}$

PEC agricultural soil (mg/kg_{dwt})	$5.5.10^{-6}$
PEC natural soil (mg/kg_{dwt})	$1.07.10^{-5}$

3.1.7 Measured regional data in the environment

There are no measured regional aquatic, atmospheric or soil concentrations of furfural submitted or available.

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) ASSESSMENT

3.2.1 General

The subsequent paragraphs contain a summary of the ecotoxicity studies with furfural as originally provided in HEDSET (1997). In addition, a literature search was carried out (CDROM Toxline Plus 1985-1997).
In a number of ecotoxicity studies no measures were taken to prevent volatilization from test vessels/tubes. In these cases, the actual concentrations may have been lower than the nominal ones in view of the volatility of furfural.

3.2.2 Aquatic compartment (incl. sediment)

3.2.2.1 Toxicity to fish (and other vertebrates)

Acute toxicity
The short-term toxicity studies with furfural and freshwater fish are summarised in Table 3.19.

Table 3.19 Short-term toxicity of furfural to freshwater fish.

No.	Species	Exp (h)	LC50 mg/l	Method	Anal. (y/n) closed/open	RI*	Reference
1	*Gambusia affinis*	96	24	standard (cf. OECD 203)	no data	2a	Wallen et al., 1957
2	*Lepomis macrochirus*	48	16	standard	y, open	1a	Turnbull et al.,

				(cf. OECD 203)			1954
3	*Leuciscus idus melanotus*	48	29	standard	no data	2a	Juhnke & Luedemann, 1978
4	*Pimephales promelas*	96	32	US EPA	no data	1a	Verschueren, 1983
5	*Poecilia reticulata*	14 d	10.5	OECD 204	y, closed	1a	Deneer et al., 1988

RI Reliability index (see Appendix 2)

Table 3.19 shows that the short-term LC50-values for freshwater fish range from 10.5 to 32 mg/l. The LC50-value from test no. 5 (prolonged toxicity test; semistatic with daily renewal) is corrected for furfural losses during the test and therefore considered to have the highest reliability.

Toxicity data for marine fish are not available.

Long-term toxicity

Table 3.20 Long-term toxicity to fish.

Species	**Method**	**Duration [days]**	**Criterion**	**Value [mg/l]**	**Endpoint**	**Reference**
Zebrafish (embryo and sac-fry stages) (*Brachydanio rerio)*	SS, M	12	NOEC	0.33	behaviour & morphology of fish larvae	Witters, 2005 RI*: 1a

SS = semi-static; M = measured concentrations

RI Reliability index (see Appendix 2)

In a 12-day early-life stage toxicity test (semi-static with daily renewal of test solutions) with embryo and sac-fry stages of zebrafish (OECD 212) by Witters (2005) a nominal NOEC of 0.47 mg/l was determined. Nominal test concentrations ranged between 0.47 mg/l and 15 mg/l. Substance related effects were seen on survival of embryos/fertilized eggs (e.g. 100% mortality at the three higher concentrations 3.75, 7.5 and 15 mg/l), hatching time of eggs, cumulative mortality of larvae and on normal behaviour and morphology of fish larvae. Effects on behaviour and morphology of the fish larvae proved to be most critical with a NOEC at the lowest concentration tested (i.e. 0.47 mg/l nominally). Test concentrations measured in the 0.47 mg/l nominal test solution ranged from 0.33-0.41 mg/l in the freshly prepared solution, 0.04-0.49 mg/l after 6 hours of exposure and between <0.01 mg/l (i.e. <dl.) and 0.25 mg/l after 24 hours of exposure. It is noted that the decrease in furfural

concentrations was much higher in the solutions that contained larvae (>98% decrease) than in solutions containing eggs or in blank solutions without organisms (about 50%-60% decrease), indicating that the loss of furfural is due to both physico-chemical and biological processes. (see also footnote 1). Since all 24-hour measurements in the 0.47 mg/l nominal test solutions with larvae resulted in concentrations below the limit of detection, no time-weighted average exposure concentrations could be calculated from those data. Measurements performed in 0.47 mg/l solutions without organisms (blank solutions) showed furfural concentrations of 0.46, 0.43 and 0.18 mg/l at t=0, 6 and 24h, respectively. From these data the geometric mean exposure concentration was calculated as 0.33 mg/l, which is considered to be the best estimate of the actual exposure concentration corresponding with 0.47 mg/l nominally. Hence, the 12-day NOEC for effects on larval behaviour and morphology is determined to be 0.33 mg/l.

3.2.2.2 Toxicity to aquatic invertebrates

Acute toxicity

For *Daphnia magna* two tests are available which are presented in Table 3.21. The LC50 for this crustacean is found to be in the range of 13 to 29 mg/l and is in the same order of magnitude compared to the fish LC50-values.

Table 3.21 Short-term toxicity of furfural to freshwater invertebrates.

No.	Species	Exp (h)	LC50 mg/l	Method	Anal. (y/n) closed/open	RI	Reference
1	*Daphnia magna*	72	13	unknown	no data	2a	Hessov, 1975
2	*Daphnia magna*	24	29	standard	n, closed	2a	Bringmann & Kühn, 1982

Toxicity data for marine invertebrates are not available.

Long-term toxicity

1 According to Deneer et al. (1988), aldehydes are readily reactive compounds that undergo reations *in vivo*. The main detoxication pathway for these substances is oxidation to the corresponding acids. Furthermore, aldehydes readily interact with various nucleophilic entities, e.g. amino- and thiol groups (see also the Human Health section in this RAR). This may explain the more rapid loss of furfural from the test solutions with larvae.

Table 3.22 Long-term toxicity to freshwater invertebrates.

Species	Method	Duration [days]	Criterion	Value [mg/l]	Endpoint	Reference
Daphnia magna	FT, M	21	NOEC	1.9	reproduction and growth	Palmer et al., 2005 RI*: 1a

FT = flow-through; M = measured concentrations
RI Reliability index (see Appendix 2)

In a 21-day flow-through life-cycle toxicity test with the cladoceran *Daphnia magna* (OECD 211) by Palmer et. al. (2005) a NOEC of 1.9 mg/l (actual concentration) was determined. Nominal test concentrations ranged between 0.25 mg/l and 4.0 mg/l. Measured concentrations (0.24-3.7 mg/l) were within the range of 84 to 105% of nominal throughout the study. Significant treatment-related effects (reductions in survival, reproduction and growth) were seen at 3.7 mg/l (actual concentration) only.

3.2.2.3 Toxicity to aquatic plants (e.g. algae)

Acute toxicity data for aquatic plants are not available. The results of two long-term tests are summarised in Table 3.23. NOEC-values of 2.7 and 31 mg/l are found for blue-green and green algae, respectively. The algae test results are based on 8-day tests which may not be fully equivalent to algae growth inhibition data from standard tests measuring the impact on exponentially growing algae.

Table 3.23 Long-term toxicity of furfural to freshwater plants.

No.	Species	Exp (d)	NOEC (mg/l)	Method	Anal. (y/n) closed/open	RI	Reference
1	*Microcystis aeruginosa*	8	2.7	standard	n, closed	2a	Bringmann & Kühn, 1978
2	*Scenedesmus quadricauda*	8	31	standard	n, closed	2a	Bringmann & Kühn, 1978

Toxicity data for marine plants are not available.

3.2.2.4 Toxicity to microorganisms (e.g. bacteria)

Only one short-term toxicity test is performed; the data are summarised in Table 3.24

Several NOEC-values are available for protozoa and one for bacteria. These values are summarised in Table 3.25.

Table 3.24 EC50-values for toxicity of furfural to microorganisms.

No.	Species	Exp (min)	EC50 mg/l	Method	Anal. (y/n) closed/open	RI	Reference
1	Activated sludge bacteria	30	760	OECD 209	n, closed	1a	Volskay & Grady, 1988

Table 3.25 NOEC-values for toxicity of furfural to microorganisms.

No.	Species	Exp (h)	NOEC (mg/l)	Method	Anal. (y/n) closed/open	RI	Reference
1	*Chilomonas paramaecium*	48	3.9	standard	n, closed	2a	Bringmann & Kühn, 1980
2	*Entosiphon sulcatum*	72	0.59	standard	n, closed	2a	Bringmann & Kühn, 1978
3	*Pseudomonas putida*	8 d	16	standard	n, closed	2a	Bringmann & Kühn, 1976
4	*Uronema parduczi*	20	11	standard	n, closed	2a	Bringmann & Kühn, 1980

3.2.2.5 PNEC for the aquatic compartment (incl. sediment)

Water

Long-term test results are available for organisms representing three trophic levels (freshwater plants, invertebrates and fish). The lowest long-term NOEC was found in the fish toxicity test with embryo and sac-fry stages of *Brachydanio rerio* (OECD 212); the NOEC for the most sensitive endpoints (behaviour and morphology of fish larvae) was calculated as 0.33 mg/l (actual concentration). According to the TGD, the OECD 212 study may be used as an alternative to the fish early life stage toxicity test (OECD 210) for substances with an LogKow of less than 4.

Furthermore, in addition to mortality several relevant sub-lethal endpoints were included in this test with furfural (hatching time of eggs, and behaviour and morphology of larvae) and this 12-d test with *B. rerio* covers two early life stages (embryonal stage and sac-fry stage).

Hence, the NOEC determined in this 12-day study may be used as a long-term toxicity parameter. The application of an assessment factor 10 (based on long-term tests for fish,

Daphnia and algae) results in a **PNEC for aquatic organisms of 33 µg/l** (from PNEC = NOEC/10).

Sediment

There are no data for sediment-dwelling organisms. A PNEC for sediment could be calculated using the equilibrium partitioning method. However, measured data for the concentration of furfural in sediment are lacking, so a quantitative risk characterization of furfural for sediment can not be performed. In addition, the low absorption potential of furfural suggests that sediment is probably not a relevant compartment for the environmental risk assessment of furfural.

3.2.2.6 PNEC for microorganisms

According to the recent TGD (2003), toxicity data for both bacteria and protozoa should be taken into account for the derivation of the PNEC micro-organisms. However, this is restricted to ciliated protozoa, constituting the most important class of protozoa in sewage treatment plants (STPs) . The protozoa tested with furaldehyde are all flagellates and thus the PNEC derivation will only based on the bacteria data. There are two options then: 1) the *Pseudomonas putida* test result (NOEC: 16 mg/l) is used and as it is a NOEC-value, the PNEC would be equal to this NOEC, or 2) the result of the activated sludge respiration inhibition test (EC50: 760 mg/l) is used which would lead to a PNEC of 760/100 = 7.6 mg/l. Preference is given to the lowest value. This results in a **PNEC micro-organisms of 7.6 mg/l**.

3.2.3 Terrestrial environment

3.2.3.1 Toxicity to soil dwelling organisms

No data available.

3.2.3.2 Toxicity to terrestrial plants

No data available.

3.2.3.3 Toxicity to soil microorganisms.

No data available.

3.2.3.4 PNEC for terrestrial compartment

No ecotoxicological data available to derive a PNEC for the terrestrial compartment. The equilibrium partitioning method (TGD) leads to a **PNEC soil of 0.014 mg/kg wet weight**.

3.2.4 Atmosphere

No data available.

3.2.5 Non compartment specific effects relevant to the food chain (secondary poisoning)

There are no specific data available for top-predators. Therefore the $PNEC_{oral}$ is derived from toxicity data for laboratory mammals. Starting from a lowest oral NOAEL for repeated-dose effects of 53 mg/kg bw/d derived in a semi-chronic (90-days) study with dietary dosing of furfural in microencapsulated form (Jonker 200a,bc, See section 4.1.2.6) and using both a conversion factor (NOAEL to NOEC) of 20 (rat > 6 wks) and an assessment factor of 30, a **$PNEC_{oral}$ of 35.3 mg/kg food** is derived (from $PNEC_{oral}$ = {(53 x 20)/30}).

3.3 RISK CHARACTERISATION

3.3.1 Local risk characterisation

3.3.1.1 STP effluent

The PNEC micro-organisms for furfural is 7.6 mg/l. For the risk characterisation this value is compared with the PEC_{STP} for the different exposure scenarios. The local PEC_{STP} values and the corresponding PEC/PNEC values are presented in Table 3.16 and Table 3.26, respectively. From Table 3.26 it can be seen that for all the scenarios the PEC/PNEC values are below 1 (**conclusion ii**).

Table 3.26 Local risk characterisation ratios (PEC/PNEC values).

Scenario	**PEC/PNEC STP**	**PEC/PNEC water**	**PEC/PNEC Soil**	**PEC/PNEC fish-eating predators**	**PEC/PNEC worm-eating predators**
Ia production site 1 (Austria)	0.013	0.307	0.236	$8.2.10^{-4}$	$6.44.10^{-5}$
Ib production site 2 (Spain)	0	$3.84.10^{-3}$	0.031	$2.45.10^{-5}$	$2.81.10^{-5}$
II processing furan derivates chemical industry: site specific	0	$3.84.10^{-3}$	$3.36.10^{-3}$	$2.45.10^{-5}$	$3.36.10^{-6}$
IIIa processing extr. solvent min. oil & fuel ind: site specific 1 (air)	n.a.	n.a.	n.a.	n.a.	n.a.
IIIb processing extr. solvent min. oil & fuel ind: site specific 2 (air)	n.a.	n.a.	n.a.	n.a.	n.a.
IIIc processing extr. solvent min. oil & fuel ind: generic (largest site)	0.0119	0.277	0.256	$8.6.10^{-4}$	$9.68.10^{-5}$
IVa production chem. tracer min. oil & fuel ind: site specific air	n.a.	n.a.	n.a.	n.a.	n.a.
IVb production chem. tracer: generic EU tonnage	0.055	**1.28**	0.99	0.0034	$2.75.10^{-4}$
IVc use chem. tracer min. oil & fuel ind: site specific waste w.	$3.60.10^{-4}$	0.0121	$7.66.10^{-3}$	$4.63.10^{-5}$	$3.15.10^{-6}$
IVd use chem. tracer min. oil & fuel ind: generic (largest site)	$5.81.10^{-3}$	0.138	0.105	$3.75.10^{-4}$	$2.97.10^{-5}$
IVe use chem. tracer: generic EU tonnage	0.0221	0.513	0.4	0.00136	$1.10.10^{-4}$
Va formulation for manufacturing refractories, site 1	0.111	**2.55**	**2.0**	0.0067	$5.48.10^{-5}$
Vb formulation for manufacturing refractories, site 2	0.166	**3.83**	**3.14**	0.0101	$9.54.10^{-4}$
VI use as intermediate for pesticide manufacture	0.29	**6.69**	**5.32**	0.0176	$1.51.10^{-}$
VII processing pulp, paper and board industry: Mean	0.62	**13.8**	n.a.	0.0	n.a.
Max.	**3.18**	**71.5**	n.a.	0.	n.a.

n.a. not available

Unintentional sources

Using the average value of 247 mg/l and the maximum value of 1280 mg/l, local PECs in effluent water were calculated of 4.7 mg/l and 24.2 mg/l, respectively, for the pulp industry (see section 3.1.2.1 and 3.1.4.1). With the PNEC micro-organisms for furfural of 7.6 mg/l, the calculated PEC/PNEC values for a local STP at the pulp and paper industry are 0.62 (mean) and 3.2 (maximum). For this scenario site-specific measured effluent concentrations and measured data from other pulp and paper industries in the EU are needed to refine this conclusion (see also surface water). Since this considers an unintentional source beyond the scope of this EU risk assessment, there will be no follow-up of this scenario in the context of Regulation 793/93/EC.

3.3.1.2 Surface water

For the risk characterisation for surface water the PNEC water of 33 µg/l is compared with the concentrations in surface water for the different exposure scenarios. The local concentrations in surface water and the PEC/PNEC ratios are presented in Table 3.16 and Table 3.26, respectively. From Table 3.26 it can be seen that for some scenarios (IVb, Va, Vb and VI), the PEC/PNEC ratios are above 1. As no further refinement of either PECs or PNECs is possible, a need for further limiting the risks is indicated for these scenarios **(conclusion iii)**. For scenario number VI (use as intermediate for pesticide manufacture) the PEC/PNEC remains above 1, when the most recent production volume of 400 t/y (1999) is used instead of the volume of 1500 t/y. For the remaining scenarios (Ia, Ib, II, IIIa,b,c, IVa,c,d,e) the PEC/PNEC values are below 1 (**conclusion ii**).

Unintentional sources

Local concentrations in surface water of 455 µg/l (mean) and 2,360 µg/l (max) can be calculated for a UK pulp and paper company (see section 3.1.4.1). With the PNEC for water of 33 µg/l, the PEC/PNEC ratios for surface water at the pulp and paper industry are much higher than 1, with values of 13.8 (mean) and 72 (max.). For this particular site the PEC can be refined by submitting site-specific information on the dilution factor. However, more data from the pulp and paper industry in the EU are needed to refine this scenario for the pulp and paper industry. Since this considers an unintentional source beyond the scope of this EU risk assessment, there will be no follow-up of this scenario in the context of Regulation 793/93/EC.

3.3.1.3 Sediment

A quantitative risk characterisation of furfural for sediment is not performed. Neither toxicity data for sediment-dwelling organisms nor measured concentrations in sediment are available. The low absorption potential of furfural suggests that sediment is probably not a relevant compartment for the environmental risk assessment of furfural.

3.3.1.4 Atmosphere

A quantitative risk characterisation for the exposure of organisms to furfural in air is not possible, because a PNEC for air could not be derived.

3.3.1.5 Terrestrial compartment

For the risk characterisation of the terrestrial compartment the PNEC soil of 0.014 mg/kg is compared with the concentrations in soil for the different exposure scenarios. The local concentrations in soil and the PEC/PNEC ratios are presented in Table 3.16 and Table 3.26, respectively. From Table 3.26 it can be seen that for the scenarios Va, Vb and VI, the PEC/PNEC ratios are above 1 and hence a risk is indicated and. c**onclusion (i)** applies. The terrestrial PNEC is derived through the equilibrium partitioning method and there is therefore scope to refine this PNEC through testing. However, no testing is proposed for the terrestrial compartment since for these scenarios also conclusion iii is drawn for the local aquatic compartment (See section 3.3.1.2). The development of risk reduction measures for the aquatic compartment should take account of the conclusions for the terrestrial compartment.

For scenario number VI (use as intermediate in pesticide manufacture) the PEC/PNEC remains above 1, when the most recent production volume of 400 t/y (1999) is used instead of 1500 t/y.

The PEC/PNEC ratios for the remaining sites (scenarios Ia, Ib, II, IIIc, IVa,b,c,d,e) are all lower than 1 (**conclusion ii**).

3.3.1.6 Non compartment specific effects relevant to the food chain

Following the TGD the PEC values for fish-eating and worm-eating predators are calculated as the average of the local PEC values and regional PEC values in fish and worm (TGD, 1996).

Table 3.26 shows that the PEC/PNEC values are lower than 1 for all exposure scenarios (**conclusion ii**).

3.3.2 Regional risk characterisation

The regional PEC values for all environmental compartments and the corresponding PEC/PNEC ratios are presented in Table 3.18 and Table 3.27, respectively. Table 3.27 shows that all regional PEC/PNEC values are lower than 1 (**conclusion ii**).

Table 3.27 Regional risk characterisation ratios (PEC/PNEC).

	PEC/PNEC Water	**PEC/PNEC Soil**
Regional scenario	$3.84.10^{-3}$	$3.53.10^{-4}$

3.4 PBT ASSESSMENT

In order to protect the marine environment against unpredictable or irreversible long-term effects, substances must be submitted to a so-called PBT-assessment. Available data must be tested to the PBT-criteria in the TGD (EC 2003). For substances that do not fulfil all three PBT criteria, but are known to be persistent and bioaccumulating, vPvB (very persistent and very bioaccumulating) criteria are set.

3.4.1 Persistence

For furfural several aerobic as well as anaerobic biodegradation test results are available (See section 3.1.1); the total dataset is considered sufficient for drawing conclusions on the degradation potential of furfural and persistence within the scope of the PBT assessment.
From the overall results of the studies it is concluded that furfural is readily biodegradable. Furfural also proved rapidly biodegradable under anaerobic conditions.

It is concluded that furfural does not meet the persistence criterion.

3.4.2 Bioaccumulation

No experimental data on bioaccumulation are available. On the basis of the high water solubility (83 g/l) and the low Log Kow (0.41), furfural is not expected to bioaccumulate. The calculated BCF_{fish} of 1.41 l/kg and $BCF_{earthworm}$ of 0.95 l/kg (results EUSES version 1.0 calculations, from section 3.1.1.) confirm a low bioaccumulation potential.
It is concluded that furfural does not meet the bioaccumulation criterion.

3.4.3 Toxicity

The criterion for environmental toxicity for PBT substances is NOEC (long term) < 0.01 mg/l. Long term test results are available for algae (NOEC: 2.7 and 31 mg/l; Bringmann & Kühn, 1978), invertebrates (NOEC: 1.9 mg/l; Palmer et al, 2005) and fish (NOEC: 0.33 mg/l; Witters, 2005). Hence, the lowest measured NOEC (long-term) is 0.33 mg/l.
With respect to human health hazards furfural is classified as a Category 3 carcinogen (R40; limited evidence of a carcinogenic effect). A decision whether or not this evidence is sufficient to consider furfural as (T)oxic within the framework of the PBT assessment has not been taken. Such a decision is not needed since the scientific evidence on P and B is of enough weight for a final conclusion of the PBT assessment.

Conclusion of the PBT assessment:
It is concluded that furfural does not meet the criteria for PBT or vPvB substances.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General introduction

The human population can be exposed to furfural via the workplace, via the use of consumer products, and indirectly via the environment.

Furfural is a colourless, oily liquid, which turns reddish brown on exposure to light. It can be smelled at concentration levels of 0.25-1.0 mg/m^3 (DECOS, 1996). The substance is industrially obtained from pentosan in agricultural residues such as corncobs (primary source), rice hulls, oat hulls, bagasse, etc. and from bark of wood. Furfural is furthermore a by-product from the production and storage of fruit juices, wines, and medical solutions. It is also a degradation by-product from the thermal/chemical treatment of hemicellulose feedstocks and refuse for chemical and fuel production. Finally it is also a major contamination of evaporation condensate from sulphite pulping processes used in the pulp and paper industry (DECOS, 1996; Rivard and Grohmann, 1991; Vinogradova et al., 1968). The major uses of furfural are given in section 2.2. In table 4.1 an overview of occupational limit values for furfural is given.

Table 4.1 Occupational limits values for furfural

Country/ Organization	8-hour TWA (in mg/m^3)	15 min. STEL (in mg/m^3)	Remarks	References
United Kingdom/HSE	8	20	MEL value	HSE (2002)
USA/ACGIH	7.9			ACGIH, 2003
France	8	15		INRS, 1986
The Netherlands	8		under revision	SZW, 1996; DECOS, 1996
Sweden	8	40		Swedish National Board of Occupational Safety and Health, 1993

4.1.1.2 Occupational exposure

Exposure can occur during the production of the substance, and during the use in several industries (see chapter 2.2). The latter includes the petrochemical industry, where furfural is used for selective solvent extraction of petroleum distillate, in the resin and refractory industries, where resins and friction products like abrasive wheels and refractory materials are produced, and in foundries (Gregg *et al*., 1997; HSDB, 1998). In the HEDSET (1997) it is indicated that the majority of the substance is used for the production of furan derivatives.

The following data are used for the occupational exposure assessment:

- physico-chemical data of furfural and, if available, of products containing furfural;
- data regarding processes of the substance and products containing furfural; temperatures at which processes take place; amount of furfural in the products;
- data from product registers provided by countries of the EU;
- data from several exposure databases provided by countries of the EU (Finland and Norway);
- data from the literature (open and 'grey') regarding exposure to furfural or analogues;
- results from models.

The exposure is assessed using the available information on the substance, processes and work tasks. More detailed information on these parameters may lead to a more accurate exposure assessment.

In this part of the assessment, (potential) external exposure is assessed using relevant models and other available methods in accordance with the Technical Guidance Documents and the agreements made at official Meetings of Competent Authorities. The internal dose depends on the external exposure and the percentage of the substance that is absorbed (either through the skin or via the respiratory system).

The (potential) external exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). If the risk assessment, using the potential exposure, indicates that risks may be expected, the use of personal protective equipment may be one of the measures to decrease actual risks, although other measures are preferred (technical and organisational). In fact this is obligatory following harmonised European legislation.

Knowledge of the effectiveness of PPE in practical situations is very limited. Furthermore, this effectiveness is largely dependent on site-specific aspects of management, procedures and training of workers. A reasonable effective use of proper PPE for the skin is tentatively assumed to reduce the external dermal exposure with 85%. For respiratory exposure the

extent of protection depends largely on the type of PPE used. Without specific information, a reduction of 90% will be used for respiratory exposure, which is equivalent to the assigned protection factors for supplied-air respirators with a half mask in negative pressure mode (NIOSH, 1987). Better protection devices will lead to higher protection. Imperfect use of the respiratory protection will lower the protection factor in practice compared to the assigned factor. The estimations of reduction are not generally applicable "reasonable worst case" estimations, but are indicative values based on very limited data. Furthermore, reduction of the external exposure does not necessarily reflect a reduction of an absorbed dose. It is noted, that the use of PPE may result in a relatively increased absorption through the skin (effect of occlusion), even if the external skin exposure is decreased. This effect is very substance-specific. Therefore, in the risk assessment it is not possible to use default factors for reduction of exposure as a result of the use of PPE.

In some specific situations a preliminary assessment of the possible influence of PPE exposure will be made. This regards situations in which the failure to use adequate protective equipment properly often lead to acute adverse effects on the worker. Examples of such situations are manual handling of very corrosive substances and handling materials with high temperatures.

Some literature is available regarding the production process of the substance and the same holds for some processes in which the substance is used. There is not much information available regarding the use of furfural as a precursor for furfural derivatives, the amount of the substance used, and the concentration of furfural in the resulting products. It is assumed that furfural is fully converted during the use as a precursor.

The Danish product register states that around 80% of the substance in Denmark is used for the production of products which ultimately contain 10-80% of the substance. In this register no product types were given, i.e. they were stated to be confidential. Opdijke (1978) mentioned that the concentration of furfural in soap, detergents, creams, lotions and perfume varied from 0.0005 to 0.1%. The total amount of the substance used for this purpose in the United States was about 500 kg in 1978 (Opdijke, 1978).

Since both the concentration and the amount of the substance used are low, the process is assumed to be of minor importance compared to other processes where furfural is used. This process will, therefore, not be taken into account in the occupational exposure assessment.

Another known source of furfural is the pulp and paper industry. Furfural occurs unintentionally in the evaporation condensate from sulphite pulping processes and is drained

off in a diluted form (about 15%) in wastewater (IPCS, 2000). No significant exposure is expected from this source and therefore these processes will not be taken into account in the occupational exposure assessment. However, in one pulp processing company the furfural by-product is purified and sold as such. This scenario is addressed in the production of furfural.

The following exposure scenarios will be considered:
scenario 1: production of furfural
scenario 2: production of furfural derivatives
scenario 3: production of resins, refractory materials and abrasive wheels
scenario 4: use as an extractant/solvent in the petroleum refining industry

Scenario 1: production of furfural

The substance is industrially mainly obtained from pentosan in agricultural residues such as corncobs (primary source), rice hulls, oat hulls, bagasse, etc. Furfural is produced in a batch or a continuous digester, where the pentosans are hydrolysed into pentoses and subsequently cyclohydrated to furfural (Opdijke, 1978; Kirk-Othmer, 1984).

Production process

The two production companies provided some information on the production process.
Company B produces furfural by a discontinuous acid hydrolysis in a closed system. This is followed by continuous distillation in a distillation column at atmospheric pressure. After distillation the furfural is stored in tanks with nitrogen. According to the producer possible exposure scenarios are discharging of the autoclave (duration is 4 hours per day), discharging of the rectifier (vacuum distillation process; duration is 1 hour per day) and loading of tank cars (duration is 15 minutes, once every 3 to 4 days). In company C furfural is produced as a by-product during pulp processing in a closed system with automatic process control. No information is given on chemical processing and purification of furfural, but it is assumed that these steps are similar to company B. According to the producer exposure can only take place during shut down and maintenance (Company C, 2000).
The production of furfural by a continuous method of hydrolysis of bark using acetic acid as a catalyst is described extensively by Vinogradova *et al.* (1968), and it is assumed that the

processes are largely similar. Therefore, the process of bark hydrolysis as described by Vinogradova *et al.* (1968) is used as a basis for the exposure assessment.

The technological process of furfural production consists of 1) the hydrolysis of bark and 2) the distillation of the hydrolysis products with isolation of furfural (Vinogradova *et al.*, 1968).

The hydrolysis of bark is carried out in continuous process at 190°C under a pressure of 12 atmosphere. Initially, Preliminarily steamed bark and sharp steam is taken into this first hydrolysis step. At the start of the process low boiling products are isolated: methanol, formic acid and acetic acid. On further hydrolysis of the wood, fume is formed which contains up to 5% furfural, 1.5% organic acids and methanol, as well as a strong residue of cellolignin. The cellolignin is continuously removed from the lower part of the hydrolyser and conveyed by means of a pneumatic conveyor to the adjacent shop for the preparation of carbonated coal. The furfural containing fume is led away from the upper part of the hydrolysis through the main gas valve to the cyclones for cleaning from mechanical admixtures of bark and cellolignin which are carried along by the fumes.

After leaving the cyclones, the cleaned fume is condensed. The condensate enters the rectifying column from which first the methanol is taken away, at 110-115°C the acid water (acetic acid and its homologues) is distilled off. At a higher temperature the fraction containing up to 30% furfural is distilled off. This is strengthened to 95% by neutralising the residue with a solution of calcinated salt. A second rectifying step is carried out in order to obtain 99.8% furfural. The process proceeds in a closed apparatus made from stainless steel. Cleaning of the cyclones from cellolignin and bark (every 5 days) and cleaning of the hydrolisers is carried out by hand (Vinodagrova *et al.*, 1968).

Measured data

Company B provided measurement data on autoclave discharge and rectifier discharge. Measurement method, duration and the exact number of measurements are not given. The number of measurements is assumed to be six per scenario, since the producer states that the measurements were performed three times per year in 1998 and 1999. Concentrations ranged from 0.5 to 10 ppm (2 to 40 mg/m^3). Measurements are summarised in Table 4.2.

Vinodagrova *et al.* (1968) performed furfural measurements by a method of fast indication (not specified by the authors, it might be a dräger tube). In the hydrolysing section furfural concentrations did not exceed the maximum permissible concentration (10 mg/m^3), only near

the hydrolysers the concentrations were 20-30 mg/m^3. Upon opening the hydrolysers for cleaning, the content of furfural in the air increased for a short time up to 50-70 mg/m^3. No number of measurements was given. In the rectification section the concentration did not exceed the permissible level (also no number of samples given). Only during cleaning by hand and selection of samples from the collector of commodity furfural and the condensation refrigerators the concentrations of the substance in air increased up to 40-60 mg/m^3. Also some stationary measurements near parts of the equipment were taken (Vinogradova *et al.*, 1968). All measurements are summarised in Table 4.2.

Di Pede *et al.* (1991) also performed measurements during the production of furfural from wood extraction (time weighted average concentrations; no duration given). These data are also summarised in Table 4.2.

More recent measurements were made in a South African production unit of furfural (Ecoserv, 2001). Five samples (between 3 and 6 hours) were collected on two consecutive days from workers with the functions "Plant shift analyst", "Shift maintenance", "Senior operator", "Services plant assistant" and "Fitter". All measured values were below the analytical limit of detection (5 μg/sample, i.e. below 0.47 mg/m^3, as calculated from the lowest sample volume of 10.7 L; see Table 4.2).

Table 4.2 Exposure data during the production of furfural.

Substance	**Industries or tasks**	**Number of samples**	**Exposure Levels (mg/m^3)**	**Reference**
Furfural	Autoclave discharge	6*	2 -40	Company B, 2000
	Rectifier discharge	6*	2 -40	
Furfural	Production:			Vinogradova *et al.,*
	Hydrolysing section	n.p.	<10	1968
	Near hydrolysers	n.p.	20-30	
	Opening for cleaning	n.p.	50-70**	
	Floating piston of inverted valve	12	20-90 (m.f. 60-70)	
	Main gas valve	8	3-70 (m.f. 55-60)	
	Level regulator	10	5-40 (m.f. 12-20)	
	water drain	8	3.5-75 (m.f. 10-30	
	double screw conveyor	12	1-87 (m.f. 20-30)	
Furfural	production: extraction section	17***	> 8 in 4 locations	Di Pede *et al.,* 1991
Furfural	production	5	< 0.47	Ecoserv, 2001

n.p: not provided

m.f.: most frequent

* probable number of measurements is 6; three measurements a year in 1998 and 1999.

** short time exposure measurement, no exact duration given

*** exposure was measured in 17 locations, in which in 4 locations the exposure was above 8 mg/m^3 (time weighted average concentrations; no duration given, but probably over 8 hours).

Exposure modelling

The exposure assessment by modelling can be distinguished in the production of the substance, including quality control sampling, drumming and cleaning, and maintenance.

The production of the substance is performed in a closed system. Breaching of the system probably occurs during autoclave discharge, rectifier discharge, quality control sampling and drumming. During the closed production process EASE estimates an inhalation exposure of 0.1 ppm (0.4 mg/m^3; the conversion factor was given in the HEDSET (1997) to be 3.93 at 25°C) assuming a closed, non breached system. Rectifier discharge, drumming and quality control sampling is assumed to occur in the presence of local exhaust ventilation (LEV). The inhalation exposure during these activities is estimated as 0.5-3 ppm (2.0-11.8 mg/m^3), assuming non dispersive use in the presence of LEV. Since consequent use of LEV cannot be generally assumed for the pulp and paper industry, and can also not be assumed for autoclave discharge, exposure without use of LEV is also estimated. The inhalation exposure during drumming and quality control sampling without the use of LEV is estimated to be 10-50 ppm (39-197 mg/m^3).

Dermal exposure during the general production process is assumed to be negligible. Drumming of furfural is assumed to occur via a transfer line; dermal exposure is therefore assumed to occur only incidentally. The same holds for quality control sampling. Dermal exposure during drumming and quality control sampling is estimated to be 0-0.1 mg/cm^2/day, assuming non-dispersive use, direct handling and incidental contact. Assuming that the half of both hands (420 cm^2) could be exposed a total exposure due to skin contact is calculated to be 42 mg/day (= 420*0.1).

During cleaning and maintenance the operator exposure (both inhalation and dermal) is estimated to be higher, since LEV is assumed not to be present or less effective. In the literature (Vinogradova *et al.*, 1968) it was stated that the hydrolysers (cyclones) were cleaned by removing the bark rests by hand. The method of cleaning may have changed, since this publication dates from 1968. EASE estimates an inhalation exposure of 10-50 ppm (39-197 mg/m^3), assuming non-dispersive use, direct handling with dilution ventilation. In

the process described, the cleaning of the hydrolysers occurred every 5 days. In this assessment it is assumed that the evaporation is equivalent to that of the pure substance (reasonable worst case assessment).

Dermal exposure during cleaning and maintenance is estimated to be 1-5 mg/cm^2/day, assuming non dispersive use, direct handling and extensive contact with the material in the processing equipment. The removal of the bark (or other starting material) may lead to contact with furfural. However, the concentration of furfural in the material in the equipment will be limited. It is assumed that the material contacted may contain at most 10% furfural (expert judgement). When it is furthermore assumed that both hands and part of the forearm could be exposed (1300 cm^2), the exposure due to skin contact is estimated to be 5*0.1*1300= 650 mg/day.

Conclusion

The exposure measurements provided by industry and found in the literature provided rather limited information. Most are measurements concern stationary measurements. The highest concentration was measured near the hydrolysing equipment. The time weighted average concentration in the hydrolysing section was however less than 10 mg/m^3. The measurement data provided by company B are most recent and give more specific exposure information for the production activities autoclave discharging and rectifier discharging. The most recent data set (Ecoserv, 2001) has by far the lowest exposure values.

For the risk characterisation a distinction will be made between production activities, drumming, quality control sampling and discharging of the autoclave and rectifier, and cleaning and maintenance operations.

Production activities

Comparing the measurements with the estimates made by EASE, the lower range of the EASE assessment (without LEV) is reasonably well in line with the industry data. Therefore, for the different activities during production a reasonable worst case respiratory exposure level is estimated to be 40 mg/m^3. The typical exposure is estimated to be 10 mg/m^3, based on the exposure measurements and expert judgement. During the production process itself the exposure is estimated to be less. The typical exposure is estimated to be negligible (based on the lower limit of EASE), while the reasonable worst case exposure is estimated to be 0.4 mg/m^3 (the upper limit of the estimate made with EASE). The measured "full shift" exposure

levels presented by Ecoserv (2001) are all below the limit of detection. This limit is close to the upper limit of the EASE estimate for closed system. It is unclear how far the workers for whom exposure was measured were engaged in tasks related to opening of installations. However, it is clear that activities with 40 mg/m^3 of exposure could not have been conducted for hours. So, either these activities and exposures are of very short duration (minutes), or the situation in this company is substantially different from the situation measured in Company B in 1998-1999.

Because no information to the contrary is available, it is assumed that the measured results of Company B are reasonable values for tasks done during a substantial part of the work shift and that workers can perform more than one of the mentioned tasks during the day. Therefore, it is assumed that drumming, quality control sampling and discharging of the autoclave and rectifier occurs four to six hours per day. Exposure due to the production process could occur during the remainder of the work shift. This results in a calculated reasonable worst case full shift exposure level for a worker involved in several processes with breaching of the closed system of 30 mg/m^3 ((6*40+2*0.4)/8). The personal exposure data from Ecoserv (2001) show that production can be done with much lower exposure levels. However, these data are too limited in number and detail to allow the other measured values to be disregarded (that are also very limited in number and detail of information).
Because it is assumed that the measured data are not short-term data, no information is available to estimate short-term exposure levels. Based on a pragmatic approach, exposure levels twice that of long-term exposure levels are considered possible for short-term exposure (15 minutes). For tasks during production related to opening of the installations, the estimated short-term exposure level is therefore 80 mg/m^3.

Cleaning and maintenance

Exposure during cleaning and maintenance is assumed to be higher. This activity is further assumed to be performed by other workers. Since the exposure estimates are quite limited, both the exposure measurements and the estimates made by EASE are used for the risk characterisation. Comparing the estimate made by EASE with the concentration measurements, EASE appears to give higher values. Considering this and the fact that the amount of the substance in the equipment is assumed to be limited, approximately the lower limit of the exposure assessment by EASE will be used for the risk characterisation (40

mg/m^3; typical value). The reasonable worst case exposure is estimated to be 70 mg/m^3 (the highest concentration measured by Vinogradova et al., 1968). Approximately the middle of the exposure assessment by EASE will be used for the short-term exposure (120 mg/m^3).
No specific information on dermal exposure is available. Therefore the estimates made using EASE are used for risk characterisation. Dermal exposure during drumming and quality control sampling is estimated to be 42 mg/day, while dermal exposure during cleaning and maintenance is estimated to be 650 mg/day.

Scenario 2: production of furfural derivatives

Furfural is used as a precursor for a variety of aliphatic and heterocyclic compounds. It is the source for, among others, furfuryl alcohol, tetrahydrofurfuryl alcohol and furan (Company A, 1980).
Although hardly any information is provided by the notifier regarding this process, it is assumed that the substance is fully converted during the process. No exposure data were provided by the notifier, or found in the literature.

Exposure modelling

During the production of furfural derivatives, the highest exposure will probably occur the moment the substance is added to the reaction vessel. Since it probably concerns the addition of large amounts of furfural into a reactor it is assumed that this is performed via a transfer line. Inhalation exposure during this activity is estimated to be 0.5-3 ppm (2.0-11.8 mg/m^3), assuming non-dispersive use in the presence of LEV. The conversion process is assumed to occur in a closed system. Assuming no breaches during this process, an inhalation exposure of 0-0.1 ppm (0.4 mg/m^3) is estimated.
Dermal exposure during transfer of furfural is estimated to be 0-0.1 mg/cm^2/day, assuming non-dispersive use, direct handling and incidental contact. Assuming an exposed area of half of both hands (420 cm^2), the total daily exposure is calculated to be 42 mg/day.

Conclusion

Since no exposure data are available, the estimates made by EASE will be used for the risk characterisation. It has to be considered that the EASE estimates are based on very limited information on the production process.

A typical value for inhalation exposure during adding of furfural is estimated as 2 mg/m^3, while the reasonable worst case exposure is estimated to be 12 mg/m^3 (upper limit of the exposure assessment). The typical exposure during the conversion process is estimated to be negligible, while the reasonable worst case exposure during this process is estimated as 0.4 mg/m^3 (both based on EASE). Exposure during adding is estimated to occur up to 4 hours per day (reasonable worst case estimate). During the remainder of the working day, exposure will occur due to the conversion process. This results in a calculated reasonable worst case full shift exposure level for a worker involved in several processes with breaching of the closed system of 6 mg/m^3 ((4*12+4*0.4)/8).

Dermal exposure during adding of furfural is estimated to be 42 mg/day. The dermal exposure during the conversion process is estimated to be negligible.

Scenario 3: formulation of resins, refractory materials and abrasive wheels

Furfural is used for the production of resins, refractory materials, resin bonded abrasive wheels and moulds. In resins bonded abrasive wheels and refractory products furfural is used as a wetting and vulcanising agent (HSDB, 1998; Company A, 1980). It is assumed that the process of exposure is similar for all production processes of the several products. Historically, furfural was also used during the production of brake linings (Gregg *et al.*, 1997). In the scenario also the processing of resins, *e.g.* in acid proof cement, is included.

To produce resins, furfural is mostly used in combination with phenol. Furfural and phenol react readily to form a fusible soluble resin. Furfural phenol condensation products are mostly used in the two-stage form. These are characterised by long flow properties which are useful in moulding large or complicated parts where thin sections aggravate the problem of precure. Furfural-phenol resins are also used as varnishes and as resin binders (Company A, 1980). The manufacturing of resins is normally performed in closed systems with material fed from storage tanks to reactors via pipe lines and metering/weighing equipment. In this process furfural is used with other chemicals (*e.g.* phenol, formaldehyde) which are thought to be more toxic than furfural. No exposure measurements were available (Gregg *et al.*, 1997).

Furfural is also used in the manufacturing of refractory materials and friction products such as abrasive wheels.

Manufacture of refractory materials involves the mixing of various dry powdered ingredients such as phenolic resins, graphite and refractory materials with silica. In general, the mixers

used are more like large cement mixers. Once thoroughly mixed the 'mix' is partially dried in rotary driers. The dried material is sized and blended prior to pressing.

Measured data

Gregg *et al.* (1997) gave furfural measurements, provided by the HSE, performed in the refractory industry. The exposure measurements were distinguished in measurements performed before and after 1987 (see Table 4.3). The measured values varied from 3 to 189 mg/m^3. The highest concentration measured after 1987 was 104 mg/m^3. The exposure was reported to be dependent on: 1) effectiveness of seals in glands, pumps and dryers; 2) whether lids and covers are kept closed as required; 3) efficiency of the local exhaust ventilation enclosures and 4) their operational efficiency.

The processing of grinding wheels is similar to the manufacturing of refractory products. For the manufacture of grinding wheels, furfural is poured into a mixer containing abrasives, extenders and binders, which are mixed together to produce a homogeneous mixture. The 'mix' is sieved and used for the production of the grinding wheels, which can be produced in hot or cold moulding (Gregg *et al.*, 1997). Furfural acts as a temporary plasticizer and wetting agent in the mix, which is subsequently cold moulded and then baked to cure the resin (Company A, 1980). The abrasive grain is wetted with 2 to 3% of furfural, or a solvent mixture containing furfural, prior to addition of the pulverised phenolic resin. Throughout the production process there is potential for exposure. Only limited exposure measurements are available and these are reported in Table 4.3. The exposure patterns are expected to be similar to that of the manufacturing of refractories (Gregg *et al.*, 1997).

Results of measurements during the production of abrasive and fireproof products are reported by BGAA (1996). A total of 19 measurements (duration > 1 hour, reported as 8-hr time weighted averages) were done in 6 companies in the period 1991-1995. The higher exposure levels were found during filling and moulding. Other processes monitored were shaping and firing.

Exposure to furfural in resin can also occur in foundries during various activities undertaken in the mould and core shops. Furfural is used for the manufacturing of moulds from resin. Some exposure measurements were performed in Czechoslovakia. The measurements were performed close to a mixer, during working with moulds, during pouring and in the core shop. It is not clear whether it concerned stationary measurements. The highest exposure occurred near the mixer and during working with the moulds. The duration of the

measurements was not given (Gregg *et al.*, 1997). The exposure data are summarised in Table 4.3.

More or less comparable is the use of acid proof cement, resin or mortar. This use was reported to lead to exposure during laminating or cladding. Measurements (n = 24) were done for more than one hour in 6 companies. Part of the measurements was done in situations with LEV and part in situations without LEV. The highest exposure levels were found during the processing of the material in confined spaces (BGAA, 1996). In the processing in confined spaces the use of proper personal protective equipment, probably with independent air supply, is a normal procedure.

Arvin *et al.* (1975) referred to by Gregg *et al.* (1997) measured the exposure of 15 employers working in a wheel manufacturing company. Furfural levels were measured in the vicinity of the mixing operation. The total sampling time over 4 shifts was approximately 23 hours. The results of the study are summarised in Table 4.3.

Table 4.3 Exposure data of formulation of products.

Substance	Industries or tasks	Number of samples	Exposure levels (mg/m^3)	Reference
furfural	refractory industry			HSE, referred to by Gregg *et al.*, 1997*
	- pre 1987	23	8-198 (SD 40.2); AM 59; GM 44	
	- after 1987	78	3.2-104 (SD 19.8) AM: 26; GM 21	
furfural	manufacturing friction products (abrasive wheels)			Gregg *et al.*, 1997**
	about 2 m above mixing chamber	n.p.	12-60	
	serving area	n.p.	12	
furfural	production of abrasive and fireproof products	19	50% = 12.9 90% = 37.0 95% = 37.7	BGAA, 1996
furfural	wheel manufacturing	?***	13.8-72.7	Arvin *et al.*, 1975; after Gregg *et al.*, 1997
	mixing operation		90% > 19.7	
furfural	Foundries			Cakrtova and Flek, 1981, referred to by Gregg *et al.*, 1997*
	close to mixer	8	9.6-29.9; AM 18.2	
	working with moulds	7	5.9-21; AM 13.4	
	pouring	2	6.8-7.2; AM 7.0	
	core shop	8	5.8-12.4; AM 8.4	
furfural	foundries****	4	39-42	Gregg *et al.*, 1997
furfural	acidproof construction (plastics and container industry)			BGAA, 1996

	without LEV	11	50% < lod 90% = 9.9 95% = 24.9	
	with LEV	13	50% < lod 90% = 98.4 95% = 147.8	

n.p.: not provided

lod: limit of detection

* : no duration of measurements given;

** : short term measurements, no duration given;

*** : probably stationary measurements in the vicinity of the mixing operation; number of measurements was not given; sampling time over 4 shifts was approximately 23 hours; the range of 10 minute averages is given in the table; during 90% of the sampling time (23 hours) the exposure was higher than 19.7 mg/m^3;

**** : no activities described; no reference made to the authors of the original source, also no duration given.

Exposure modelling

The highest exposure in the formulation step will probably occur during the mixing operation. The formulation itself is assumed to occur in a closed system. Exposure may also occur during moulding, extruding and vulcanisation of the resin or resin bonded abrasive wheels. Company A (1980) mentioned that the concentration of furfural as wetting agent was about 2 to 3%, while Cralley and Cralley (1989) mentioned that the concentration of furfural as a vulcanising agent was about 1%. For the exposure assessment a distinction is made between mixing and moulding and vulcanisation.

Mixing

Exposure will mainly occur during adding of furfural to the mixing tank. Since furfural is stored in tanks and drums, it is assumed that the substance is added via a transfer line. Assuming that the procedure of adding is performed at room temperature, with non-dispersive use, in the presence of local exhaust ventilation, EASE estimates an inhalation exposure of 0.5-3 ppm (2.0-11.8 mg/m^3). Dermal exposure during adding is estimated to be 0-0.1 mg/cm^2/day, assuming non-dispersive use, direct handling and incidental contact. When it is furthermore assumed that the half of both hands (420 cm^2) could be exposed, a total dermal exposure of 42 mg/day is estimated.

The duration of exposure due to this activity is assumed to be limited to up to one hour.

Moulding and vulcanisation of resin

Inhalation exposure can occur due to cold and hot moulding of abrasive wheels, during moulding of miscible phenolic resin products and during vulcanisation of the resin.
In Cralley and Cralley (1989) it is stated that the concentration of furfural in a vulcanising accelerator is about 1%. Company A indicated that the concentration of the substance as a wetting agent is about 3%. A reasonable worst case concentration of furfural in resin is therefore assumed to be 5%.
The highest exposure is assumed to occur during vulcanising the resin, due to the high temperature (100-200°C) and the fact that vulcanisation could occur in an open system. In Cralley and Cralley (1989) it is stated that curing takes place during 15 to 60 minutes at a temperature of 100-200 °C. Assuming non-dispersive use, with LEV, an inhalation exposure of 10-50 ppm (40-197 mg/m^3) is estimated. The vapour pressure of the substance is calculated by EASE as 147 kPa. Considering a reasonable worst case concentration of the substance in the resin of 5%, a partial vapour pressure of 7.4 kPa is calculated. Only when the substance would occur in the resin in a concentration higher than 20%, the 'partial' vapour pressure of the substance would lead to categorisation by EASE as highly volatile, which would result in a higher exposure estimate.
Exposure due to vulcanisation will occur only incidentally (up to 2 hours per day). During the remainder of the day the exposure is assumed to be in the range of the exposure during mixing.
Dermal exposure during hot moulding is assumed to be negligible, as a result of the high temperature and the same holds for vulcanisation. Dermal exposure during cold moulding is estimated as 0.1-1 mg/cm^2/day, assuming non-dispersive use, direct handling and intermittent contact. Assuming an exposed area of the half of both hands (420 cm^2) and a concentration of the substance in the resin of 5%, a total dermal exposure of 21 mg/day is estimated.

Conclusion

Comparing the exposure estimates made by EASE with the exposure data, it appears that the estimate for mixing is reasonably well in line with the measured data, while the exposure estimate for moulding and vulcanisation appears to give higher values. Since no distinction could be made between the exposure measurements performed for moulding, vulcanisation and mixing activities, only one value will be derived for use in the risk characterisation. In this assessment it is assumed that the several activities together could occur in one full shift. The typical value is estimated as 12 mg/m^3 (estimate made by EASE for mixing operation).

The reasonable worst case exposure is estimated as 40 mg/m^3 (based on the values given by Gregg *et al.*, 1997 and by BGAA, 1996). Based on the highest measured exposure levels and the estimate by EASE it is concluded that a reasonable worst case estimate for short term exposure levels (up to 15 minutes) is 100 mg/m^3.
The dermal exposure is estimated as 63 mg/day, the sum of the exposure during mixing and moulding.

Scenario 4: use as an extractant/solvent in the petroleum refining industry

Furfural is used as a selective solvent or extractant for several purposes, such as refining of petroleum oil, extraction of butadiene from C4 streams and decolourising of wood rosin (removing colour bodies from crude FF grade wood rosin; Company A, 1980). Below, the several refining and extraction processes are briefly described. The principle of extraction seems to be similar for all extraction processes.

Oil refining

Furfural is one of the most widely used solvents in the refining of lubricating oils to increase the stability under operating conditions and to improve the viscosity index. Ratios of furfural to oil may vary from as little as 0.25:1 to as much as 10:1 (Company A, 1980).
The furfural refining process involves extraction of raw lubricating stock with furfural at temperatures generally below 121°C to yield refined oil and an extract. The undesirable aromatic and olefinic components of the oil are selectively dissolved by furfural and separated from the desired paraffinic and naphthenic components. In practice, oil enters near the bottom of a counter current extraction column, and furfural is applied at a point near the top. The extract is removed from the bottom of the column with the bulk of furfural. Furfural is separated from the extracted material and recovered for re-use by flash distillation followed by steam distillation to remove the residual traces of furfural. Furfural water mixtures from the steam distillation are readily separated in a decanter by drawing off the lower layer which consists of about 92% furfural and 8% water. This layer is subsequently dried for reuse. Furfural losses are generally 0.03% or less per cycle (Company A, 1980).
In the report of Gregg *et al.* (1997) it is stated that operators in this industry work a 12 hour shift system in which exposure to furfural occurs intermittently, several times a day. The sources and activities that contribute to the potential exposure to furfural include: process sampling of furfural extracts, leaks from pumps, glands etc., and maintenance work on the

system or components attached to the system, process inspection, cleaning of spills, drains and pits. Exposure levels resulting from maintenance work were around 5 mg/m^3. The duration of exposure is not presented.
The other available exposure data from the petrochemical industry are given in Table 4.4.

Extraction of unsaturated C4 and C5 hydrocarbons
Furfural is an extractive distillation medium in the process for purification of butadiene and isoprene. C4 hydrocarbons that have similar boiling points, have widely different soluble characteristics. When distillation is carried out in the presence of furfural, the relative volatility of the several C4 hydrocarbons is altered sufficiently to effect ready separation.
The same principle applies to C5 streams containing isoprene. During these processes furfural is recovered. Furfural losses are extremely small (0.01-0.02% of the circulation rate; Company A, 1980).

Decolourising of wood rosin
Furfural is also used to remove colour bodies from wood rosin to produce a light coloured product, capable of competing with gum rosin used in the soap, varnish and paper industries.
Most of the colour bodies, which produce the characteristic ruby red colour of crude rosin, are removed by fractional steam distillation. Other undesirable colour bodies are extracted with furfural from a solution of the crude rosin in warm gasoline. Since furfural and gasoline are almost totally immiscible at low temperatures, furfural gasoline-rosin mixtures separate into two layers on cooling.
Light coloured resin is obtained from evaporation of the gasoline layer, and the furfural is recovered by distillation of the other layer (Company A, 1980).

Solvent and processing aid for coal and coal products
Separation of anthracene from crude anthracene oil is performed by selective crystallisation or sublimation. It is heated up to 80°C, with a minimum quantity of furfural needed to effect solution at that temperature. Upon subsequent cooling, about 95% of the anthracene crystallises out at a purity of greater than 80%. A second crystallisation from the furfural can raise the anthracene level to approximately 93% with only 2% of carbazole remaining as a contaminant (Company A, 1980).
The principle of all of the above described processes seems to be similar.

Measured data

Gregg *et al.* (1997) provided some exposure data of the petrochemical industry. The Finnish exposure register also provided some exposure data. It is not certain what activities were performed during those measurements. These exposure data are summarised in Table 4.4.

Concawe (1999) presented data from petrochemical companies for (mostly) furfural extraction units in the High-viscosity Index units of the petrochemical companies and for the furfural units in the Base Oil Extraction. These exposure data are summarised in Table 4.5 and Table 4.6.

Table 4.4 Exposure data in the petrochemical industry.

Substance	**Industries/tasks**	**Number of samples**	**Exposure levels (mg/m^3)**	**Reference**
furfural	petrochemical industry			Gregg *et al.*, 1997 *
	8 hr-TWA			
	short term	n.p.	<0.1-48 AM: <0.1-19	
		n.p.	1.9-70 AM: 4.2-32	
furfural	petrochemical plant	n.p.	< 7.3	Pawlowicz *et al.*, 1984 (referred to by Gregg *et al.*, 1997)
furfural	xylose manufacture	7	6.7-59; AM: 21.7	Finnish exposure register, 1997**

n.p.: not provided

* : no activities described, no duration and no number of samples given; it is not known whether it concerns personal or stationary samples; 10 different monitoring regimes were performed leading to different AMs;

** : mean sampling time 97 minutes, ranging from 32-129 minutes; it all concerned continuous activities, with an exposure which could occur continuously.

Table 4.5 Exposure levels to furaldehyde in the petrochemical industry: High-viscosity index unit (Concawe, 1999)

Job	Task	n	Duration (min)	Exposure level (mg/m^3)	Exposure level (8-hr TWA; mg/m^3)	Remarks
Operator	Outside duties FEU	4	665-690	0.12-0.26	0.17-0.37	2 night and 2 day shift operators
Several emission points	Static sampling near possible emission points	8	620-665	< 0.01-7.7	-	1 spillage and three fugitive emissions
Operator	Outside duties FEU	5	695-730	0.1-0.2	0.2-0.3	2 night and 3 day shift operators
Operator	Outside duties FEU	4	677-734	< 0.01	< 0.01	2 night and 2 day shift operators
Operator	Mainly PDU Operations FEU Operator Shut-down preparation	2 2 5	705-720 705-720 660-720	< 0.01 < 0.01-3.2 < 0.01-1.2	< 0.01 < 0.01-4.8 < 0.01-1.7	2 night shift operators low value for steaming exchangers and columns non-typical tasks
Operator	Steaming exchangers, draining, shut-down preparations, general shut-down tasks	8	630-700	< 0.01-2.9	< 0.01-4.2	several non-typical tasks related to shut down; one worker (2.0 mg/m^3) wore a full-face cartridge respirator for part of the work period
Plant cleaner	Several, including removing of end covers, cleaning of MDU, removing and spading of parts	7	570-660	< 0.01-2.7	< 0.01-3.7	several non-typical tasks related to shut down; two workers (1.2 and 2.7 mg/m^3) wore a full-face cartridge respirator
Operator	FEU starting up problems FEU starting up troubleshooting FEU isolation, sampling and no FEU work FEU starting up	2 2 3 2	675 720 625-645 695	4.5-5.2 > 105 < 0.01 4.8-5.8	6.3-7.3 > 160 < 0.01 7.0-8.4	non-typical exposure; no PPE worn non-typical exposure; no PPE worn non-typical: starting up; no PPE worn
Several emission points	Static sampling near possible emission points	8	600-860	< 0.01- > 73	-	spillages and fugitive emissions
Several emission points	Static sampling near possible emission points	6	615-790	1.5 - >40	-	spillages and fugitive emissions
By a tank	Static sampling at one tank on several days	15	600-860	< 0.01- > 83	-	fugitive emissions
Operator	Outside duties FEU	6	660-720	< 1 - 9.8	< 1-15	3 night and 3 day shift operators; no PPE worn
Several emission points	Static sampling near possible emission points	18	575-615	< 1 - 25	-	spillages and fugitive emissions
Operator	Outside duties FEU	4	650-720	< 1 - 1.1	< 1-1.5	2 night and 2 day shift operators; no PPE worn
Operator	Outside duties FEU	4	645-720	< 0.01 - 0.26	< 0.01-0.37	2 night and 2 day shift operators; no PPE worn
Several emission points	Static sampling near possible emission points	8	645-795	0.32 - 9.5	-	spillages and fugitive emissions

n = number of samples FEU = Furfural extraction unit
PDU = Propane deasphalting unit MDU = MEK Dewaxing unit

Table 4.6 Exposure levels to furfural: Furfural Unit of Base Oil Extraction (Concawe, 1999)

Job	n	Duration (min)	Mean (mg/m^3)	Geometric mean (mg/m^3)	GSD	Range (mg/m^3)
Supervisor	11	480	0.102	0.085	2.0	n.p.
Operator	10	480	1.267	0.607	3.9	n.p.
Operator	1	480	0.48			
Operator - routine tasks	71	480	1.1	n.p.	n.p.	< 0.1 - 3.2
Operator - routine tasks	5	60	26	n.p.	n.p.	12 - 45
Routine maintenance tasks	12	60	3.2	n.p.	n.p.	< 0.1 - 8.5

n.p. = not presented

Exposure modelling

The refining or extraction process with furfural will mainly occur in closed systems. Exposure is assumed to be possible during connecting and disconnecting of transfer lines (only incidentally, since furfural is recovered during most processes), as a result of leaks in the system, during inspection of the system, quality control sampling and cleaning and maintenance activities. Both inhalation and dermal exposure is assumed to be possible.

Inhalation exposure during the distillation step is assumed to be low (up to 0.1 ppm (0.4 mg/m^3)), since it is performed in a closed system. Inhalation exposure due to connecting and disconnecting of transfer lines, inspection of the system and quality control sampling is estimated as 0.5-3 ppm (2.0-11.8 mg/m^3), assuming non-dispersive use in the presence of LEV.

Dermal exposure during connecting and disconnecting of a transfer line, and quality control sampling is estimated as 0-0.1 mg/cm^2/day, assuming non-dispersive use, direct handling and incidental contact. Assuming an exposed area of the half of both hands (420 cm^2), the dermal exposure is estimated as 42 mg/day.

Inhalation exposure during cleaning and maintenance is assumed to be higher than during the other activities. In the exposure assessment it is assumed that the equipment is rinsed with a suitable solvent before opening. Before rinsing, the equipment will not have contained pure furfural. The remaining concentration of furfural in the equipment after flushing is estimated as 10% of the concentration in the column before rinsing. Only when the resulting concentration after rinsing is less than 0.6%, the exposure will be negligible; the 'partial' vapour pressure of the substance will then be below 1 Pa (0.6% of 173 Pa = 1 Pa). In the information provided by Company A (1980) it was stated that ratios for furfural to oil might vary from 0.25:1 (concentration approximately 25%) to as much as 10:1 (concentration

approximately 90%). The concentration after rinsing the equipment will therefore always be higher than 0.6%. A reasonable worst case estimate of concentration of furfural in the contamination after flushing is 5%.

EASE estimates an inhalation exposure of 10-50 ppm (39-197 mg/m^3), assuming non-dispersive use, direct handling and dilution ventilation. The 'partial' vapour pressure may vary from 1 to 17.3 Pa (= 0.6-10% of the vapour pressure of furfural at room temperature)

Cleaning and maintenance in this scenario is assumed to be a substantially more small-scale activity, leading to less potential contact as compared to scenario 1. Dermal exposure during cleaning and maintenance in this process is estimated to be 0.1-1 mg/cm^2/day, assuming non-dispersive use, direct handling and intermittent contact. Assuming a concentration of the substance in the column of 5% (reasonable worst case assessment), and an exposed area of half of both hands (420 cm^2), the total dermal exposure is estimated to be 21 mg/day (5*420*0.05).

Conclusion

The exposure data derived from the literature are rather limited with little available data on the number of measurements and activities performed were provided. Recent data from Concawe (1999 provides more details. From these data it appears that stationary sampling for fugitive emissions leads to substantially higher exposure levels than personal sampling of workers. Furthermore it appears that short term exposure levels can be substantially higher than full shift levels. During specific non-typical situations (that occur only infrequently) very high exposure levels were measured. Considering the estimations made by EASE, a higher exposure would occur during cleaning and maintenance. However, when the exposure data are considered, no distinction can be made between processes related to the distillation (quality control sampling, inspection of the process and connecting and disconnecting of the transfer lines) and cleaning and maintenance activities. Therefore, one value will be derived for use in the risk characterisation. It is assumed that the duration of the activities together could occur full shift.

Comparing the exposure data with the estimates made by EASE, it appears that the exposure estimated by EASE is higher than the more detailed exposure data presented by the industry. Therefore, the data of Concawe (1999) will be used as a basis for the estimation of exposure levels to be used in the risk characterisation. However, since the data by Gregg *et al.* (1997) and from the Finnish exposure register (1997) cannot be fully disregarded, a level of 25

mg/m^3 is chosen as a reasonable worst case full shift exposure level. This level is between the highest full shift value in the data by Industry (15 mg/m^3) and the other data (48 mg/m^3). The typical value during the several activities is estimated to be 2 mg/m^3 (derived from exposure data from Concawe, 1999). Based on the limited information on short-term exposure levels and on the estimate by EASE for non-dispersive use and dilution ventilation, a short term exposure level (duration of approximately 15 minutes) of 100 mg/m^3 is concluded.

Dermal exposure is estimated as 42 mg/day during the distillation step, and as 21 mg/day due to cleaning and maintenance activities.

Conclusion of the exposure assessment

In Table 4.7 the conclusions of the exposure assessment are summarised.

Table 4.7 Conclusions of the exposure assessment

Scenario	**Activity**	**Frequency**	**Duration**	**Inhalation – RWC**		**Inhalation - Typical concentration**		**Dermal**	
			(hr)	**(mg/m^3)**	**Method**	**(mg/m^3)**	**method**	**mg/cm^2/day**	**dose (mg/day)**
Production	general (closed system)	225	2-6	0.4	EASE	negligible	EASE	negligible	negligible
	production activities	225	4-6	40	Lit. exp.	10	EASE, lit.	0.1	42
	short term	225	0.25	80	Exp.				
	full shift	225	8	30[#]	Calculated	7.5[#]	calculated		
	cleaning and maintenance	50-100	6-8	70[##]	Lit. exp.	40	EASE	0.5	650
	cleaning and maintenance short term	50-100	0.25	120	Lit. exp.				
Product derivatives	general	100-200	2-6	0.4	EASE	negligible	EASE	negligible	negligible
	adding	100-200	2-4	12	EASE, exp.	2	EASE, exp.	0.1	42
	full shift	100-200	8	6[#]	Calculated	1[#]	calculated		
Production refractories etc.	mix, mould etc.	100-200	6-8	40	Lit., exp.	12	EASE	0.1	63
	short term	100-200	0.25	100	Lit., EASE				
Use of furfural	refining etc.	225	6-8	25	Lit.	2	lit.	0.1	42
	short term[*]	225	0.25	100	Lit., EASE				
	cleaning and maintenance	50-100						0.05	21

Full shift exposure is calculated by the following formula:

	$E_{a1}*d_{a1} + E_{a2}*d_{a2} / d_t$ in which: $E_{a1,2}$ = estimated exposure during activity 1 or 2; $d_{a1,2}$ = duration of exposure for activity 1 or 2 (to obtain a reasonable worst case estimate, the longest duration for the highest exposure activity is taken; the total exposure duration in these cases is assumed to be 8 hours); d_t = total duration of the exposure (full shift; normally 8 hours)
##	short-term exposure level is 120 mg/m^3 (15 minutes)
RWC	reasonable worst case exposure
Exp.	expert judgement
lit.	literature
•	including cleaning and maintenance

4.1.1.3 Consumer exposure

Consumer exposure may occur from products to which furfural is added intentionally and products naturally containing furfural. The latter will be considered under 'Indirect exposure via the environment' (4.1.1.4).

With respect to the intended use, furfural is added in several products (see chapter 4.1.1.1). From the mentioned uses the use as flavouring substance and fragrance are the most important for consumer risk assessment. However, the exposure information provided by several countries did not mention any of these consumer products. Canada, Denmark, U.S., Sweden, Austria, Spain, UK, Finland and the Czech Republic responded to the exposure questionnaire. Most countries do not know whether there is consumer exposure. Norway stated that furfural is not used in consumer products as mentioned in the Norwegian Product Register. Denmark stated that 12 products containing furfural were mentioned in the Danish Product Register. It is unclear which of these 12 products are available for consumers. However, as most of these products containing furfural were produced in quantities <1 ton, with only three products containing 10-80% furfural produced at a maximum of 5 tonnes, it is assumed that exposure to other products will be of minor importance.

Rather old data indicate that furfural can be found as a fragrance material in soap, detergents, creams and lotions and in perfumes. The concentrations in these products vary from 0.0005 to 0.1% (Opdyke, 1978). No data are available on the actual use of furfural as a fragrance.

In the EU, furfural is used as a flavouring substance. It is known to be used in 10 separate food categories, including baked goods, frozen dairy, meat products, soft candy, gelatin puddings, non-alcoholic beverages, alcoholic beverages, gravies, hard candy and chewing gum. The average maximum use levels in these food categories range from 4.2 mg/kg in gravies to 63 mg/kg in meat products (Adams *et al*., 1997).

In the USA furfural has a Flavour and Essence Manufacturers Association (FEMA) GRAS (Generally Recognized As Safe) status. In 1993, the EU Scientific Committee for Food and WHO came to the conclusion that direct use of furfural as a flavouring substance is not appropriate (WHO, 1993; SCF, 1993), and that its use as a solvent should be restricted to situations where alternatives are not available, e.g. for the purification of food oil extraction

of unsaturated components. Carry-over into food should be reduced to the lowest extent technically possible (WHO, 1993). In a re-evaluation of furfural, however, WHO considered the use of furfural as flavouring agent to be of no safety concern to humans (WHO, 2001). In addition, in 2004 the Panel on Food additives, Flavouring substancess, Processing aids and Materials in contact with food [AFC] of the European Food Safety Authority (EFSA, successor to the former SCF) concluded that there was sufficient data to derive an ADI for furfural of 500 µg/kg bw/d (EFSA, 2004).

Furfural is also on the EU list of assessed food contact materials (the "Synoptic Document"; EC, 2003) as a list 7 substance. Incorporation into this list followed the release of an opinion by the SCF in 1986 (SCF, 1987). The current entry is no longer up to date. According to EC directive 2002/72/EC (EC, 2002) furfural may not be used as a constituent of food contact materials.

Furfural is known to occur in tobacco smoke. A single cigarette may provide up to 400 µg of furfural. Furfural was used in the past as a flavouring substance in tobacco. It may also originate from the combustion of the tobacco itself (Sleijffers *et al.*, 2006).

It is also mentioned that furfural is used as solvent for shoe dye (HSDB, 1997), however, no data on concentrations are available.

Furfural was qualitatively detected in indoor air above a floor finished with a natural oil 4-5 months after its application (HSDB, 1997).

Furfural was also detected as an emission from the burning of jack pine, cedar, oak and ash in a fire place (HSDB, 1997).

The total indoor concentrations of nine aldehydes amounted 21.75 to 62.27 ppb, from which furfural was the most abundant. The outdoor concentration amounted 10.88 to 19.12 ppb. However, the furfural concentration was not mentioned (Zhang *et al.,* 1994).

Based on the fact that quantitative data are only available for use as fragrance material and as flavouring substance, two exposure scenarios are considered for furfural: I. Fragrance material (in case there is actual use of furfural as fragrance) and II. Flavouring substance.

Scenario I

When furfural is added as fragrance material the main exposure routes are the inhalation or dermal route. Furfural concentrations vary from 0.005-0.03% in soap, from 0.0005-0.003% in detergents, from 0.0025-0.01% in creams and lotions and from 0.04-0.1% in perfume (Opdyke, 1978). More recently, the Research Institute for Fragrance Materials (RIFM) estimated consumer exposure to furfural in fragranced cosmetic products. The SCCNFP (2004) have adjusted the RIFM data according to the SCCNFP Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 5th revision. The estimate of consumer exposure as calculated by the SCCNFP (2004) is adopted in this exposure assessment and is comparable to the method described in the TGD. Quantitative information is presented in the sections below.

Cosmetic products

When furfural is used in perfume/eau de toilette, inhalation of the aerosol generated when spraying the perfume /eau de toilette is considered minor as the aerosol will be diluted in a bathroom/toilet (5 m^3) and exposure will be limited to 10-15 minutes. Hence, it is assumed that there is only dermal exposure when the perfume/eau de toilette is applied.

The SCCNFP made a calculation of the dermal exposure to furfural in cosmetic products. The results are given in Table 4.8.

Table 4.8. Calculation of exposure to furfural in cosmetic products.

Type of product	**Application quantity in g per application**	**Application frequency per day[c]**	**Retention factor[d] (%)**	**Fragrance compound in product[e] (%)**	**Furfural in fragrance compound[f] (%)**	**Furfural in product (ppm)**	**Exposure to furfural (µg/day)**	**Exposure to furfural for 60 kg person (µg/kg/day)**
Body lotion	8	1	100	0.4	0.036	1.44	11.52	0.192
Face cream[a]	0.8	2	100	0.3	0.036	1.08	1.728	0.029
Eau de toillete[b]	0.75	1	100	8.0	0.036	28.8	21.6	0.36
Fragrance cream	5	0.29	100	4.0	0.036	14.4	20.8	0.348
Deodorant	0.5	1	100	1.0	0.036	3.6	1.8	0.03
Shampoo	8	1	1	0.5	0.036	1.8	0.14	0.002

Bath products	17	0.29	1	2.0	0.036	7.2	0.355	0.006
Shower gel	5	2	1	1.2	0.036	4.3	0.432	0.007
Toilet soap	0.8	6	1	1.5	0.036	5.4	0.259	0.004
Hair spray	5	2	1	0.5	0.036	0.13	0.18	0.003
Toothpaste	1.4	2	17	1.0	0.002	0.2	0.095	0.002

[a] including make up and foundation

[b] includes all hydroalcoholic products (i.e. prfums, aftershaves, colognes etc.)

[c] to allow comparison with animal studies, use is expressed as a daily exposure although in fact it is based on weekly figures in order to take account of usage patterns which would not otherwise be evident.

[d] retention factors for skin are taken from "Notes of Guidance for Testing of Ingredients for Their Safety Evaluation"

[e] concentration of the fragrance mixture in a cosmetic product has been determined by senior technical representatives of the cosmetic industry

[f] concentration of a fragrance ingredient in a fragrance mixture is based on data obtained by the fragrance industry from the examination of commercialized formulations containing the fragrance ingredient (expressed as the upper 97.5th percentile concentration)

The total consumer exposure to the fragrance ingredient is determined by adding figures for the different product types. In view of all the above assumptions, this figure has to be regarded as conservative; it is most unlikely that a consumer will consistently use a number of different consumer products which are all perfumed with the upper 97.5th percentile level of the fragrance ingredient. On the basis of Table 4.8 it is estimated that the maximum external dermal exposure of furfural is 1 µg/kg bw/day. This value will be taken forward to the risk characterisation.

Scenario II

When furfural is used as a flavouring substance in food the main exposure route is by ingestion. Furfural is used in 10 separate food categories. The average maximum use levels in these food categories are given in Table 4.9.

Table 4.9 Average maximum use levels of furfural in food.

Food type	Concentration furfural in mg/kg food	Reference
Baked goods	50.0	Adams *et al*., 1997
Frozen dairy	44.3	Adams *et al*., 1997
Meat products	63.2	Adams *et al*., 1997
Soft candy	52.6	Adams *et al*., 1997
Gelatin puddings	32.8	Adams *et al*., 1997
Non-alcoholic beverages	28.4	Adams *et al*., 1997
Alcoholic beverages	7.0	Adams *et al*., 1997
Gravies	4.2	Adams *et al*., 1997
Hard candy	21.0	Adams *et al*., 1997
Chewing gum	56.4	Adams *et al.,* 1997

Based on the most recent reported annual volumes of furfural as flavouring substance in the USA (3470 kg) and Europe (3613 kg), FEMA (Flavour and Extract Manufacturers Association) estimated the daily 'per capita' intake [2)] (eaters only) of furfural from use as a flavouring ingredient at approximately 8 and 9 µg/kg bw for the USA and Europe, respectively (WHO, 2001). The value of 9 µg/kg bw/d for Europe will be used for risk assessment. Next to this estimated daily "per capita intake", the EFSA-AFC panel (2004) used a theoretical added maximum daily intake (TAMDI) which is estimated to be 136 µg/kg bw. This TAMDI estimate has been calculated from intake estimates of flavourable beverages, foods and "particular food", under the assumption that all such foods eaten by consumers contain furfural at all times and that these foods are flavoured at maximum permitted furfural concentrations. Thus TAMDIs are worst case estimates, which may be orders of magnitude above the actual intake (SCF, 1999). The latter value will also be taken forward to the Risk Characterisation.

2) intake (µg/d) calculated as follows: [[annual volume, kg) x ($1x10^9$ µg/kg)]/[population x correction factor x 365 days]], where population (10%, 'eaters only') = 26 x 10^6 for the USA and 32 x 10^6 for Europe; correction factor (0.8 for the USA and 0.6 for Europe) represents the assumption that only 80%/60% of the annual volume of a flavouring substance was reported in poundage surveys. Intake (µg/kg bw/d) calculated as follows: (µg/d)/body weight, where body weight = 60 kg.

4.1.1.4 Indirect exposure via the environment

The environmental emissions of furfural for the production, processing and formulation sites are summarized in Table 3.16 (section 3.1.5). On the basis thereof the estimated furfural concentrations in air, drinking water and food for all relevant life-cycle steps are presented in Table 4.10 (EUSES calculation, version 2.0.3). Table 4.10 shows that the concentrations in air, drinking water and food all are the highest for scenario Vb (formulation for manufacturing refractories, site 2). For this local scenario the total daily intake is calculated to be 11 µg/kg bw/day (see Table 4.11). The main routes of exposure in scenario Vb are air (41%), drinking water (28%) and intake of leaf crops (28%). Regional exposure is described in Table 4.12.

Table 4.10 Furfural concentrations in various environmental compartments relevant for exposure human indirectly via the environment (local scale; all relevant scenario's).

	I-a	I-b	II	III-c	IV-b	IV-c	IV-d	IV-e	V-b	VI
Concentration in air, C_{air} (µg/m)^3	2.1E-03	2.67	0.240	3.81	0.764	0.0493	0.0817	0.296	15.2	11.4
Concentration in drinking water, C_{drw} (µg/l)	8.33	1.04	0.134	8.75	34.7	0.335	3.74	13.9	104	77.8
Concentration in wet fish (mg/kg)	1.18E-02	1.56E-04	1.56E-04	0.0124	0.049	4.74E-04	5.28E-03	0.0197	0.147	0.11
Concentration in root tissue (mg/kg)	2.27E-03	1E-03	1.29E-04	3.42E-03	9.67E-03	1.22E-04	1.05E-03	3.89E-03	0.0336	0.0252
Concentration in leaves (mg/kg)	4.65E-05	3.04E-02	2.73E-03	0.0434	8.8E-03	5.63E-04	9.41E-04	3.41E-03	0.174	0.13
Concentration in meat (mg/kg)	3.66E-07	1.94E-06	1.76E-07	3.08E-06	2.06E-06	4.97E-08	2.21E-07	8.2E-07	1.53E-05	1.15E-05
Concentration in milk (mg/kg)	3.66E-06	1.94E-05	1.76E-06	3.08E-05	2.06E-05	4.97E-07	2.21E-06	8.2E-06	1.53E-04	1.15E-04

C_{air}: annual average local PEC in air (total)
C_{drw}: maximum value of annual average local PEC in surface water multiplied by a purification factor (in this case 1) or concentration in groundwater

Table 4.11 Daily doses (mg/kg bw/day) of furfural through intake of food and air (local scale; all relevant scenario's).

	I-a	I-b	II	III-c	IV-b	IV-c	IV-d	IV-e	V-b	VI
Daily dose through intake of air[1]	6.67E-07	8.47E-04	7.62E-05	1.21E-03	2.43E-04	1.57E-05	2.59E-05	9.41E-05	4.84E-03	3.63E-03
Daily dose through intake of drinking water	2.38E-04	2.97E-05	3.82E-06	2.5E-04	9.9E-04	9.58E-06	1.07E-04	3.98E-04	2.96E-03	2.22E-03
Daily dose through intake of fish	1.93E-05	2.56E-07	2.56E-07	2.03E-05	8.04E-05	7.78E-07	8.67E-06	3.23E-05	2.41E-04	1.81E-04
Daily dose through intake of leaf crops	7.97E-07	5.21E-04	4.69E-05	7.44E-04	1.51E-04	9.65E-06	1.61E-05	5.85E-05	2.98E-03	2.23E-03
Daily dose through intake of root crops	1.25E-05	5.49E-06	7.07E-07	1.87E-05	5.31E-05	6.67E-07	5.79E-06	2.13E-05	1.84E-04	1.38E-04
Daily dose through intake of meat	1.57E-09	8.33E-09	7.57E-10	1.33E-08	8.85E-09	2.14E-10	9.52E-10	3.52E-09	6.6E-08	4.95E-08
Daily dose through intake of milk	2.93E-08	1.55E-07	1.41E-08	2.47E-07	1.65E-07	3.98E-09	1.78E-08	6.57E-08	1.23E-06	9.22E-07
Local total daily intake	2.71E-04	1.4E-03	1.28E-04	2.24E-03	1.52E-03	3.63E-05	1.63E-04	6.04E-04	0.0112	8.41E-03

[1] the bioavailability for oral intake is considered to be 90%; the bioavailability for inhalation is considered to be 100%.

Table 4.12 Daily doses (mg/kg bw/day) of furfural through intake of food and air (regional scale).

Daily dose through intake of air	5.51E-07
Daily dose through intake of drinking water	3.16E-06
Daily dose through intake of fish	2.56E-07
Daily dose through intake of leaf crops	3.43E-07
Daily dose through intake of root crops	1.22E-07
Daily dose through intake of meat	2.61E-11
Daily dose through intake of milk	4.87E-10
Regional total daily intake	4.43E-06

Natural occurrence

Furfural is virtually ubiquitous in nature. It is formed, naturally or during processing or cooking, from acid hydrolysis or heating of polysaccharides which contain pentose and hexose fragments (Adams *et al*., 1997; MAFF, 1997). According to WHO (1993) furfural is also transferred into food from its use as extraction solvent or as component of flavouring mixtures. It is reported that furfural has been found in several essential oils from plants, in distillation waters of several essential oils, in Ceylon cinnamon essential oil and in oils as lemon grass, calamus, eucalyptus, sandalwood and tobacco leaves (HSDB, 1997).

Furfural has been identified as a natural volatile compound in many foods such as fruits (apples, apricots, cherries, citrus fruits, berries, grapes, etc., at levels up to 0.34 mg/kg), vegetables (carrots, cabbage, onions, potatoes, at levels up to 0.01 mg/kg), alcoholic beverages (beer, brandies, rum, whiskey, wine, at levels up to 67 mg/kg), coffee (at levels up to 255 mg/kg) (Feron *et al*., 1991), and bread and bread products (at levels up to 26 mg/kg) (Adams *et al*., 1997).

Furfuryl alcohol, which can be readily converted to furfural *in vivo* has been found in highest concentration in heated skimmed milk (230 mg/kg) and coffee (90-881 mg/kg: it is not clear whether the origin is the milk or beans). FEMA calculated a total potential daily intake of approximately 300 µg/kg bw/day for furfural and precursors of furfural (i.e. furfuryl alcohol and furfuryl esters) from natural occurrence in food (Adams *et al*., 1997).

Conclusion

With EUSES, for local exposure the highest estimated daily intake dose via food and air was found for scenario Vb, formulation for manufacturing refractories, site 2 (11 µg/kg bw/day). The main exposure routes are air, drinking water and intake of leaf crops.

For regional exposure, the total daily intake estimated by EUSES is 4 ng/kg bw/day. For the natural occurrence of furfural in food, FEMA calculated a total potential daily intake of approximately 300 µg/kg bw/day for furfural and precursors of furfural from natural occurrence in food. The total daily intake estimated by EUSES can be considered negligible compared to the natural occurrence.

4.1.1.5 Combined exposure

Humans can be exposed to furfural during work, via consumer products (flavourings and fragrances) and indirectly via the environment. Table 4.13 gives an overview of the combined exposure to furfural.

Table 4.13 Overview of combined exposure to furfural

	Exposure in µg/kg bw/day		
Workers exposure	oral	inhalatory	dermal
Production: - Full shift - cleaning and maintenance		4300 10000	600 9300
Production of derivatives Full shift		900	 600
Production of refractories Mix, mould, etcetera		5800	900
Use of furfural - refining, etcetera - cleaning and maintenance		3600 -	600 300
Consumer exposure			
cosmetic products (fragrances)			1
food flavouring substance	9-136		
Indirectly exposed via the environment			
local (scenario Vb, highest exp.)	11		
regional (EUSES calculation)	0.004		
natural occurrence in food (estimation by FEMA)	300		

4.1.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

4.1.2.1 Toxico-kinetics, metabolism and distribution

Animal data

Nomeir *et al.* (1992) studied the toxicokinetics of furfural by single dose administration of ^{14}C-furfural by gavage and doses ranging from 0.13-12.5 mg/kg bw using male Fischer 344 rats (4/group). The vehicle used was corn oil. After 72 hours at all doses, 85% of the radioactivity was excreted in urine, primarily in the first 24 hours, and 2% in the faeces. At the highest dose level, 7% was exhaled as CO_2. At the highest dose level, in total about 0.6% (or less) was found in the tissues examined. The concentrations of ^{14}C found in liver and kidneies were proportional to the dose. For the lower dose levels no concentrations could be found in the other tissues studied (plasma, blood cells, heart, lung, brain, adipose tissue, skeletal muscle, spleen, thymus). Highest concentrations of ^{14}C were found in liver and kidney with the lowest concentration in the brain. The following metabolites were found in urine: furoylglycine (76-80% of the radioactivity), furoic acid (1% of the radioactivity), and furanacrylic acid (3-4% of the radioactivity). Over this dose range, the relative amounts of the metabolites were linear. No unchanged furfural was found in urine. Furanacryluric acid was not determined. Based on this study, it is concluded that after oral treatment (gavage) with ^{14}C-furfural, absorption by the gastro-intestinal tract of rats was at least 90-95%.

In another study (Parkash and Caldwell, 1994), male and female Fischer 344 rats (5 animals/group) were administered single gavage doses of ^{14}C-furfural at 1, 10, or 60 mg/kg bw and male and female CD1 mice (5 animals/group) were administered single gavage doses of 1, 20, or 200 mg/kg bw. More than 60% of the radioactivity was found in urine during the first 24 hours in both species. After termination of the study (72 hours), faecal elimination was 3-7%, 5% was exhaled, less than 1% was found in the carcasses, while 76-100% of the radioactivity was found in urine. The following metabolites were found in urine:

* Furoylglycine (± 80% of the radioactivity in all dose groups for rats and mice);
* Furoic acid (± 2% of the radioactivity in high dose male rats and mice; up to 10% in mid and high dose female mice. In the other dose groups, it was not detected);

* Furanacryluric acid (10-35% of the radioactivity in all dose groups for rats and mice);
* Furanacrylic acid (2% of the radioactivity in high dose female rats only; in all other dose groups it was not detected);
* One unidentified very polar metabolite (2% of the radioactivity in all dose groups for male rats; 1% in high dose male mice. In all other dose groups it was not detected)

The increased excretion of the free acids at higher dose levels indicates that glycine conjugation was capacity limited, probably by the supply of endogenous glycine for conjugation. Minor differences in the metabolic profile as a function of dose size, sex, and species were found. It is concluded that absorption of furfural by the gastro-intestinal tract of mice and rats exposed by gavage, is 81-100% based on the results of this study.

In a study of Laham and Potvin (1989), 10 male Sprague-Dawley rats were orally dosed (by gavage) with furfural (single dose of 50 mg/kg bw in distilled water). After 3 consecutive days, the following metabolites were found in urine (analyzed by GC-MS): furoylglycine (33.5% of the dose), unconjugated furoic acid (2.8% of the dose), furanacryluric acid (1.6% of the dose), and furanacrylic acid (1% of the dose). Based on this study, at least 39% of furfural is absorbed by the gastro-intestinal tract in rats. The remaining 60% of the administered dose was not accounted for. Because of the poor recovery, the study is considered of limited relevance.

The following metabolic pathway is proposed for rats and mice after oral dosing of furfural (Irwin, 1990). Biotransformation of furfural may take place in two ways. The major part is oxidized to furoic acid, which is excreted either free or conjugated with glycine (i.e., as furoylglycine). The smaller part condensates with acetic acid giving rise to 2-furanacrylic acid which is excreted in conjugated form (i.e., as 2-furanacryluric acid), see figure 4.1.2.1. However, figure 4.1.2.1 does not indicate the pathway leading to CO_2-production.

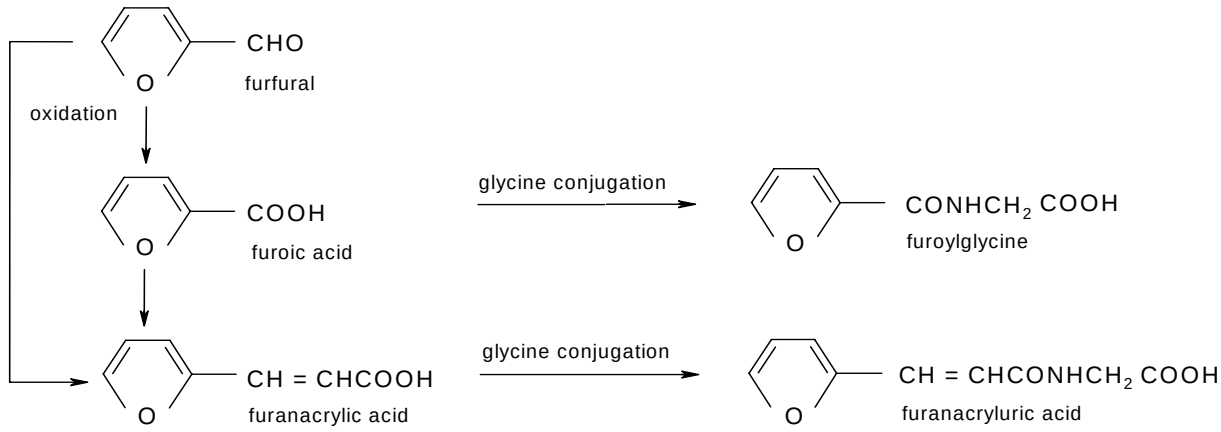


Figure 4.1.2.1 Metabolic pathway in rats and mice, orally exposed to furfural, as proposed by Irwin (1990)

Human data

Flek and Sedivec (1978) describe four different experiments in which human volunteers were exposed to furfural by inhalation and skin contact.

In the first experiment males (n=3-4) were exposed by inhalation (whole body) for 8 hours to furfural concentrations of 15, 20, and 31 mg/m^3. Inspired and expired air were analyzed and pulmonary retention, i.e., the difference of furfural concentration in inspired and expired air, was determined (once between the 2nd and 3rd and once between the 5th and 7th hour of exposure). The mean value of 78% (75-82%) pulmonary retention was unrelated to the level and duration of exposure. In the urine samples taken, no unchanged furfural was detected. Free furoic acid was detected in negligible amounts (not quantified). Furoylglycine was determined as main metabolite (not quantified). The amount of furanacryluric acid ranged from 0.5 to 5%. The amount of furoylglycine excreted within 24 hours was higher in all subjects than would correspond to the retained quantity of furfural (120-130%), indicating dermal uptake by whole body exposure. Less than 1% was exhaled unchanged (only furfural was analyzed in inspired and expired air).

In the second experiment males (n=4) were exposed by inhalation only for 8 hours to a furfural concentration of 30 mg/m^3. Elimination of 'total furoic acid', i.e., furoic acid free or bound to glycine, in urine was determined. The excreted 'total furoic acid' reaches its maximum at the end of exposure and then decreases exponentially to its normal level (the

normal level was reached 11 hrs after termination of exposure). Biological half-life of absorbed furfural in humans is about 2-2.5 hours based on 'total furoic acid' in urine.

In the third experiment four males remained for 8 hours in a room with a furfural contaminated atmosphere (30 mg/m^3). Uptake by inhalation was avoided by breathing uncontaminated air via a gas mask. Again, elimination of 'total furoic acid' in urine was determined. The excreted 'total furoic acid' reached its maximum at the end of exposure and then decreased exponentially to its normal level (the normal level was reached 6 hrs after termination of exposure). It was estimated that uptake of furfural vapour via the skin in this experiment (temperature and relative humidity are not mentioned) was about 30% of the uptake via the respiratory tract as measured in the second experiment. It is reported that the excreted amount was rather variable in different individuals and depended on the microclimate. Under higher temperatures (27-29^{o}C and a relative humidity of 70-80%) a twofold excreted amount of 'total furoic acid' was reached. These observations were not quantified.

In the last experiment, three males submerged their left hand up to the wrist in a vessel containing pure furfural (liquid) for 15 minutes. Inspiration was avoided by wearing a respiratory mask. Again, 'total furoic acid' in urine was determined. The excreted 'total furoic acid' reached its maximum at about 2 hrs after termination of exposure. From the total amount of excreted metabolite it is calculated that about 26.6 mg furfural (ranging from 20.8 to 37.9 mg) was absorbed by the hand surface (i.e., 3 µg/cm^2/min, range 2.2 - 4.5 µg/cm^2/min). It is noted that these experiments were poorly reported.

Conclusion

After oral exposure of rats to ^{14}C-furfural, at least 90% is absorbed from the gastro-intestinal tract. After inhalatory exposure to furfural, pulmonary retention in humans was 78%. When humans are exposed to furfural vapours (30 mg/m^3), the dermally absorbed quantity of furfural is about 30% of the amount absorbed through inhalation. After dermal exposure to liquid furfural, about 3 µg furfural per cm^2 of skin per minute is absorbed in humans.

Limited data are available on the distribution of furfural after oral administration in animals. At 72 hrs post dosing, in total about 0.6% (or less) of a radioactive dose was found in the tissues examined. The concentrations of ^{14}C found in liver and kidney were proportional to

the dose. Highest concentrations were found in liver and kidney with the lowest concentration in the brain. Data are too limited to speculate about placental transfer or secretion into milk.

It is proposed that biotransformation of furfural in rats and mice may take place in two ways. The major part is oxidized to furoic acid, which is excreted either free or conjugated with glycine (i.e., as furoylglycine). The smaller part condensates with acetic acid giving rise to furanacrylic acid which is excreted in conjugated form (i.e., as furanacryluric acid). An unidentified metabolite was found in urine of rats and mice. Minor differences in metabolic profile in animals as a function of dose size, sex, and species are found. The main metabolite in humans found in urine after inhalation exposure is furoylglycine. Besides furoylglycine, furanacryluric acid was found. Furoic acid was found in negligible amounts in human urine after inhalation. Differences between the metabolites observed in humans and animals, may be explained by differences in exposure route and duration, and the dose levels administered (e.g., free furoic acid may be formed due to an overload of the glycine conjugation) and is not necessarily caused by species differences.

In animals after oral exposure, 76-100% of the radioactivity was found in urine, faecal elimination was 2-7%, 5-7% was exhaled as CO_2, and less than 1% is found in the carcasses. Biological half-life of furfural after inhalation in humans is about 2-2.5 hours.

4.1.2.2 Acute toxicity

Animal data

Oral

The LD_{50} values for rats varied between 50 and 149 mg/kg bw (Fassett, 1963; Castelli *et al.*, 1967; Kuznetsov, 1966, 1967 (all cited in DECOS, 1996); Sax, 1984). More recent rat studies indicate that the acute oral LD_{50} is to be found at the higher end of this range: in a developmental toxicity range-finding study (Nemec, 1997a) only 1/8 deaths were observed at 150 mg/kg with 10 days dosing (see section 4.1.2.9). Also, the NOAEL for repeat gavage dosing in the NTP dose ranging study was 120 mg/kg (Irwin 1990), and NOAELs of 100 (HDT) and 96 mg/kg/day, respectively, were observed by Chengelis (1997) and Appel (2001a) in 28 day studies (see section 4.1.2.6).

The LD_{50} values for mice, dogs, and guinea pigs were higher. They varied between 400-500 mg/kg bw for mice (Fassett, 1963; Lucik *et al*, 1961; Kuznetsov, 1967 (all cited in DECOS, 1996)), 650-950 mg/kg bw for dogs (Fassett, 1963; Deichmann, 1969 (both cited in DECOS, 1996)). The LD_{50} for guinea-pigs was 541 mg/kg bw (Kuznetsov, 1967 cited in DECOS, 1996). Details on all these studies are lacking.

In a study by Shimizu and Kanisawa (1986), morphological changes of the liver were studied. After a single gavage administration of aqueous solutions of 50 mg furfural/kg bw to 32 male six-week old Wistar rats, at 6, 12, 24 and 48 hours after dosing, 8 animals per time point were sacrificed. Results were compared to a group of control rats. Livers from treated animals showed scattered eosinophilic globules and a significant increase in the number of mitotic hepatocytes, most prominently after 6 hours. The incidence of mitosis at 6 hours was 24.88 ± 8.52 in the treated animals compared with a control incidence of 1.75 ± 0.43 and incidences decreased at subsequent analysis, suggesting rapid recovery from a single dose. Further, after the single administration, there was no zonal or massive necrosis. Mortality was not reported.

Inhalation

LC_{50}-value for the rat after 1 hour exposure, was found to be 4075 mg/m^3 (Terrill *et al.*, 1989; Terrill, 1987), after 4 hour exposure, 600 (Marhold, 1972 cited in DECOS, 1996) and 924 mg/m^3 (Terrill *et al.*, 1989). An LC_{50} of 688 mg/m^3 in rats (Terrill *et al.*, 1989) and of 490 mg/m^3 in mice were reported after exposure to furfural for 6 hours (Woods and Seevers, 1955).

Exposure of 10 rats (5 males and 5 females) for either 3 or 6 hours to 1280 mg/m^3 resulted in death of all animals during or after the first exposure, whereas a 3 hours exposure to 640 mg/m^3 did not induce any mortality. Exposure for 6 hours to 640 mg/m^3 resulted in the death of 1 out of 10 animals after one, four and five days and two animals died after 8 days of treatment (Muijser, 2001; Arts *et al.*, 2004).

Apart from the studies by Terrill (1987) and Muijser (2001), for most of these studies details are lacking.

Signs of toxicity in male and female Sprague-Dawley rats (5/sex/group) *during* exposure for one hour to furfural concentrations of 1922, 3910, 4708, and 7223 mg/m^3 include languid

behaviour (in all exposure groups) and prostration, squinted eyes, and polypnea (in the highest exposure group). After exposure to 3910 and 4708 mg/m^3 for one hour the signs included prostration, respiratory distress, and increased secretory responses. The incidences of these findings generally followed a treatment-related pattern (no data are available about the severity). After exposure to 7223 mg/m^3 for one hour all rats were found dead after 30 minutes post-exposure. In the other dose groups most survivors fully recovered within the 14-day post-exposure period. Treatment-related findings at necropsy consisted of pale spleen and changes in the respiratory tract. The report does not discriminate between effects seen in survivors and non-survivors. In this study a 1 hour LC_{50} of 4075 mg/m^3 was established (Terrill, 1987; Terrill *et al.*, 1989). No effects were observed on body weight (Terrill *et al.*, 1989; Terrill, 1987; Gupta *et al.*, 1991).

Dermal

An LD_{50} of >310 mg/kg bw in rabbits (Moreno, 1976 cited in Opdijke 1978), and <10000 mg/kg bw in guinea-pigs (Fassett, 1963 cited in DECOS, 1996) were found. A dose of 620 mg/kg bw is reported to be lethal to rabbits (Moreno, 1976 cited in Opdijke, 1978). However, details on these studies are lacking. In a limited reported study by Woods and Seevers (1955), all rabbits (n=6, strain unknown) died after 12-hour dermal exposure (occlusive conditions) to undiluted furfural, 1000 mg/kg bw. Amounts ranging from 45-500 mg/kg bw to the skin of 22 rabbits were without fatal effect.

Subcutaneous

LD_{50}-values after subcutaneous injection were 148 mg/kg bw in the rat (Deichmann, 1969 cited in DECOS, 1996), 214-850 mg/kg bw in the dog (Jeffroy and Servauz, 1896 cited in DECOS, 1996; and Sax, 1984) and 119-223 mg/kg bw in the rabbit (Sax, 1984; Castellino *et al.*, 1963).

Intraperitoneal

LD_{50}-values were 102 mg/kg bw in the mouse (Klucik *et al.*, 1961 cited in DECOS, 1996) and 20-121 mg/kg bw in the rat (Fassett *et al.*, 1963; Castelli *et al*., 1967, both cited in DECOS, 1996).

Twenty-one male Wistar rats were divided into three groups of seven rats. The first group received 20 mg/kg bw furfural intraperitoneal in 0.1 ml propylene glycol, and the second group 50 mg/kg bw. The controls were given 0.1 ml propylene glycol intraperitoneal. Six hours after the injection, animals were autopsied and liver histoenzymology was studied. The furfural exposure led to a concentration-related decrease of succinic dehydrogenase and ATP-ase activity, and to a concentration-related increase in the activity of acid phosphatase and DNA-se II. The activity of alkaline phosphatase was depressed equally in both groups. Histoenzymatic and morphological investigations evidenced cell injury, which results in an increased intracellular catabolic process (Jonek *et al.*, 1975). Konecki *et al.* (1974) found that exposure led to damage of the mitochondria and of their enzymes in the small intestine.

Human data

The reflex effect of small concentrations of furfural vapour on humans, the threshold of its smell, its effect on the light sensitivity of the eye, and on the electric activity of the cerebral cortex, were studied by Ubaydullayev (1970). Due to the unclear toxicological relevance of the studied parameters and the absence of nervous symptoms in animals exposed to rather high concentrations of furfural vapour for prolonged periods of time, this study is not considered useful for risk assessment.

No relevant and reliable data are available on the acute toxicity of furfural in humans except for irritating effects (see paragraph 4.1.2.3 Irritation).

Conclusion

Although it is unlikely that these studies were performed according to OECD or EU guidelines, and most data were of older date and only limitedly reported, the rapporteur considers the amount of data available from different publications sufficient to fulfil the Annex VIIA requirements for acute oral and inhalation toxicity. For acute dermal toxicity only limited data were available. An LD_{low} of 620 mg/kg bw for rabbits has been reported.

However, details on this study are lacking.

Based on the data available, the CMR Working Group decided (November 2003) that furfural is toxic (T) after oral and inhalation exposure and harmful in contact with skin and should be classified as T; R23/25 and Xn; R21 (under Directive 67/548/EEC).

4.1.2.3 Irritation

Animal data

Skin

Furfural is reported to induce skin irritation at a level of 500 mg/24 hours in rabbits (DECOS, 1996; Sax, 1984), but details (e.g., scores) are not available. Furthermore, intensive but reversible skin irritation was reported in guinea pigs after three daily 4-hour dermal applications of neat liquid furfural. With 5% furfural a very mild reaction was noted, whereas applications of 1% furfural did not produce any signs of irritation throughout the study (Agakishiyev (1989) cited in Cocker *et al.*, 1992). In a further study, furfural was applied to intact shaved skin for 4 hours on 20 successive days,. Application of undiluted furfural resulted in hyperplasia, hyperkeratosis and exfoliation of the epidermis. Similar but less severe effects were observed with 5 and 1% furfural (Agakishiyev (1990) cited in Cocker *et al.*, 1992). In a limited reported study by Woods and Seevers (1955), undiluted furfural (45-1000 mg/kg bw) was applied to the shaven non-abraded skin of rabbits (occlusive conditions) for 48 hours. After another 48 hours, mild local irritation was observed in the 45-500 mg/kg bw exposure groups. No data are available on the extent (e.g., scores) and reversibility of this irritation. However, in the 1000 mg/kg bw group, all rabbits died within 12 hours, but no evidence of irritation was observed at the site of administration after 12 hours furfural application.

Further details are not available on these studies.

Based on these data, it is concluded that furfural causes mild irritating effects after prolonged skin contact (i.e., 48 hours).

Eyes

In a limited description of a study by Woods and Seevers (1955), undiluted liquid furfural was instilled in the eyes of 15 male adult white rabbits. Slight oedema of the conjunctiva was observed after the application of 0.001-0.002 ml. After exposure to 0.04 ml, marked irritation, with eyelid spasm, for about 5 days was reported. The eyes appeared grossly normal on day 7. Application of 0.09-1 ml furfural resulted in eyelid spasm for 7 days with gross corneal opacity. The eyes appeared grossly normal at day 9.
Furfural vapour is reported to be irritating to the eyes of rabbits (DECOS, 1996; Sax, 1984), but no details (e.g., scores) are available in the secondary literature. Despite the limited data, it is concluded that furfural is irritating to the eyes.

Inhalation

The sensory irritation potential of furfural was investigated in B6C3F1 and Swiss-Webster mice. Sensory irritation was quantified by measuring respiratory rate (RR) depression during inhalation exposures according to Alarie, in which an RD_{50} value was defined as the concentration eliciting a 50% decrease in RR. RR's were recorded during a 5 minute pre-exposure, 10 minute exposure, and a 5 minute recovery period. According to the authors, B6C3F1 mice exposed to furfural showed a rapid decrease in RR at the onset of exposure which was sustained throughout the exposure period with little or no recovery. Swiss-Webster mice exhibited a continuously decreasing RR during the exposure period, particularly at the higher exposure concentration (exposure range about 118-3930 mg/m^3). RD_{50} values were 920 mg/m^3 (95% confidence limits: 684-1285 mg/m^3) and 1128 mg/m^3 (849-1580 mg/m^3) for B6C3F1 and Swiss-Webster mice, respectively (Steinhagen and Barrow, 1984).
Repeated exposure resulted in respiratory tract irritation (see for a more extensive description paragraph 4.1.2.6 and 4.1.2.8). These studies have been summarised below, briefly.

In several repeated exposure studies repiratory tract irritation has been observed. Furfural-induced histopathological changes were observed in the nose only in syrian golden hamsters exposed to furfural vapours in conentrations up to 2165 mg/m^3 for 6 hours/day, 5 days/week for a period of 13 weeks. They consisted of focal atrophy of the olfactory epithelium often accompanied by accumulation of sensory cells in the lamina propria as well as the occurrence of cyst-like structures lined by flat or cuboidal epithelium which were often filled with

mucinous material and cellular debris. The incidence and degree of these changes were clearly dose-related.

Rabbits were exposed up to 1000 g/m^3 by inhalation, for 4 hours/day, 5 days/week, until death (<80 days) At 1000 g/m^3/h rabbits showed signs of irritation of the conjunctiva and the mucosa of the upper respiratory tract. At autopsy, the lungs appeared congested and oedematous. There were no further detailed assessments of the animals.

F344 rats (5 animals/sex/group) were exposed to furfural vapour for 28 days at concentrations up to 1280 mg/m^3 for 6 hours/day. Histopathological changes were limited to the nasal passages, consisting of both respiratory epithelial lesions such as squamous metaplasia and atypical hyperplasia, and olfactory epithelial changes characterized by epithelial disarrangement. At the lowest concentrations of 20 and 40 mg/m^3 effects were generally limited to the anterior part of the nose (metaplasia and hyperplasia of transitional respiratory epithelium). At higher exposure concentrations (≥80 mg/m^3) treatment-related changes of the lining epithelium were also seen in more posterior areas of the nose. Incidence and severity were higher at higher concentrations

Human data

Data on irritating properties of furfural vapour observed in humans are reported by ACGIH (2001). A study performed by the NIOSH in a grinding wheel plant revealed a general higher incidence of eye and respiratory tract irritation which was attributed to furfural vapours which were detected at concentrations ranging from 20 to 63 mg/m^3. Eye irritation, manifested by itching, burning, tearing and/or redness, was reported by 11 of 15 workers. Ten workers noted frequent nasal irritation (stuffiness, dryness or soreness, and in one case, occasional bloody nasal discharge). Seven individuals reported dryness of the mouth or throat (ACGIH, 2001).

NIOSH conducted a health hazard evaluation at a manufacturer of aluminium graphite tubes. Irritating effects on eyes, mouth, throat, and nose, and respiratory symptoms were reported. Eleven of the 15 (73%) time weighted average personal breathing zone furfural concentrations (range 0.3-4.2 ppm) exceeded the threshold limit value of 8 mg/m^3 (2 ppm).

However, the influence of other hazardous substances (respirable particles and phenol) and factors cannot be excluded, but are unknown (NIOSH, 1995). Therefore, the results are not useful for evaluation purposes of furfural.

No further human data on skin irritation are available.

Conclusion

Although the available animal studies were not performed according to OECD or EU guidelines, and all data were of older date and only limitedly reported, the rapporteur considers the data available sufficient to fulfil the Annex VIIA requirements for irritation of furfural to eyes and skin.

Furfural liquid causes mild skin irritation after prolonged contact (i.e., 48 hours) and also after repeated exposure. After repeated dermal dosing, less extensive signs of irritation were observed with diluted furfural. Notwithstanding the limited character of the studies, the relatively high concentrations used, the exposure conditions applied (48 hours, under occlusion or repeated exposure) and the mild nature of the effect, the CMR Working Group for Classification and Labelling of Dangerous Substances decided in 2000 that furfural should be classified as irritating to the skin under Directive 67/548/EEC. Furthermore, the CMR Working Group of the Directive 67/548/EEC concluded that furfural is irritating to eyes and respiratory tract (Classification:Xi; R36/37/38 under Directive 67/548/EEC).

4.1.2.4 Corrosivity

No indications are available that furfural is corrosive (see irritation).

Classification is not warranted.

4.1.2.5 Sensitisation

The sensitising potential of furfural (concentration induction and challenge: 100%) was assessed in a Buehler test using 10 male and 10 female Hartley Albino guinea pigs (Kern, 1997). The rationale for performing this test instead of a Maximisation test was not detailed in the test report. In the induction phase, no negative control was used, but otherwise, from a

technical point of view the test was performed according to OECD test guideline 406. Some (very) slight skin reactions were observed after challenge. As these reactions were also found in the negative controls (i.e. treated with furfural in the induction phase, but not treated with furfural in the challenge phase), furfural is not considered to be a skin sensitizer based on the results of this test.

In a GLP compliant guinea pig maximization test (OECD 406), furfural (99.62% purity) was administered to 10 Hartley strain guinea pigs per sex (treatment group), with a control group of 5 animals per sex (Illovo Sugar, 2003). Based on pilot work, the intradermal induction dose applied was 5% furfural in propylene glycol and the dermal induction dose was undiluted furfural (0.2 mL). Application of the intradermal dose elicited very slight erythema with oedema in 14/20 treated animals. Application of the topical induction dose (48 hours under occlusion) elicited very slight erythema in 13/20 and very slight oedema in 8/20 animals, respectively. The challenge dose was 0.2 mL of 25% furfural in acetone applied under occlusion for 24 hours. Skin reactions (very slight erythema) were observed in 3/20 treated animals 24 hours after challenge and in 2/20 after 48 hours. No responses were seen in controls. The sensitivity and reliability of the techniques were assessed in a positive control study conducted within 6 months of the start of the furfural study. The positive control substance, 2-mercaptobenzothiazole elicited the expected positive response.
Based on this it is concluded that furfural has no sensitiszing potential in this test system.

Male Hartley guinea pigs were daily treated intracutaneously for 7 days with 0.1 ml of 1% solutions (saline containing 1% Tween 80) of different aldehydes, including furfural (Watanabe *et al*., 2001). Three weeks later, furfural was injected in concentrations of 0.25, 0.50, and 1.0% and skin reactions were monitored up to 24 hours. Furfural showed only a response in 1 of three animals tested. Because of the deviant study design, low animal numbers and the availability of a well-performed OECD-conform guideline study, this study is not taken into account.

No data were found on respiratory sensitisation.

Human data

There are no case reports on sensitisation induced by furfural in humans. In a few secondary sources (Sittig *et al.*, 1991; Borelli, 1988; Foussereau *et al.*, 1982), furfural is mentioned as a possible contact allergen. However, no further details were available to substantiate these findings.

Conclusion

The data submitted are considered acceptable with regard to the basic requirements as specified in Annex VIIA of Directive 67/548/EEC. Thes data available allow the conclusion that furfural is not sensitising to the skin and classification and labelling according to the Annex I of Directive 67/548/EEC is not required.

4.1.2.6 Repeated dose toxicity

Animal data

The results of what are concluded to be the most relevant repeated dose toxicity studies for the risk assessment are summarized in Table 4.14.

Oral

The 28-day toxicity study of furfural was determines in a well performed study, conducted according to OECD test guideline 407 (including neurotoxicity screening). Sprague-Dawley rats (6/sex/dose) were administered the test substance by gavage at doses of 0, 30, 55, and 100 mg/kg bw/d. The vehicle was reverse osmosis-treated water. One female died in the control group at day 22. No treatment-related findings were found. The NOAEL for systemic and neurotoxicity was 100 mg/kg bw/d (highest dose-level tested; Chengelis, 1997).

In another well performed 28-day toxicity study (essentially according OECD 407) groups of Fisher 344 rats (5/sex,dose) were exposed daily by gavage to 6, 12, 24, 48, 96 and 192 mg/kg bw/d furfural (as dilution in corn oil). Twice during the study the highest dose was lowered for both males and females to 144 and 120 mg/kg bw/d, respectively. Three females of the highest dose died due to treatment at days 10, 11 and 28. No treatment-related findings were observed, apart from the mortality at the highest dose, and an increased liver-weight in

females of the highest dose group. This latter observation could not be satisfactorily interpreted due to the small size of this group (only two surviving rats). The NOAEL from this study is 96 mg/kg bw/d (Appel, 2001a).

Table 4.14 Repeated dose toxicity.

Study	NOAEL	LOAEL	Effects	Ref.
Oral toxicity				
subacute, rat (14 days, diet [a]; 30, 60, 90, 120 , and 180 mg/kg bw/d)	120 mg/kg bw/d	180 mg/kg bw/d	Decreased plasma ALAT in females, and corresponding increase in liverweight	Jonker, 2000a
subacute, rat (5 d/wk, 12 doses over 16 days, gavage; 15, 30, 60, 120, 240 mg/kg bw/d)	120 mg/kg bw/d [b]	240 mg/kg bw/d [b]	Increased mortality, laboured breathing	Irwin, 1990
subacute, mouse (5 d/wk, 12 doses over 16 days, gavage; 25, 50, 100, 200, 400 mg/kg bw/d)	200 mg/kg bw/d [b]	400 mg/kg bw/d [b]	Mortality	Irwin, 1990
subacute, rat (7 d/wk, 4 wk, gavage; 6, 12, 24, 48, 96 and 192 (120) [c] mg/kg bw/d)	96 mg/kg bw/d	192 (120)	Mortality in females, increased liverweight ?[d]	Appel, 2001a
subacute, rat (7 d/wk, 4 wk, gavage; 30, 55, 100 mg/kg bw/d)	100 mg/kg bw/d	n.a.	No treatment-related findings	Chengelis, 1997
semichronic, rat (13 wk, diet [a]; 30, 60, 90, 180 mg/kg bw/d)	53 mg/kg bw/d [e]	82 mg/kg bw/d [e]	Microscopic liver changes and slight haematological changes (males)	Jonker, 2000b,c
semichronic, rat (13 wk, 5 d/wk, gavage; 11, 22, 45, 90, 180 mg/kg bw/d)	<11 mg/kg bw/d [b]	11 mg/kg bw/d [b]	Cytoplasmic vacuolization of hepatocytes	Irwin, 1990
semichronic, mouse (13 wk, 5 d/wk, gavage; 75, 150, 300, 600, 1200 mg/kg bw/d)	75 mg/kg bw/d [b]	150 mg/kg bw/d [b]	Decrease in body weight, histopatho-logical changes in liver	Irwin, 1990
Inhalation toxicity				
subacute, rat (5 d/wk, 4 wk, (20), 40, 80, 160, 320, 640, 1280 mg/m^3 (6 h), and (160), 320, 640, 1280 mg/m^3 (3h))	<20 mg/m^3 (local effects); 320 mg/m^3 (systemic effects)	680 mg/m^3	Meta- & hyperplasia of transitional resp.epithelium (anterior part nose); Mortality	Muijser, 2001; Arts *et al*., 2004
semichronic, hamster (13 wk, 6 hr/d, 5 d/wk, 77, 448, 2165 mg/m^3)	77 mg/m^3 (local effects);	448 mg/m^3	Atrophy and hyperplasia of the olfactory epithelium;	Feron *et*

Study	NOAEL	LOAEL	Effects	Ref.
	448 mg/m^3 (systemic effects)	2165 mg/m^3	Marginally decreased body weights	*al.*, 1979; 1984

a) microencapsulated furfural in a carrier of maltodextrin and mixed sugars; b) based on a limited study design, see text below; c) due to mortality this dose level was lowered twice to 144 and 120 mg/kg bw/d resp. during the study; d) the small number of surviving rats precludes a treatment association for this finding; e) actual dose in target dose of 60 mg/kg bw/d.
n.a. not applicable

In a range-finding study conducted by the NTP to determine the doses to be used in a 2-year

study, F344/N rats, 5/sex/group, received gavage doses of furfural in corn oil, 5 days per week, for 12 doses over 16 days (Irwin, 1990). Doses were 15, 30, 60, 120, or 240 mg/kg bw/d. Survival of rats that received 240 mg/kg bw/d was reduced with eight rats dying, due to treatment. No mortality occurred at the lower dose levels. Final mean body weights of furfural exposed rats were similar to those of the vehicle controls. Laboured breathing was seen in rats that received 240 mg/kg bw/d. Rats that received 120 mg/kg bw/d were slightly inactive.

In the same study, B6C3F1 mice (5/sex/group) were exposed under the same exposure regimen to 25, 50, 100, 200, or 400 mg/kg bw/d. One male mouse died in the highest dose group due to treatment. At both 25 and 200 mg/kg bw/d, one female died. Both deaths were considered gavage-related. Final mean body weights of furfural exposed mice were similar to those of vehicle controls. The NOAEL in this study was 200 mg/kg bw/d based on mortality.

In both studies, no data were available on clinical signs, food/water consumption, ophthalmoscopy, haematology, clinical chemistry, urinalysis and organ weights. Necropsy and histopathologic examination were performed on all animals. No compound-related histologic lesions were found in the treatment groups.

Another range-finding study to determine the doses to be used in a 2-year study was performed by the NTP (Irwin, 1990). Rats and mice were administered furfural for 13 weeks by gavage. The observations included mortality, body weight, organ weights (including reproductive organs), necropsy, histopathology (full pathology, including reproductive organs). These observations were made for all vehicle control animals, rats receiving 90 and 180 mg/kg bw/d, and all mice dying before the end of the study or receiving 300, 600, or 1200 mg/kg bw/d. Liver and lung pathology was carried out for all rats.

F344 rats (10/sex/group) received 11, 22, 45, 90, or 180 mg furfural/kg bw/d in corn oil. Survival of rats in the highest dose groups was reduced with mortality in 5 out of 20 rats that received 90 mg/kg bw/d and 19 out of 20 rats that received 180 mg/kg bw/d. Some of these deaths were considered gavage-related (3 males and 1 female at 180 mg/kg bw/d, and 1 male

and 3 females at 90 mg/kg bw/d). All other deaths were considered to be due to furfural exposure. No further details on cause of death are specified. Mean body weights of furfural exposed male rats were increased in a dose-related manner (significant increases were seen at 45 (+5%) and 90 mg/kg bw/d (+7%), dose-related). Females were not affected. Despite the statistically significant increase, the toxicological relevance is doubted given the absence of this effect in all other oral repeated-dose toxicity studies. An increase in absolute lung weight (not dose-related) was observed in male rats at doses of 22, 45, and 90 mg/kg bw/d. Increases in absolute (45 and 90 mg/kg bw/d) and relative kidney weight (90 mg/kg bw/d) and in absolute and relative liver weight (90 mg/kg bw/d) were observed in male rats with only an increase in absolute kidney weight (22 and 90 mg/kg bw/d) in female rats. A dose-related decrease was seen in relative brain weight (22, 45, and 90 mg/kg bw/d) in male rats. Cytoplasmic vacuolization of hepatocytes, primarily in the centrilobular regions, was increased in treated male rats at all doses (incidence: 4/10, 10/10, 10/10, 10/10, 9/10 in control, 11, 22, 45, and 90 mg/kg bw/d group, respectively; minimal to mild in all dose and vehicle groups). As the liver is the main target organ of furfural and mild centrilobular necrosis is observed in male F344/N rats in an oral carcinogenicity study (Irwin, 1990), it cannot be excluded that this effect is treatment-related although an increase in severity is absent. The effects on absolute lung weight (males) and absolute kidney weight (females) at 22 mg/kg bw/d are considered to be not toxicologically significant, since there was no dose-relationship. The changes in relative brain weight (males) are not toxicologically significant, because no changes in absolute brain weights were observed. Therefore, within the limited study design, the NOAEL is <11 mg/kg bw/d based on the cytoplasmic vacuolization of hepatocytes observed in male rats.

B6C3F1 mice (10/sex/group) were exposed under the same exposure regimen to 75, 150, 300, 600, or 1200 mg furfural/kg bw/d (Irwin, 1990). Survival of mice in the highest dose groups was reduced with mortality in 18 out of 20 mice that received 600 mg/kg bw/d, and in all mice at 1200 mg/kg bw/d died. In male mice mean body weights were decreased in a dose-related way (significant decreases were seen at 150 (-5%) and 300 (-6%) mg/kg bw/d). Increases in relative liver and lung weight (300 mg/kg bw/d) were observed in male mice. Increases in absolute kidney and liver weight (300 mg/kg bw/d) were observed in female

mice. Increased relative liver weight was observed in females and an increased relative kidney weight was found in males at 75 mg/kg bw/d. These changes in relative organ weights were not considered to be treatment-related as changes in body weight were observed and there was no dose-response relationship. Furthermore, the changes in liver weight were not accompanied with histopathological changes at the lowest dose levels.
Centrilobular coagulative necrosis and multifocal subchronic inflammation of the liver were present in treated male mice at 150 mg/kg bw/d and higher doses, and in female mice at 300 mg/kg bw/d. Within the limited study design, the NOAEL is 75 mg/kg bw/d based on the decreased body weight and histopathological changes in the liver.

In a study intended for evaluation of morphological changes of the liver after oral administration (diet) of furfural during 90-120 days, effects on the liver (weight increase and proliferative cholangoiofibrosis together with necrosis) were indicated at high dose levels in Wistar rats (up to 20-40 ml/kg feed; Shimizu et al., 1986, 1989). The reliability of the doses used on this study is doubted. Dose levels were presented in ml/kg feed at levels which correspond with lethal doses in other studies. However, the volatility of furfural was not taken into account and the actual intake of furfural may probably be less.

In a 14-day range-finding study with microencapsulated furfural in a carrier of maltodextrin and mixed sugars, groups of five male and five female Fischer 344/N rats were fed a diet containing furfural at concentrations providing doses of 0, 30, 60, 90, 120, and 180 mg/kg bw per day (Jonker, 2000a). An additional control group received basal diet containing the encapsulation material only. The animals were examined daily with body weights and food consumption recorded weekly. Necropsy was performed at 14 days and the tissues were examined histologically. Clinical chemical and urinary parameters were also examined.
There were no clinical signs of toxicity, and the body weights and food consumption were normal in all groups. Cholesterol and phospholipid concentrations were slightly increased in males at the two higher doses, but these changes were not dose-related. Similarly, females at some doses had decreased blood urea nitrogen and creatinine concentrations, but these changes were not dose-related. A significant decrease in the plasma activity of alanine aminotransferase was found in females at the high dose, which corresponded to significant

increases in the absolute (111%) and relative (115%) weights of the liver in these animals. The NOAEL therefore was 120 mg/kg bw per day (Jonker, 2000a).

In a subsequent 13-week toxicity study, groups of 10 Fischer 344 rats of each sex were fed diets containing microencapsulated furfural (carrier, maltodextrin and mixed sugars) providing a nominal dose of 0, 30, 60, 90, or 180 mg/kg bw per day. The actual doses found by analysis of the food were 0, 26, 53, 82, and 160 mg/kg bw per day for males and 0, 28, 57, 86, and 170 mg/kg bw per day for females (Jonker, 2000b). An additional control group received a diet containing the encapsulated material without furfural. The animals were examined daily for clinical signs of toxicity, and body weights and food consumption were measured weekly. Animals at the high dose and controls underwent an ophthalmoscopic examination, while all animals were examined for clinical parameters. Gross examinations were performed at autopsy, with measurements of organ weights and extensive histological examination of a range of organs.

There were no clinical signs of toxicity, and body weights and food consumption were unaffected by treatment. The animals given the high dose showed no ophthalmoscopic changes when compared with controls. Some changes in clinical chemistry were seen. The haematological changes included a decreased red blood cell count in males dosed at 180 mg/kg bw per day and increased corpuscular volume and mean corpuscular haemoglobin in males dosed at 90 and 180 mg/kg bw per day. Females at the high dose showed decreased alkaline phosphatase activity, increased γ-glutamyltransferase activity, increased plasma concentration of albumin, and decreased plasma concentration of potassium. Males at the high dose showed decreased alanine aminotransferase activity, increased plasma concentration of albumin, and increased albumin:globulin ratio. Increased albumin:globulin ratios were also found in males at 30 and 90 mg/kg bw per day but not in those at 60 mg/kg bw per day.

At necropsy, the absolute and relative weights of the liver were increased in males at 180 mg/kg bw per day, but there were no gross pathological changes. Microscopic examination revealed changes in the liver in 5/10 males at 90 mg/kg bw per day and in 10/10 males at 180 mg/kg bw per day. The changes were found mainly in the perilobular region and were characterized by cells having less coarse cytoplasm, an increased occurrence of clumps of

eosinophils, a less dense periphery, and more prominent nucleoli in the nucleus. The changes seen at 90 mg/kg bw per day were not severe, and those in rats at 180 mg/kg bw per day were slight with none being accompanied by signs of degeneration or necrosis. No changes were observed in the livers of females, and there were no signs of hepatotoxicity such as degeneration, necrosis, or inflammation. No bile-duct proliferation was seen. The NOAEL was 60 (i.e. 53) mg/kg bw per day (Jonker, 2000c).

An additional description of toxicological effects after repeated (chronic) exposure is presented in section 4.1.2.8 'Carcinogenicity'.

Inhalation

The inhalation toxicity of furfural was studied in Syrian golden hamsters (10 animals/sex/group). Each group was repeatedly exposed to furfural vapour at concentrations of 0, 77, 448, and 2165 mg/m^3 for 6 hours/day, 5 days/week for a period of 13 weeks. Examinations included mortality, body weight, haematology, clinical chemistry, urinalysis, organ weights and histopathology. At the highest exposure level furfural induced irritation of the eyes and nose, slight growth retardation, i.e. a statistically significant decreased body weight at the end of week 6 (-9%), 8 (-9%), 12 (-8%) and 13 (-8%), mainly in males, and an increased relative liver weight in males. Gross examination at autopsy did not reveal pathological changes that could be attributed to furfural exposure. The increased relative liver weight in males was not considered treatment related, given the absence of histopathological changes in the liver, the absence of liver effects in a 52 week study with Syrian golden hamsters (see 4.1.2.8 Carcinogenicity, 'inhalation'), and the decreased body weight (data on absolute liver weight were not presented). Furfural-related histopathological changes were observed in the nose only. They consisted of focal atrophy of the olfactory epithelium often accompanied by accumulation of sensory cells in the lamina propria as well as the occurrence of cyst-like structures lined by flat or cuboidal epithelium which were often filled with mucinous material and cellular debris. The incidence and degree of these changes at the 448 and 2165 mg/m^3 levels were clearly dose-related. No compound related alterations were detected at the lowest exposure concentration of 77 mg/m^3 which was accepted as a NOAEL

for local effects (Feron *et al.*, 1979, 1984). The NOAEL for systemic effects is 448 mg/m^3.

Rabbits (no data on group size and strain) were exposed to 200, 500, and 1000 g/m^3/h by inhalation, for 4 hours/day, 5 days/week, until death (<80 days) in a study in which limited toxicological parameters were assessed. However, rabbits died after 17-20, and 8-10 days of exposure to 500 and 1000 g/m^3/h, respectively. At 1000 g/m^3/h rabbits showed signs of irritation of the conjunctiva and the mucosa of the upper respiratory tract. At autopsy, the lungs appeared congested and oedematous. There were no further detailed assessments of the animals. At 500 g/m^3/h rabbits showed renal lesions and anaemia. No changes were found in hepatic functions. Rabbits exposed to 200 g/m^3/h did not show any signs of toxicity after 60-80 days of exposure (Castellino *et al.*, 1963). Gross examination and histopathology of the nose was not performed.

Furfural vapour was applied to F344 rats (5 animals/sex/group) for 28 days at target concentrations of 40, 80, 160, 320, 640, and 1280 mg/m^3 for 6 hours/day, controls received clean air (Muijser, 2001; Arts *et al.*, 2004). In parallel groups (5/sex/group), rats were also daily exposed for 3 hours per day to 320, 640 and 1280 mg/m^3. Clinical signs, food consumption, body and organ weights, haematology and clinical chemistry, macroscopic necropsy and histopathology were used to elucidate toxic effects. The latter two examinations focussed on the known target organs of toxicity of furfural, including the liver. In the two highest dose groups treatment-related mortality was observed. All animals dosed at 1280 mg/m^3 died during or after the first treatment (in both the 6 and 3 hours exposure regimes). At 640 mg/m^3 death occurred in the 6 hours exposure regime only, with one animal dying after one, four, and five days, and two after days 8 of treatment. The groups showing mortality were removed from the study and additional groups were introduced on exposure regimes of 20 mg/m^3 for 6 hours, and 160 mg/m^3 for 3 hours. Up to and including 320 mg/m^3 no significant treatment-related changes were observed in the investigated parameters. Histopathological changes were limited to the nasal passages, consisting of both respiratory epithelial lesions such as squamous metaplasia and atypical hyperplasia, and olfactory epithelial changes characterized by epithelial disarrangement. At the lowest concentrations of 20 and 40 mg/m^3 effects were generally limited to the anterior part of the nose (metaplasia

and hyperplasia of transitional respiratory epithelium). At higher exposure concentrations (≥80 mg/m^3) treatment-related changes of the lining epithelium were also seen in more posterior areas of the nose. Incidence and severity were higher at higher concentrations Interestingly, the histopathological changes in the nasal passage of animals exposed for 3 hours a day were with respect to incidence and degree less to much less than the changes seen in animals exposed to the same *daily* dose for 6 hours. From the results of this study the authors came to the following conclusions:

- the exposure-mortality relation appears to be very steep, and mortality appears to be related to received dose instead of concentration;
- the local effects observed in the nose appear to be *more* dependent on duration rather than concentration, and
- the NOAEC for local effects actually was lower than 20 mg/m^3, whereas that for systemic effects was 320 mg/m^3.

Further reference is made to section 4.1.2.8 'Carcinogenicity' for additional data on toxicity after repeated inhalation exposure.

Dermal

Studies of liver and kidney function, haematopoiesis, and some blood coagulation tests in rabbits (no data on group size and strain) showed a serious compromising of these functions by daily subcutaneous injections of furfural (25, 2.5, 0.5, or 0.2 mg/kg bw/d). Injections were given for 5 days/week until death (<80 days). Death occurred after 7-12 injections, 16-30 injections, and 38-66 injections, at 25, 2.5, and 0.5 mg/kg/d, respectively. In the three highest dose groups changes in kidney and liver function tests, accompanied by histological effects, and effects on blood parameters were observed. In the lowest dose group, no deaths occurred and no statistically significant changes in function tests or at autopsy were seen (Castellino *et al*., 1963). Because of the limited reporting and the route of administration (subcutaneous), this study is not considered useful for risk assessment.

Furfural was applied to intact shaved skin of guinea pigs (8-10 group) for 4 hours on 20 successive days,. Application of undiluted furfural resulted in hyperplasia, hyperkeratosis and

exfoliation of the epidermis. Similar but less severe effects were observed with 5 and 1% furfural. A dose-related decrease in body weight was observed, accompagnied by a increase in relative (but not absolute) liver weight. Relative spleen and kidney weights were unaffected. Other observations included large fatty droplets in the liver, white pulp hyperplasia in the spleen and local infiltration, multinucleation and "albumin dystrophy" in the convoluted epithelium of the kidney (Agakishiyev (1990) cited in Cocker *et al.*, 1992). The study is too limited to be useful for risk assessment of dermal exposure to furfural.

Human data

In a study of Vinogradova *et al.* (1968), 65 workers in a furfural manufacturing industry were examined. The population consisted of 43 men and 22 women. Exposure concentrations varied from up to 10 mg/m^3 (hydrolysing section), 20-30 mg/m^3 (near hydrolysers), and 50-70 mg/m^3 for short periods of time upon opening for cleaning purposes. Complaints were of periodic headaches, dizziness (less frequently), general weakness, over irritation, and symptoms of dyspepsia. No significant changes were detected in haematology, biological indices or functioning of the internal organs. Twenty-six cases showed decreased blood chlorine contents. There was some suppression of the activity of cholinesterase in the blood plasma and erythrocytes (not further specified). It was not clear whether the symptoms started after contact with furfural or if they were already existing before. No details were provided on the control group, the way the workers were examined (i.e. monitored for furfural) or the way the exposure was assessed (Vinogradova *et al.*, 1968).

Conclusion

The data submitted are considered acceptable with regard to the basic requirements as specified in Annex VIIA of Directive 67/548/EEC for risk characterisation. The available data permit the derivation of a NOAEL for repeated-dose inhalation and oral toxicity. No suitable studies are available to assess toxicity after repeated dermal exposure.

However, the effects observed after repeated exposure were considered to not fulfill the criteria for classification according to Directive 67/548/EEC for systemic effects.

Oral exposure

Most studies performed with this route of exposure used administrations of furfural by gavage. NOAELs derived, varied from 200 down to < 11 mg/kg bw/d. The various studies differed in quality of design and reporting with some being (nearly) according to OECD guidelines and others clearly not. The lowest NOAEL, i.e. <11 mg/kg bw/d, is derived from a sub-chronic range-finding study with rats (Irwin, 1990). At all gavage dose levels, cytoplasmic vacuolization of hepatocytes in the centrilobular region in male rats was found. This effect is considered treatment-related, given the occurrence of mild centrilobular necrosis in male rats in an oral carcinogenicity study with gavage administration.

In more recent studies by Jonker (Jonker, 2000a-c) furfural was applied via the diet in a microencapsulated form to prevent loss of the compound due to its volatility. In the 13-week dietary study, effects included minor hepatocellular alterations in males, but not in females, at doses of 82 and 160 mg/kg bw/d. The NOAEL in this study, therefore, was established at the next lower dose-level of 53 mg/kg bw/d (with corresponding targeted exposure value of 60 mg/kg bw/d), a value clearly higher than the one achieved with gavage administration.

Having taken note of the fact that a complementary study showed that furfural was rapidly and completely released from this microencapsulation in an aqueous environment (Buck, 2000) the NOAEL from this diet study is chosen as starting point for the risk characterisation for repeated oral exposure for the following reasons: (i) dietary administration of a test compound avoids the unwanted high peak exposures associated with gavage application; (ii) microencapsulation adequately circumvents loss of furfural due to volatization and results in an instantaneous release of this substance in the aqueous environment of the GI-tract; (iii) dietary exposure avoids the use of (for this substance) corn oil exposure, that is known to be associated with morphological liver changes upon prolonged exposure; (iv) the gavage study of Irwin (1990; 13-week study in rats) has a limited design, being a range-finding study only. The JECFA (Joint FAO/WHO Expert Committee on Food Additives; WHO, 2001) came to the same conclusion after evaluating the 13-week dietary study by Jonker (2000b,c).

Inhalation exposure

Of the available studies the one reported by Muijser (2001; Arts *et al.*, 2004) has the lowest NOAEC: <20 mg/m^3 for local effects. At this concentration metaplasia and hyperplasia of transitional respiratory epithelium were observed at the anterior part of the nose. This study is

considered suitable for the risk characterisation for local effects after repeated inhalation exposure.

The lowest NOAEC for systemic effects is also found in the Muijser (2001; Arts *et al.*, 2004) study: 320 mg/m^3. According to the authors this concentration corresponds to 92 mg/kg bw/d (assuming 100% absorption, ventilation rate of 0.8 l/kg bw, and an oral absorption of 100%; Muijser, 2001; Appel, 2001b; Arts *et al.* 2004).In this review 90% oral absorption is used to derive a NOAEC of about 100 mg/kg bw/day). This concentration of 320 mg/m^3 will be taken as starting point for the risk characterisation for systemic effects after repeated inhalation exposure.

There are clear species-differences in sensitivity to furfural-induced toxicity. Rats appear clearly more sensitive to furfural toxicity than both Syrian golden hamsters and rabbits. Although differences in metabolism may be one factor underlying these differences, data to substantiate this are not available.

Dermal exposure

No dermal repeated-dose toxicity data are available that can be used for the risk characterisation. From the two available no observed effect levels from repeated dose toxicity studies, i.e. for oral and inhalation exposure, the oral NOAEL of the 13-week diet study with rats will be used to evaluate the systemic toxicity after dermal exposure in the risk characterisation.

4.1.2.7 Mutagenicity

It should be noted that not all studies described, especially with respect to the 'miscellaneous' ones, are focussed on mutagenicity. However, the studies described are considered to be relevant for the evaluation of the (non)genotoxicity of furfural.

Prokaryotic cells, in vitro

In Table 4.15, a number of relevant *in vitro* tests with prokaryotic cells are summarized. Weak positive results are reported in Ames tests, mainly with TA100. Some bacterial studies with furfural were negative, however, they had in general inadequacies in reporting (Soska *et*

al., 1981; Shinohara *et al.*, 1986; Dillon *et al.*, 1992). Furfural caused DNA damage in the REC-assay using Bacillus subtilis (Shinohara *et al.*, 1986).

Drosophila melanogaster

The mutagenicity of furfural was studied in Drosophila by Woodruff *et al.* (1985) and Rodriquez-Airnaz *et al.* (1992). The results are summarized in Table 4.16. The tests by Rodriquez-Airnaz *et al.* (1992) indicate that furfural is mutagenic/clastogenic in Drosophila in germ and somatic cells.

A questionable increase in sex-linked recessive lethal mutants was observed in the study of Woodruff *et al.* (1985). The biological significance of this increase is questionable, because the number of lethals in the control group is very low (0/5865). The difference in sex-linked recessive lethal mutants would not have been statistically significant, if the number of lethals had been 1/5865, which would have been considered to be a normal finding. Furfural did not produce reciprocal translocations in Drosophila. The studies of Woodruff *et al.* (1985) are considered to be negative.

Mammalian cells, in vitro

In Table 4.17 a number of relevant *in vitro* mutagenicity studies using mammalian cells are summarized. Furfural is clearly genotoxic in *in vitro* mammalian cell systems producing chromosome aberrations in CHO and V79 cells, SCE's in CHO cells and human lymphocytes and gene mutations in mouse lymphoma cells in the absence of metabolic activation. Furfural did not induce DNA-repair in nasal epithelial tissues *in vitro*.

Human data:

Unscheduled DNA synthesis

Lake *et al.* (2001) reported on UDS tests in precision-cut liver slices of four human donors *in vitro*. These liver slices were cultured for 24 h in medium containing $^{[3H]}$thymidine and 0-10 mM furfural. Small increases in net grain count (i.e. nuclear grain count less mean cytoplasmic grain count) observed with 2-10 mM furfural were not due to any increase in the nuclear grain count. Rather, it was the result of concentration-dependent decreases in the mean cytoplasmic grain counts and to a lesser extent in nuclear grain counts, due to furfural-

induced cytotoxicity. In contrast, marked increases in UDS (both net grain and nuclear grain counts) were observed in human liver slices with positive controls (0.02 and 0.05 mM 2-acetylaminofluorene, 0.002 and 0.02 mM aflatoxin B_1 and 0.005 and 0.05 mM 2-amino-1 methyl-6-phenylimidazo[4,5-*b*]pyridine). From this study it is concluded that furfural was unable to induce UDS in these human specimens.

Mammals, in vivo

The studies are summarized in Table 4.18. No increase in chromosome aberrations and SCE's in mouse bone marrow cells have been reported (Irwin, 1990; Abbott *et al.*, 1991). Although no toxicity was observed at the target cells after intraperitoneal injection, the dose levels tested were considered to be high enough. Subramanyam *et al.* (1989) observed an induction of chromosome mutations in a bone marrow metaphase test with mice. However, evaluation of this result is not possible since this abstract only provided a very limited description, and no paper has been published since then in a peer reviewed journal.

Lake *et al.* (2001) reported on UDS tests in hepatocytes of male and female B6C3F1 mice and of male F344 rats, after *in vivo* administration. Furfural was dosed by gavage at levels of 0 (control), 50, 175 and 320 mg/kg bw to mice, and 0, 5, 16.7 and 50 mg/kg bw to male rats. Preliminary toxicity studies had established the two top doses, 320 and 50 mg/kg in the mouse and rat, respectively, as the maximum tolerated doses for these species. Hepatocytes were isolated by liver perfusion either 2-4 or 12-16 h after treatment, cultured in medium containing $^{[3H]}$thymidine for 4 h and assessed for UDS by grain counting of auto radiographs. Furfural did not produce any statistically significant increase or any dose-related effects on UDS in mouse and rat hepatocytes, whereas UDS was markedly induced by three positive controls under these conditions, i.e. 2-4 h after dosing these species with 20 mg/kg dimethylnitrosamine, and 12-16 h after treatment with 200 mg/kg *O*-aminoazotoluene and 50 mg/kg 2-acetylaminofluorene, respectively.

Furfural was examined for its *in vivo* potential to induce gene mutations of the *λ lacZ*-gene in the liver of the male transgenic $CD2F_1$ (BALB/c × DBA/2) mice, strain 40.6, with *lacZ*- as reporter genes (Steenwinkel and Krul, 2003). For genotoxicity studies with transgenic animals, no regulatory guideline is currently available. Therefore the study was performed

under GLP conditions according to a protocol designed according to guidance provided by review papers in the public literature (Gorelick, 1995; Gorelick and Mirsalis, 1996). This protocol was implicitly accepted by the EU Member States after a written round of commenting, preceding ESR TMII, 2001. As a key-study, it will be described in somewhat more detail.

The genotoxicity study was performed with 5 groups: three furfural dose groups and one negative control group (receiving vehicle only) each comprising 13 mice and 2 reserve mice, and one positive control group receiving a known mutagen (ethylnitrosourea- ENU) comprising 8 mice and 2 reserves. The mice (including reserves) in the furfural groups were dosed at 75, 150 and 300 mg/kg bw/day in corn oil by gavage for 28 consecutive days. ENU was dissolved in 5% DMSO in saline and administered via intraperitoneal injection on days 5-9 of the study at 50 mg/kg bw/d. On day 28, 3 animals in each of the furfural-treated groups and the control group were sacrificed to obtain data on the hepatotoxicity of the test substance. Hepatotoxicity was assessed by clinical chemistry (plasma ALAT, ASAT, alkaline phosphatase, bilirubin, cholesterol, triglycerides, phospholipids, total protein, albumin and globulin) and by histopathological evaluation of liver slides. In addition, body and organ weights were monitored throughout the study.

After a manifestation period of 34/35 days, on days 62 and 63 of the study the livers and samples from other GI-tract tissues of the remaining animals were fixed and collected for mutation analysis. Mutation analysis was carried out in livers of 8 animals per group of the two controls (vehicle and positive controls) and the furfural groups. Per liver sample at least 5 000 (but preferably > 120 000) plaque forming units (PFU) were examined (one PFU corresponds to one recovered copy of the *λgt10lacZ*-shuttle vector).

There were three early decedents in the group receiving 300 mg furfural/kg/day (two during treatment showing no clinical signs, and one during the manifestation period showing hunched posture and piloerection) and one in the group receiving 75 mg furfural/kg/day (during the manifestation period, showing sluggish behaviour). As no alternative cause of death could be ascertained for any of these four animals, the study authors considered these deaths as treatment-related. No clinical signs were observed in any of the other animals. Body weight in the groups treated at 75, 150 and 300 mg/kg bw/day showed a dose-related increase compared to the negative controls in the first week of the treatment period. In the

post treatment period the difference between control group and groups treated with furfural up to 150 mg/kg bw/d gradually disappeared. The 300 mg/kg group maintained a higher body weight also during the post treatment phase of the study. Evaluation of clinical chemistry parameters in blood from the mice sacrificed for hepatotoxicity assessment revealed a statistically significant increase in triglyceride content at the highest dose level of 300 mg furfural/kg bw/day. These affected mice also showed statistically significant increases in absolute and relative liver weight and, at histopathological evaluation, centrilobular hypertrophy of the liver. The liver of one of these mice also showed focal haemorrhage accompanied by an inflammatory reaction. The liver weight increase was not a permanent change as there was no effect on liver weight in the animals killed on days 62/63 (34/35 days after the last dose). It can be concluded that at the highest dose level there was some evidence of hepatotoxicity.

The range of PFU numbers studied and the mutation frequencies observed are given in the following table:

GROUP		**range PFUs**[1]	**MF**[2]
Furfural	0	96 - 111 (2) 129 - 434 (6)	61 ± 23 (8)
	75	28 - 106 (4) 146 - 226 (3)	41 ± 7 (7)
	150	67 (1) 123 - 364 (7)	54 ± 21 (8)
	300	143 - 371 (8)	37 ± 16 (8)
ENU		105 - 118 (2) 131 - 365 (6)	246 ± 95 (8)

1 Between brackets, the number of animals is given for the range of PFUs (in thousands). For animals for which < 120000 PFU were recovered the number are given separately. However, for statistical evaluation all animals belonging to one group were taken together.
2 MF mutation frequency. Data in the table are mean ± sd for 10^6 PFUs

For the DNA extracted from the livers of the negative control group animals the observed mutation frequency is comparable to the laboratory background data. The differences between the negative control group and the furfural treatment groups were not significant. It is concluded that oral administration of furfural in corn oil at levels up to and including 300

mg/kg/day is not associated with an increase in the induction of mutations in liver cells of *λ1acZ* transgenic mice.

Human data:

Gomez-Arroyo and Souza (1985) analysed SCE's in workers occupationally exposed to furfural. No statistically significant difference was found compared with controls. However, no adequate data on exposure were available.

Miscellaneous, in vitro

No activity was detected in a prophage induction test (Soska *et al.*, 1981) and the chloroplast-bleaching test using Euglena gracilis, strain Z (Soska *et al.*, 1981). Meyberg *et al.* (1987) examined furfural on its cytotoxicity in a 'Pollen-test system'. The ED50 (effective dose), the concentration estimated to hamper the growth of the tube of the 'Pollen' with 50% was used as a criterion of toxicity. The ED50 value of furfural was 730 µmol/l which was much higher than, e.g., the ED50 of triethylleadchloride (ED50 = 7 µmol/l), which has high cytotoxicity for plants.

Interaction with DNA

The alkaline unwinding assay and protection of cleavage sites from the action of various restriction enzymes were used to study the interaction of furfural with calf thymus DNA. Alkaline unwinding experiments showed the formation of an increasing number of strand breaks in duplex DNA with increasing furfural concentrations and with time of reaction (Uddin and Hadi, 1995; Hadi *et al.*, 1989). Treatment of λ phage DNA with furfural resulted in reaction of furfural exclusively with AT base pairs. For this reaction a minimum of 3-4 consecutive AT base pairs were required (Hadi *et al.*, 1989). The reaction of furfural with AT base pairs in duplex calf thymus DNA was confirmed by the same group using single-strand-specific nuclease (Uddin, 1993).

In an immunological, non-radioactive DNA synthesis-inhibition test using HeLa S3 cells, furfural was able to inhibit DNA synthesis by 50% at a level of 3 mM (Heil and Reifferscheid, 1992).

Replicative DNA synthesis

Male B6C3F1 mice were exposed to 0, 100, or 200 mg/kg furfural by gavage. After 24, 39 and 48 hours, hepatocytes were prepared and replicative DNA synthesis (RDS) was assessed. The maximum RDS incidence value was observed in the 200 mg/kg group and amounted to 1.43% 48 hours after exposure. Furfural shows mitogenic activity in this test (Miyakawa *et al.*, 1991). It should be noted that many non-genotoxic (i.e., *Salmonella*-negative) carcinogens are positive in this test.

Oncogen activation

Reynolds *et al.* (1987) found differences in the pattern of oncogen activation between furfural-induced and spontaneously-occurring liver carcinomas in B6C3F1 mice. The results of this study suggest that furfural caused an increased incidence in mouse liver tumours at least in part by induction of novel weakly activating point mutations in *ras* genes. The liver tumours studied by Reynolds *et al.* were derived from an oral carcinogenicity study with furfural in B6C3F1 mice conducted by NTP (Irwin *et al.*, 1990).

Conclusion

Although inadequacies in reporting were noted, the data available are considered sufficient to fulfill the basic Annex VIIA requirements for mutagenicity.

It is concluded that furfural has the potential to induce chromosomal aberrations and gene mutations *in vitro*. Furfural was negative in *in vitro* UDS tests with human liver slices (Lake *et al.*, 2001)

Furfural did not induce chromosome aberrations and SCEs in bone marrow cells of mice after intraperitoneal treatment. One abstract reported furfural as positive in a cytogenicity study in mouse bone marrow (Subramanyam *et al.,* 1989); however, since this paper was not published in a peer reviewed journal subsequently it could not be fully evaluated. Furfural was negative in *in vivo* UDS tests with rat and mouse hepatocytes (Lake *et al.*, 2001).

A study in λ*lac*Z transgenic mice (strain 40.6) indicated that orally administered furfural does not induce gene mutations *in vivo* in mouse liver, a tissue in which carcinogenicity was observed (see section 4.1.2.8).

The CMR Working Group decided that the available data on mutagenicity are considered to not fulfill the criteria for classification according to Directive 67/584/EEC (November 2003).

Table 4.15 Prokaryotic cells, in vitro.

Cell type	Protocol	Metabolic activation	Concentration	Toxic concentration	Result (note strain indicated)	Comments	Ref.
Bacteria, point mutations							
S. typhimurium TA98, TA100	Ames test (plate incorporation)	With and without (rat liver S9 Aroclor 1254-induced)	TA 100: 1-15 µl/plate TA98: 1-10 µl/plate	from lowest dose in both tested strains	+ (TA100, +/- S9) - (TA98, =/- S9)	Normal Ames test procedure except for a larger incubation period (3-4 days); survival has been separately determined in the concentration range 1-10 µl/plate for TA98 en TA100.	Zzienicka *et al.*, 1978
S. typhimurium TA98, TA100, TA1535	Ames test (plate incorporation)	With and without (rat liver S9 phenobarbital-induced)	0.05-60 µmol/plate	toxic, concentration is not reported	* (TA100, -S9, 60 µmol/plate) - (+S9)	Increase in revertants, however, less than 2-fold.	Loquet *et al.*, 1981
S. typhimurium TA98, TA100, TA1535, TA1537	Ames test (pre incubation)	With and without (rat and hamster S9 Aroclor 1254-induced)	33.3-6,666 µg/plate	(1) not toxic (2) toxic at ≥3,333 µg/plate	(1) - (2) * (TA100, -S9) - (+S9; TA98, TA1535, TA 1537, -S9)	Substance was tested in two laboratories. The results are given separately for each of the laboratories. The discrepancies between the laboratories are likely due to the fixed en non-optimum protocol.	Mortelmans *et al.*, 1986
S. typhimurium TA98, TA100, TA1535, TA 1537	Ames test	With and without (no further details)	500-10000 µg/plate	1) TA98 > 7500 µg/plate	1) (+) > 7500 TA100: + at 50000 µg/plate		Jones, 1979
Bacteria, miscellaneous							
Bacillus subtilis	Rec-assay	With and without	1.7 - 17 mg/plate		+	Results showed an	Shinohara *et al.*,

Cell type	Protocol	Metabolic activation	Concentration	Toxic concentration	Result (note strain indicated)	Comments	Ref.
H17 Rec$^+$, M45 Rec$^-$						increased killing in the DNA repair deficient strain, pointing to induction of primary DNA damage by furfural.	1986

***** : means equivocal); (+): means weakly positive

Table 4.16 Drosophila melanogaster

Protocol	Concentration	Result	Comments	Ref.
Chromosome loss in germ cells	3750, 5000 ppm (feeding or injection)	+ (repair-deficient females) - (repair-proficient females)	Duration feeding period unknown.	Rodriguez-Arnaiz *et al.*, 1992
Wing spot test	3750, 5000, 7500 ppm (inhalation)	+	Statistically significant increase in small single and total spots.	Rodriguez-Arnaiz *et al.*, 1992
Sex-linked recessive lethal test	100 ppm (one injection) 1000 ppm (3 days, feed)	-		Woodruff *et al.*, 1985
Reciprocal translocation	1000 ppm (3 days, feed)	-		Woodruff *et al.*, 1985

Table 4.17 Mammalian cells, in vitro.

Cell type	Protocol	Metabolic activation	Concentration	Toxic concentration	Result	Comments	Ref.
Chromosomal aberrations							
Chinese hamster V79 cells	Chromosomal aberrations	Without	500-2000 µg/ml	no data	+	A dose-related increase in number of chromosome aberrations and a dose-related decrease in mitotic index were observed.	Nishi *et al.*, 1989
CHO cells	Chromosomal aberrations	With (a) and without (b) (rat liver S9 Aroclor 1254-induced)	initial study (1): 1.5-5000 µg/ml independent repeat (2): 94-3000 µg/ml	1a ≥1500 µg/ml 1b 5000 µg/ml 2a ≥750 µg/ml (20 h); ≥188 µg/ml (44 h) 2b 3000 µg/ml (20 h); ≥375 µg/ml (44 h)	+	Test was performed according to 92/67/EC B.10.	Gudi *et al.*, 1996
CHO cells	Chromosomal aberrations	With and without (rat liver S9 Aroclor 1254-induced)	10-40 mM	no data	+	The clastogenic activity of furfural was strongest in the presence of S9.	Stich *et al.*, 1981
CHO cells	Chromosomal aberrations	With and without (rat liver S9 Aroclor 1254-induced)	200 - 1230 µg/ml	no data	+	No data on classes of aberrations were available.	Galloway *et al*., 1985
Primary DNA damage							
CHO cells	SCE	With and without (rat liver S9 Aroclor 1254-induced)	11.7 - 3,890 µg/ml	no data	+		Galloway *et al.*, 1985
Rat nasal epithelial tissue	UDS	Without	$5x10^{-7}$ - $1x10^{-3}$ M	no data	-		Wilmer et al., 1987
Human liver slices	UDS	Without	2 – 10 $*10^{-3}$ M	Marked toxicity at 10 $*10^{-3}$ M with subjects B and D	-	Donors A-D; 2-AAF, Aflatoxine B_1, PhIP clearly positive at 0.05 mM and/or below.	Lake *et al.*, 2001
Human peripheral blood	SCE	Without	3.5-14$*10^{-5}$ M	no data	+	A dose-related increase in SCE's was found. Furfural also damaged spindle fibers.	Gomez-Arroyo and Souza, 1985

Cell type	Protocol	Metabolic activation	Concentration	Toxic concentration	Result	Comments	Ref.
Gene mutations							
Mouse lymphoma cells	TK^+/TK^- assay	Without	25 - 800 µg/ml	≥400 µg/ml	+		McGregor *et al.*, 1988

Table 4.18 Mammals, in vivo.

Species	Protocol	Concentration	Result	Comments	Ref.
B6C3F1 mice	Chromosome aberrations in bone marrow cells	50 - 200 mg/kg bw (once, intraperitoneal)	-	Dose levels used represented the MTD, 1/2 MTD and 1/4 MTD. Protocol shows, only slight deviations from OECD 475.	Irwin, 1990 (NTP); Abbott *et al*.., 1991[3]
B6C3F1 mice	SCE in bone marrow cells	50 - 200 mg/kg bw (once, intraperitoneal)	-	Dose levels used represented the MTD, 1/2 MTD and 1/4 MTD. Protocol shows, only slight deviations from OECD 475.	Irwin, 1990 (NTP); Abbott *et al*.., 1991[4]
B6C3F1 mice	UDS in hepatocytes	50 -320 mg/kg bw (once,	-	Dose levels used represented the MTD, 1/2 MTD and 1/6 MTD[5]. Protocol apparently according to OECD 486.	Lake *et al.*, 2001

[3] The study of Abbott et al. (1991) shows similarities with the study reported by Irwin (1990). It is not clear whether the same study is reported twice.

[4] The study of Abbott et al. (1991) shows similarities with the study reported by Irwin (1990). It is not clear whether the same study is reported twice.

[4] i.e. $CD2F_1$ (BALB/cxDBA/2) strain of mice

[5] as established by dose-range finding studies by these investigators

Species	Protocol	Concentration	Result	Comments	Ref.
		gavage)			
F344 rats (males)	UDS in hepatocytes	5 - 50 mg/kg bw (once, gavage)	-	Dose levels used represented the MTD, 1/3 MTD and 1/10 MTD[5]. Protocol apparently according to OECD 486.	Lake *et al.*, 2001
strain 40.6[4] (males)	mutations in *λlacZ*-gene in liver cells	37.5-300 mg/kg bw/d (gavage; 28 days)	-	No OECD Guideline available for this type of study.	Steenwinkel and Krul, 2003

4.1.2.8 Carcinogenicity

Animal data

Oral (carcinogenicity)

F344/N rats, 50/sex/group, were exposed to furfural (99% pure) in corn oil by gavage during 5 days a week for 103 weeks at doses of 0, 30, and 60 mg/kg bw/d. The study was performed according to OECD 451 except for the following deviations: two instead of three dose levels, food consumption was not measured, haematology was not performed, and the report did not include all (individual) results obtained. Mean body weights of furfural exposed and vehicle control animals were similar throughout the study. Survival of high dose female rats was reduced with deaths associated with gavage administration (19/50). However, the survival rate was considered adequate to detect carcinogenic activity (mean survival in days: 650, 670 and 585 for 0, 30 and 60 mg/kg bw/d, respectively). In the lungs of female rats increased incidences of congestion were observed (6/50, 6/50, and 23/50 for 0, 30, and 60 mg/kg bw/d, respectively). Mild liver toxicity occurred at increased incidences in both furfural-treated groups of male rats (mild centrilobular necrosis; vehicle control 3/50, low dose 9/50, high dose 12/50). The tumour incidences are presented in Table 4.19. Squamous cell carcinomas (in one low dose male) and papillomas (in 2 high dose males, one low and one high dose female) were seen in the forestomach. Forestomach hyperplasia was observed at marginally increased incidences in low dose male rats, but incidences were not increased in high dose males and females. Therefore, these lesions are not considered treatment-related. Based on the results of this study, there is no evidence of carcinogenic activity for female F344/N rats that received doses of 30 or 60 mg furfural/kg bw/d. However, there was some evidence of carcinogenic activity of furfural for male F344/N rats receiving 60 mg/kg bw/d, based on the occurrence of uncommon cholangiocarcinomas in two animals (historical vehicle control: 3/2,145 male rats) and bile duct dysplasia with fibrosis in two other animals. Biliary dysplasia with fibrosis is considered to be an early stage in the development of cholangiocarcinomas (Irwin, 1990).

In the same study (Irwin, 1990) male and female B6C3F1 mice (50/sex/group) were exposed under the same regimen to 0, 50, 100, and 175 mg/kg bw/d. Mean body weights of furfural exposed and vehicle control animals were similar throughout the study. Mild liver toxicity occurred (chronic inflammation: male 0/50, 0/50, 8/49, 18/50 and female 0/50, 0/50, 1/50,

8/50, for 0, 50, 100, and 175 mg/kg bw/d, respectively, and pigmentation; male 0/50, 0/50, 8/49, 18/50 and female 0/50, 0/50, 0/50, 11/50, for 0, 50, 100, and 175 mg/kg bw/d, respectively). The relevant tumour incidences are presented in Table 4.20. An increased incidence of hepatocellular adenomas was observed in males and females (positive trend, significantly increased at high dose level for both males and females). An increased incidence of hepatocellular carcinomas was found in male mice (positive trend, significantly increased at high dose level). Despite the high incidence of spontaneous liver tumours in the control group, these tumours were attributed to treatment with furfural. Chronic inflammation of the liver may have been influential in tumour production.

Renal cortical adenomas or carcinomas in male mice ((0/50; 1/50; 1/49; 1/50) and squamous cell papillomas of the forestomach in female mice (1/50; 0/50; 1/50; 6/50) may have been related to furfural-exposure. However, given the absence of substantial renal tubular cell hyperplasia and and the fact that there was no dose relationship in the incidence of the neoplasms, the renal adenomas/carcinomas were considered not to be treatment-related. Furthermore, the squamous cell papillomas of the forestomach are difficult to associate with furfural exposure because of the low incidence, the uncertain biological potential (i.e., none progressed to malignant neoplasms), and their possible relationship to gavage administration.

Based on the results of these studies, it is concluded that furfural is carcinogenic in mice after oral administration. Less convincing evidence was found in rats.

Table 4. 19 Tumour incidences found in the carcinogenicity studies in rats by Irwin (1990).

Organ/tumour type	**Incidences**					
	0 mg/kg bw/day		**30 mg/kg bw/day**		**60 mg/kg bw/day**	
	m	**f**	**m**	**f**	**m**	**f**
Forestomach **Squamous cell carcinoma**	0/50	0/50	1/50	0/50	0/50	0/50
Squamous cell papilloma	0/50	0/50	0/50	1/50	2/50	1/50
Liver **Cholangiocarcinoma**	0/50	0/50	0/50	0/50	2/50	0/50
Bile duct dysplasia with fibrosis	0/50	0/50	0/50	0/50	2/50	0/50

m = male; f = female

Table 4.20 Tumour incidences found in the carcinogenicity studies in mice by Irwin (1990)

Organ/tumour type	Incidences							
	0 mg/kg bw/day		50 mg/kg bw/day		100 mg/kg bw/day		175 mg/kg bw/day	
	m	f	m	f	m	f	m	f
Liver								
Hepatocellular adenoma	9/50	1/50	13/50	3/50	11/49	5/50	19/50	8/50
Hepatocellular carcinoma	7/50	4/50	12/50	0/50	6/49	2/50	21/50	4/50

m = male; f = female

Oral (co-carcinogenicity)

Furfural-induced hepatic cirrhosis was used for studying the interrelation between hepatic cirrhosis and hepato-carcinogenesis. By feeding 0.03% N-2-fluorenylacetamide (2-FAA) to groups of 16 male Wistar rats for 9 weeks after 120 days of furfural feeding (20-40 ml/kg feed) and 2 weeks of basal diet, it was found that the cirrhotic liver induced by chronic furfural feeding enhanced the 2-FAA chemical hepatocarcinogenesis (Shimizu, 1986). However, this study is of limited value in the assessment of (co)carcinogenic potential of furfural, due to the limited study duration and small number of animals tested. Furthermore, the reliability of the doses used on this study is doubted. Doses were presented in ml/kg feed at levels which correspond with lethal doses in other studies. However, the volatility of furfural was not taken into account, and the actual intake of furfural may be probably less.

Inhalation (carcinogenicity)

In a study of limited duration, Feron and Kruysse (1978) exposed Syrian golden hamsters, 18-30/sex/group, 7 hours/day, 5 days/week for 12 months to furfural vapour and held them an additional 29 weeks in fresh air. Furfural concentrations varied from 1550 mg/m^3 initially to 970 mg/m^3 during the final 32 weeks of exposure. The study was performed according to OECD 413 except for some differences (12 instead of 18-24 months exposure time, presentation of the data, no nominal concentrations, and no data on food/water consumption and ophthalmoscopy). Furfural exposure caused yellowish discolouration of the animals' fur, growth retardation, atrophy and downward growth of sensory cells of the olfactory epithelium, degenerative changes in Bowman's glands, and the occurrence of cyst-like structures in the lamina propria beneath the olfactory epithelium. Furfural had no visible effect on the respiratory epithelium. Comparison of the alterations seen in the nasal cavity in

animals killed at week 52 and those killed after an extra 29 weeks of non-exposure did not show evidence for recovery of furfural-induced lesions or progression of any of the lesions. Furfural did not induce respiratory tract tumours (Feron and Kruysse, 1978).

Inhalation (co-carcinogenicity)

In a study of limited duration reported by Feron (1972) Syrian golden hamsters, 35/sex/group, received for 36 weeks weekly an intratracheal instillation of furfural (3 mg in 0.2 ml 0.9% NaCl), either alone or in combination with benzo(a)pyrene (B(a)P; 1 mg), B(a)P alone, or 0.9% NaCl solution (35 males only). Interim kills were performed on 3 animals/sex/group at week 30. The study was terminated after 78 weeks. In comparison with B(a)P alone, which induced respiratory tumours in 41 out of 62 hamsters, intratracheal instillations of B(a)P and furfural resulted in earlier development of metaplastic changes of the tracheobronchial epithelium, a shorter latent period for tracheobronchiolar tumours, and a few more squamous cell carcinomas at bronchiolar sites (males and females combined: 3 per 61 versus 0 per 62 B(a)P controls) and at lung sites (males: 2 per 32 versus 1 per 32 B(a)P controls). These results suggest a co-carcinogenic effect of furfural on the respiratory tract of hamsters. Furfural also showed an augmenting effect on the induction of peritracheal sarcomas (33%) in the group treated with B(a)P and furfural, whereas B(a)P alone induced 2% of those sarcomas. Death was most frequently due to asphyxia resulting from the obstruction of the trachea by tumours. These results seemed to show that furfural itself possessed no carcinogenicity of its own (Feron, 1972). It is agreed with the author that the number of tumour bearing hamster treated with B(a)P alone was too high to consider 1 mg B(a)P administered weekly a satisfactory threshold for studies on augmenting factors in lung carcinogenesis.

In the study of Feron and Kruysse (1978), as described in the paragraph ‘Inhalation (carcinogenicity)’, separate groups were intratracheally instilled weekly with 0.35 or 0.70 mg benzo(a)pyrene (B(a)P) in 0.2 ml 0.9% NaCl or subcutaneously injected every three weeks with 0.125 µl diethylnitrosamine (DENA) in 0.2 ml 0.9% NaCl. Total amounts of B(a)P were 18.2 and 36.4 mg, whereas a total volume of 2.1 µl DENA per hamster was used. Furfural did not enhance carcinogenicity of B(a)P or DENA.

Dermal (co-carcinogenicity)

In a study of short duration with limited numbers of test animals (CD-1 mice, 20/group),

tumour initiating potential was tested for furfural in a two-stage mouse skin carcinogenesis model using TPA (12-*O*-tetradecanoylphorbol-13-acetate) as the promoter. A total dose of 48 mg furfural was topically applied onto the dorsal skin twice a week (4.8 mg in 0.1 ml aliquots of DMSO) for 5 weeks with or without TPA treatment twice a week for the following 47 weeks (2.5 µg/ 0.1 ml acetone). 7,12- Dimethylbenz(a)anthracene (DMBA; 10 µg/0.1 ml acetone) was used as a positive, and DMSO (0.1 ml) as a negative control. Furfural in combination with TPA treatment induced eight skin tumours (7 papillomas, 1 squamous cell carcinoma) in 25% of the mice (average 0.40/mouse) whereas DMBA in combination with TPA induced tumours in all animals (average 6.7/mouse). No tumours appeared in mice treated with furfural alone. DMBA alone induced skin tumours in 35% of the mice (average 0.35/mouse) whereas TPA alone resulted in skin tumours in one animal only (5%; average 0.05/mouse) (Miyakawa *et al.*, 1991). Given the increase in number of tumours in the 'furfural + TPA' group, compared with the group treated with TPA or furfural only, it is concluded that furfural may possess tumour initiating activity. Only data on the incidence and number of skin tumours and histological types were given. The occurrence of other effects, e.g. skin irritation, was not reported.

Human data

In a population based mortality surveillance in carbon products manufacturing plants, 2219 white male, long term employees were monitored for mortality from 1974 to 1983. Among the six locations studied, there was one location with an excess of deaths from respiratory cancer (5 observed, 1.4 expected). This excess was not counted for by regional differences in death rates. The primary exposures of concern at this location were exposures to formaldehyde, silica, furfural, furfuryl alcohol, and asbestos. No data are available on the concentrations. The subjects had smoked cigarettes and had worked at least 25 years at the plant. Although insufficient data were available to confirm that exposure to asbestos and cigarette smoking was implicated in the aetiology of these data, the review could not identify any other risk factors to which this finding could be ascribed than exposure to chemicals (Teta *et al.*, 1987). This study is not suitable for a conclusion on respiratory cancer and exposure to furfural in human.

Conclusion

Oral exposure

It appears that furfural is carcinogenic in experimental animals after oral (gavage) exposure for two years in male rats and mice. In male rats, uncommon cholangiocarcinomas and bile duct dysplasia with fibrosis, considered to be an early stage in the development of cholangiocarcinomas, were observed after dosing (gavage) at 60 mg/kg bw/d. No evidence for carcinogenicity was found in female rats. An increased incidence of hepatocellular adenomas was found in mice receiving furfural orally by gavage at the highest dose of 175 mg/kg bw/d. Male mice at that dose also showed an increased incidence of hepatocellular carcinomas.

Some remarks should be made here to these gavage studies. Though not quite extended and severe, in both species target-organ toxicity was observed at dose-levels below those that induced tumours. In rats, liver tumours were observed at chronic exposure to 60 mg/kg bw/day, whereas mild centrilobular necrosis was observed at 30 mg/kg bw/day. In fact, the first centrilobular changes, i.e. hepatocellular vacuolisation, were apparent even at 11 mg/kg bw/day and at higher dose levels in a 13-week study with the same strain and exposure regime, i.e. gavage dosing.

As indicated, furfural also induces liver weight increase in male rats at dose-levels close to and below those inducing tumours: i.e. increased weight was observed at 45 mg/kg bw/day in the above mentioned subchronic study. It is of note that this toxicity induction also paralleled tumour-induction: i.e. centrilobular necrosis was found in male rats only.

It is well known that B6C3F1 mice are exceptionally sensitive to developing liver tumours, particularly under conditions of induced (chronic) liver injury. It is of note that in the concurrent male controls the liver tumour incidence already amounts to over 30%. The liver in this species is the most frequently affected tumour-site in the NTP database, and also appears to be especially sensitive to non-genotoxic carcinogens. Though the genesis of these tumours is not fully understood, their appearance is very often associated with hepatotoxicity at or below tumour-inducing test dose levels. As already mentioned, the only other remarkable observations in this target-organ is furfural-induced hepatotoxicity, i.e. centrilobular coagulative necrosis, pigmentation and multifocal inflammation, which was observed in the subchronic test at 100 mg/kg bw/day. This is just below the highest test dose of 175 mg/kg bw/day which gave rise to the observed tumour increase upon chronic exposure. As found with rat liver, toxicity induction again paralleled tumour-induction.

Although chronic inflammation occurred in the mouse in both genders, it was clearly more extensive in the livers of males. Further, in the 13-week gavage study also an increased liver weight was observed in this species at 75 mg/kg bw/day, i.e. below the chronic dose that induced liver tumours.

Inhalation and dermal exposure

No adequate studies are available to evaluate the carcinogenic potential of furfural after inhalation and dermal exposure.

After inhalation exposure, no evidence for carcinogenic effects was found in Syrian golden hamsters. However, the exposure duration of the available study (only 12 months treatment, followed by 29 weeks of non-treatment) was too limited for a proper evaluation of carcinogenicity after inhalation. A co-carcinogenic effect of furfural on the respiratory tract of hamsters was suggested based on a study with treatment of hamsters with furfural alone or in combination with benzo(a)pyrene.

Local toxicity is expected to occur after inhalation exposure given the effects found after repeated inhalation exposure by Feron *et al.* (1978, 1979, 1984). It is not clear from the available data whether tumours will develop by local toxicity. The studies showed that comparison of lesions in the nasal cavity in animals killed after 52 weeks furfural exposure and those killed after an extra 29 weeks of non-exposure did not show any evidence for recovery or progression of any of the lesions.

In 1995, IARC concluded that there is inadequate evidence in humans for the carcinogenicity of furfural, and limited evidence in experimental animals (IARC, 1995).

The CMR Working Group decided that furfural should be classified as Carc. Cat. 3 under Directive 67/548/EEC (November 2003).

Mode of action

The mode of action underlying the hepatocarcinogenic activity of furfural after oral exposure has not fully been elucidated. However, a genotoxic component clearly is not involved, as evidenced by the *in vivo* test using transgenic animals. The data do, however, point to a possible role for chronic cytotoxicity that is found in conjunction with the induction of tumours; a pathway that has also been accepted for other non-genotoxic hepatocarcinogens. It may be argued that the observed cytotoxic effects were not extended and severe enough to

explain this. However, this may be regarded as being in line with the observed tumour response. The tumour incidence in the rat is also very low, and the very sensitive mouse strain B6C3F1 already has a very high background incidence. Thus, the weak, though chronically sustained hepatotoxicity may have been sufficient to induce the low level of tumours. Secondly, it is unclear what exactly the (quantitative) nature of the relationship between toxicity and tumour-induction for different non-genotoxic hepatocarcinogens is. The true mechanisms underlying toxicity most probably differ both in qualitative and in quantitative for any chemical. For furfural, as compared with other non-genotoxic hepatocarcinogens, there may be a more prominent role for induction of mitosis by furfural, i.e. instead of clear hepatotoxicity and necrosis, as suggested by the results of the acute Wistar rat study by Shimizu and Kanisawa (1986). It is known, that a regenerative response in rat liver to toxicity or necrosis (even if this is observed only in the centrilobular region) is often located near the bile ducts, noticeable marked by the generation of so-called 'oval cells' (Laurson et al., 2005), and the bile duct area is exactly the location of the cholangiocarcinomas, which have been found after treatment with furfural.

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 (i.e. 53 mg/kg bw/d, from the dietary study as established under 'repeated dose toxicity') is taken. Because the precise mechanistic background for tumour formation is not clear, some additional margin is needed by interpreting the margin of exposure for the carcinogenicity end-point when based on repeated dose toxicity.

4.1.2.9 Toxicity for reproduction

Animal data

No fertility studies were available with furfural. However, no effects were found on the reproductive organs of both male and female F344/N rats and B6C3F1 mice in two-year gavage studies by NTP at dose levels up to 60 mg/kg in the rats and up to 175 mg/kg bw in mice. The animals were dosed 5d/wk. The following relevant tissues were examined: epididimys, penis, preputial gland, prostate, seminal vesicles, testes,coagulating gland,

clitoral gland, ovaries, uterus,vagina, and tissues from all endocrine glands (Irwin, 1990; see carcinogenicity). In (sub)chronic inhalation exposure studies Syrian golden hamsters were exposured to furfural at levels up to 2165 mg/m^3, 6h/d, 5d/wk. The following relevant tissues were examined: testes, prostate and uterus (Feron *et al.* (1978, 1979). In these studies no treatment related effects were observed at any dose level on the tissues mentioned.

In a developmental dose-range finding study performed in preparation for an OECD 414 study, Sprague-Dawley female rats (8/group) were exposed once daily by gavage to doses of 10, 50, 100, 150, 250, 350, 500, and 1000 mg/kg bw/day during gestation day 6 to 15. The vehicle was reverse osmosis-treated water. Results were only reported for 10, 50, 100, and 150 mg/kg bw/day due to the excessive mortality that was found at dose levels above 150 mg/kg bw/day. At 150 mg/kg bw/day, one female died (1/8). The NOAEL for maternal toxicity was 100 mg/kg bw/day based on several clinical observations that were made at 150 mg/kg bw/day, e.g. exophthalmia and reduction in food consumption. No developmental effects were observed in this dose-range finding study (Nemec, 1997a).

In a developmental toxicity study according to OECD 414, 3 groups of 25 Sprague-Dawley female rats were exposed to furfural once daily by gavage from gestation days 6 to 15 (Nemec, 1997b). The dose levels used were 50, 100, and 150 mg/kg bw/day and were based on the results from the range finding study. A vehicle control group was included. The vehicle was reverse osmosis-treated water. Between gestation day 6 and 15, 3/25 and 16/25 females died in the mid and high dose group. The number of deaths was relatively high and exceeded the limit of 10% for maternal deaths detailed in OECD 414 and this therefore precludes conclusions on developmental toxicity at the highest dose level. The NOAEL for maternal toxicity was considered to be less than 50 mg/kg bw/day based on clinical observations (exophthalmia during gestation day 6-18) at all dose levels. No treatment-related effects were found at scheduled necropsy in the females. The NOAEL for developmental toxicity is at least 100 mg/kg bw/day. In the 150 mg/kg bw/day dose group a not statistically significant reduction in mean fetal body weight (one litter) was observed but this dose level could not be evaluated because of the low survival (only 7 gravid females survived at this dose level). It cannot be excluded that this effect is caused by the maternal toxicity.

Human data

No data are available on toxicity for reproduction in humans.

Conclusion

No effects were observed on the male and female reproductive organs of experimental animals after oral and inhalation (sub)chronic exposures. Based on a developmental toxicity study according to OECD 414, the NOAEL for developmental effects was 100 mg/kg bw/day in Sprague-Dawley rats (highest dose-level that could be evaluated due to low survival in highest dose group, i.e. 150 mg/kg bw/day). The NOAEL for maternal toxicity was less than 50 mg/kg bw/day. No data on reproduction toxicity in humans are available.

The CMR Working Group concluded that furfural should not be classified for reproductive toxicity under Directive 67/548/EEC (November 2003).

4.1.3 Risk characterisation

4.1.3.1 General aspects

In the toxicology data set animal as well as human studies were available for review. Most of the studies were not performed according to current standards, and were, in some cases, not suitable for the overall assessment.

After oral exposure of rats to ^{14}C-furfural, at least 90% is absorbed in the gastro-intestinal tract. 76-100% of the radioactivity was found in urine, faecal elimination was 2-7%, 5-7% was exhaled, and less than 1% is found in the carcass. After inhalatory exposure to furfural, pulmonary retention in humans was 78%. When humans are exposed to furfural vapours (30 mg/m^3), the dermally absorbed quantity of furfural is about 30% of the amount absorbed through inhalation. After dermal exposure to liquid furfural, about 3 µg furfural per cm^2 skin per minute is absorbed in humans. Biological half-life of furfural after inhalation in humans is about 2-2.5 hours.

Based on these data it is concluded that 90% oral and 100% dermal and inhalation absorption are used in the risk characterisation.

It is proposed that biotransformation of furfural in rats and mice may take place in two ways. The major part is oxidized to furoic acid, which is excreted either free or conjugated with glycine (i.e., as furoylglycine). The smaller part condenses with acetic acid giving rise to furanacrylic acid which is excreted in conjugated form (i.e., as furanacryluric acid). An unidentified metabolite was found in urine of rats and mice. Minor differences in metabolic profile in animals as a function of dose size, sex, and species are found. The main metabolite in humans found in urine after inhalation exposure is furoylglycine. Besides furoylglycine, furanacryluric acid was found. Furoic acid was found in negligible amounts in human urine after inhalation. Differences between the metabolites observed in humans and animals may be explained by differences in exposure route and duration, and the dose levels administered (e.g., free furoic acid may be formed due a saturation of the glycine conjugation pathway) and is not necessarily due to species differences.

Furfural has been classified as toxic after oral and inhalation exposure and as harmful in contact with skin by the CMR Working Group of Directive 67/548/EEC.

Furfural liquid causes mild skin irritation after prolonged contact (i.e., 48 hours) and also after repeated exposure. After repeated dermal dosing, less extensive signs of irritation were observed with diluted furfural. Notwithstanding the limited character of the studies, the relatively high concentrations used, the exposure conditions applied (48 hours, under occlusion or repeated exposure) and the mild nature of the effect, the CMR Working Group for Classification and Labelling of Dangerous Substances decided in 2000 that furfural should be classified as irritating to the skin under Directive 67/548/EEC. Furthermore, the Working Group also decided that furfural is irritating to eyes and respiratory tract (Classification:Xi; R36/37/38).

Furfural is not a skin sensitiser based on the results of a Buehler test and a Maximisation test with guinea pigs. No data were available on respiratory sensitisation.

Most repeat dose toxicity studies were performed for the oral route of exposure and use gavage as the method of application. NOAELs derived via this methodology varied from 20 down to < 11 mg/kg bw/d. The various studies differed in quality of design and reporting; some were (nearly) according to OECD guidelines, whereas others were clearly not. The

lowest NOAEL, i.e. <11 mg/kg bw/d, comes from a subchronic study range finding study with rats (Irwin, 1990): at all dose levels, cytoplasmic vacuolization of hepatocytes in the centrilobular region in male rats was found. This effect is considered treatment-related, given the occurrence of mild centrilobular necrosis in male rats in an oral carcinogenicity study with gavage administration.

In more recent studies with rats by Jonker (2000a-c) furfural was applied via the diet in a microencapsulated form (to prevent loss of the compound due to its volatility). In the 13-week dietary study, effects included minor hepatocellular alterations which were observed in males, but not in females, at doses of 82 and 160 mg/kg bw/d. The NOAEL in this study, therefore, was established at the one lower dose-level of 53 mg/kg bw/d (with corresponding nominal exposure value of 60 mg/kg bw/d), a value clearly higher than the one achieved with gavage application.

Having taken note of the fact that a complementary study showed that furfural was rapidly and completely released from this microencapsulation in an aqueous environment (Buck, 2000) the NOAEL from this study is selected as the starting point for the risk characterisation for repeated oral exposure for the following reasons: (i) dietary administration of a test compound is the preferred method of exposure via this route as compared to gavage application; (ii) microencapsulation adequately circumvents loss of furfural due to volatization and results in an instantaneous release of this substance in the aqueous environment of the GI-tract; (iii) dietary exposure avoids the use of (for this substance) corn oil exposure, that is known to be associated with morphological liver changes upon prolonged exposure; (iv) the alternative key-study of Irwin (1990; 13-week study in rats) has a limited design, being a range-finding study only. The JECFA (Joint FAO/WHO Expert Committee on Food Additives; WHO, 2001) came to the same conclusion after evaluating the 13-week dietary study by Jonker (2000b,c).

Of the two available inhalation studies the one reported by Muijser (2001) and Arts *et al.* (2004) has the lowest NOAEC of <20 mg/m^3 for local effects. At this concentration metaplasia and hyperplasia of transitional respiratory epithelium were observed at the anterior part of the nose in rats. This study is considered suitable for the risk characterisation for local effects after for systemic effects after repeated inhalation exposure.

The lowest NOAEC for systemic effects was also reported by Muijser (2001) and Arts *et al.* (2004) at 320 mg/m^3. According to the authors this concentration corresponds to 92 mg/kg

bw/d (assuming 100% absorption, ventilation rate of 0.8 l/kg bw, and an oral absorption of 100%; Muijser, 2001; Appel, 2001b; Arts *et al.*, 2004). This concentration of 320 mg/m^3 will be taken as starting point for the risk characterisation for systemic effects after repeated inhalation exposure.

No dermal repeated-dose toxicity data are available that can be used for the risk characterisation. From the two available no observed effect levels from repeated dose toxicity studies, i.e. for oral and inhalation exposure, the oral NOAEL of the 13-week diet study with rats will be used to evaluate the systemic toxicity after dermal exposure in the risk characterisation.

Regarding classification according to Directive 67/548/EEC for repeated dose toxicity, it is noted that the CMR Working Group decided that the effects observed were considered to not fulfill the criteria for classification according this Directive.

It is concluded that furfural causes chromosomal aberrations and gene mutations *in vitro*. Furfural did not induce chromosome aberrations and SCEs in bone marrow cells of mice after intraperitoneal treatment. One abstract reported furfural as positive in a cytogenicity study in mouse bone marrow (Subramanyam *et al.,* 1989). However, since this paper was not published in a peer reviewed journal subsequently, it could not be fully evaluated. Furfural was negative in *in vivo* UDS tests with rat and mouse hepatocytes (Lake *et al*., 2001).
The study in the λlacZ transgenic mice (strain 40.6) indicated that orally applied furfural was unable to induce gene mutations *in vivo* in mouse liver, a tissue in which carcinogenicity was observed (see section 4.1.2.8).
The CMR Working Group decided that the available data on mutagenicity are considered to not fulfill the criteria for classification according to Directive 67/584/EEC (November 2003).

It appeared that furfural is carcinogenic in a 103 weeks oral gavage studies with rats and mice. In male rats, a low incidence of uncommon cholangiocarcinomas and bile duct dysplasia with fibrosis, considered to be an early stage in the development of cholangiocarcinomas, were observed by dosing (gavage) 60 mg/kg bw/d. No evidence for carcinogenicity was found in female rats. An increased incidence of hepatocellular adenomas was found in mice receiving furfural by gavage at the highest dose of 175 mg/kg bw/d. Male

mice at that dose also showed an increased incidence of hepatocellular carcinomas.
Some remarks should be made here to these gavage studies. In both species dose-levels that induced tumours also led to target-organ toxicity. This toxicity induction also paralleled tumour-induction. Centrilobular necrosis was found in male rats only, and chronic inflammation occurred in the livers of both genders of mice, though it was more extensive in males.
It is well known that B6C3F1 mice are exceptionally sensitive for developing liver tumours, particularly under conditions of induced (chronic) liver injury. However, there is no clear understanding of the genesis of cholangiocarcinomas in rat liver, though it is known that the site where these tumours originate in rat liver is also often associated with a regenerative response to necrosis of hepatocytes (also in case of centrilobular necrosis) near bile ducts, noticeable by the generation of so-called 'oval cells'.

No adequate studies are available to evaluate the carcinogenic potential of furfural after inhalation and dermal exposure. After inhalation exposure, no evidence for carcinogenic effects was found in Syrian golden hamsters. However, the exposure duration of the available study (only 12 months treatment, followed by 29 weeks of non-treatment) was too limited for a proper evaluation of carcinogenicity after inhalation. A cocarcinogenic effect of furfural on the respiratory tract of hamsters was suggested based on a study with treatment of hamsters with furfural alone or in combination with benzo(a)pyrene.
It should be noted that local toxicity is expected to occur after inhalation exposure given the effects found after repeated inhalation exposure by Feron *et al.* (1978, 1979, 1984). It is not clear from the available data whether tumours will develop by local toxicity.

Although the mode of action underlying the carcinogenic activity of furfural after oral exposure has not been fully elucidated, a genotoxic component apparently is not involved, as evidenced by the negative *in vivo* test using transgenic animals. The data are interpreted as indicating that the observed liver tumours were induced via some mechanism involving liver toxicity and, consequently, 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 (i.e. 53 mg/kg bw/d, from the dietary study as established under 'repeated dose toxicity') is selected. Since the precise mechanistic background for tumour formation is not clear, an additional safety margin is required when repeat dose exposure

estimates are evaluated for the carcinogenicity end-point.

The CMR Working Group concluded that furfural should be classified as Carc. Cat. 3 (November 2003).

No effects were observed in the male and female reproductive organs of experimental animals after oral and inhalation (sub) chronic exposures. Thus, no LOAEL/NOAEL for fertility could be established. In a developmental toxicity study according to OECD 414, the NOAEL for developmental effects was 100 mg/kg bw/day in Sprague-Dawley rats administered furfural by gavage (highest dose-level that could be evaluated, due to low survival in 150 mg/kg bw/day group). The NOAEL for maternal toxicity was less than 50 mg/kg bw/day. No data on reproduction toxicity in humans are available.
The CMR Working Group concluded that furfural should not be classified for reproductive toxicity under Directive 67/548/EEC (November 2003).

4.1.3.2 Workers

Assuming that oral exposure is prevented by personal hygiene measures, the risk characterisation for workers is limited to the dermal and inhalation routes of exposure.

Acute toxicity

It should be noted that the acute inhalation and dermal toxicity data are only appropriate to assess lethality after acute exposure. It is expected that other toxic effects after acute exposure will occur at lower concentrations than the lethal concentrations.

Inhalation exposure

Furfural is classified as toxic after inhalation exposure. For occupational risk assessment the short-term inhalation exposure levels (see Table 4.6) are compared with the LC_{50} values in rats, since rats are more sensitive to lethal effects of furfural than mice. Furthermore the most appropriate exposure duration in the acute studies is taken into account (see Table 4.21). The MOSs between the LC_{50}-values and the inhalation exposure levels are mentioned in Table 4.25. The MOSs are evaluated by comparison with the minimal MOS (125). In Appendix 3 the assessment factors used to establish the minimal MOS are given (table I-1). There is concern when the MOS is significantly lower than the minimal MOS.

Based upon the available data it can be concluded that acute toxic effects due to acute inhalation exposure cannot be excluded for all scenarios. It is noted that the data available for evaluation of acute inhalation exposure are limited. Given the irritating properties of furfural in humans at concentrations of 20-63 mg/m^3, it is unlikely that workers will tolerate a prolonged single exposure to the concentrations mentioned in Table 4.25. Furthermore, it is assumed that existing controls to prevent acute respiratory irritation are applied. Based on these considerations, it is concluded that furfural is of no concern for workers with regard to acute respiratory toxicity (**conclusion ii**). The conclusions are given in Table 4.25.

Table 4.21 Risk assessment for acute toxicity after inhalation exposure

Occ. Exp. sc	Short-term exposure estimate		Toxicological starting-point		MOS	Conclusion [A]
	Duration (hr)	Exposure (mg/m^3)	duration (hr)	LC_{50} (mg/m^3)		
1. Production, - cleaning and maintenance	0.25	120	1	4075	34	ii
2. Product derivatives - adding	2-4	12	4	600-924	50-77	ii
3. Prod. Refractories, etc.	0.25	100	1	4075	40	ii
4. Use of furfural - cleaning and maintenance	0.25	100	1	4075	40	ii

[A] Based on comparison of the MOS with a minimal MOS of 125.

Dermal exposure

Furfural is classified as harmful in contact with skin, LD_{50} 400-2000 mg/kg bw (rabbit). A dose of 620 mg/kg bw is reported to be lethal in rabbits (LD_{low}). This level is compared with the anticipated occupational exposure levels (see Table 4.22). The MOSs between the LD_{low}-value and the dermal exposure levels are given in Table 4.22. The MOSs are evaluated by comparison with the minimal MOS (300). In Appendix 3 the assessment factors used to establish the minimal MOS are given (table I-2). There is concern when the MOS is significantly lower than the minimal MOS.

Given the MOSs for acute dermal exposure as detailed in Table 4.22 it can be concluded that acute toxic effects due to acute dermal exposure cannot be excluded for scenario 1 'production – cleaning and maintenance'. It is noted, however, that the given MOS-values are calculated based on exposure estimates for the unprotected worker (see chapter 4.1.1.1). As a consequence of the labelling of this substance with R38 it is expected that workers will use effective personal protection products, and consequently, experience substantially lower exposures. On this basis, it is concluded that furfural is of no concern for workers with regard to acute dermal toxicity (**conclusion ii**) for all scenarios. The conclusions are given in Table 4.22.

Table 4.22 Risk assessment for acute toxicity after dermal exposure.

Occ. Exp. Sc	Exposure estimate (mg/day (mg/kg bw/day))	Toxicological starting-point (mg/kg bwday)	MOS	Conclusion[A]
1. Production				
- production activities	42 (0.6)	620	1033	ii
- cleaning and maintenance	650 (9.3)	620	67	ii
2. Product derivatives				
- adding	42 (0.6)	620	1033	ii
3. Prod. Refractories, etc.	63 (0.9)	620	689	ii
4. Use of furfural				
- refining etc.	42 (0.6)	620	1033	ii
- cleaning and maintanance	21 (0.3)	620	2067	ii

[A] Based on a worker body weight of 70 kg and on comparison of the MOS with a minimal MOS of 300.

Irritation

Acute dermal irritation

Given the effects observed in the skin irritation studies with rabbits and in view of the dermal occupational exposure in the different scenarios (<0.5 mg/m^2), it is concluded that furfural is of concern for workers with regard to acute skin irritation. However, it is assumed that existing controls (i.e., engineering controls and personal protective equipment based on classification and labelling with R38) are applied. Therefore, it is concluded that furfural is of no concern for workers with regard to skin irritation (**conclusion ii**).

Dermal irritation after repeated dose

No animal or human data are available on local skin effects after repeated dermal exposure. The risk for local effects after repeated dermal exposure cannot be derived from the oral and inhalation repeated toxicity studies, so a quantitative risk characterisation is not possible.

Eye irritation

Ocular exposure is possible via vapours or incidentally from splashing. Given the effects observed in the acute eye irritation study in rabbits with liquid furfural, the eye irritation reported by workers exposed to furfural vapour (20 to 63 mg/m^3) (ACGIH, 2001), and the eye irritation observed in a 13-week inhalation repeated-dose study with Syrian golden hamsters (Feron *et al.*, 1978; 1984), and comparing this with the estimated short-term exposure levels (12 to 120 mg/m^3), it is concluded that furfural is of concern for workers with regard to eye irritation. However, it is assumed that existing controls (i.e., engineering controls and personal protective equipment based on classification and labelling with R36) are applied. Therefore, it is concluded that furfural is of no concern for workers with regard to eye irritation (**conclusion ii**).

Acute respiratory irritation

Given the effects observed after single exposure to furfural vapour in animals and humans, and the short-term exposure level (reasonable worst-case ranging from 12 to 120 mg/m^3), it is concluded that furfural is of concern for workers with regard to acute respiratory tract irritation. However, it is assumed that existing controls (i.e., engineering controls and personal protective equipment based on classification and labelling with R37) are applied. Therefore, it is concluded that furfural is of no concern for workers with regard to acute respiratory irritation (**conclusion ii**). It is noted that the studies available did not allow a quantitative comparison of (no) effect concentrations with estimated exposure levels.

Respiratory irritation after repeated exposure

Repeated inhalation exposure may induce respiratory tract irritation. Starting-points for the risk characterisation after repeated inhalation exposure with respect to these effects are (a) the results from the repeated inhalation studies (see paragraph 4.1.2.6 'inhalation') and (b) the inhalation occupational exposure estimates (see chapter 4.1.1.2 and Table 4.7). The human data available cannot be used quantitatively. Given the estimated frequency of exposure (up to 225 d/year), chronic exposure is assumed for the risk characterisation. The MOSs between the LOAEL for local effects from the 28-day inhalation study with rats by Muijser (2001; Arts *et al.* (2004)) (<20 mg/m^3) and the inhalation exposure levels are given in Table 4.23. The MOSs are evaluated by comparison with the minimal MOS (112.5). The assessment factors used to establish the minimal MOS are given in Appendix 3 (table I-3). There is concern when the MOS is significantly lower than the minimal MOS. The conclusions are given in Table 4.23.

Table 4.23 Risk assessment for furfural for local effects after repeated occupational inhalation exposure

Scenario/subscenario	Risk characterisation for respiratory exposure		
	Estimated inhalation exposure (mg/m^3) (full shift)	MOS [A]	conclusion[B]
1. Production - full shift	30	0.7	iii
2. Production derivates - full shift	6	3	iii

3. Production refractories - mix, mould, etc.	40	0.5	iii
4. Use of furfural - refining, etc.	25	0.8	iii

[A]: based on an NOAEL of <20 mg/m^3; [B] Based on comparison of the MOS with a minimal MOS of 112.5.

Given the MOSs for inhalation exposure as mentioned in Table 4.23, it is concluded that health risks for local effects due to repeated inhalation exposure cannot be excluded for any scenario. Risk reduction measures are indicated (**conclusion iii**). It might be possible that in some industrial premises worker protection measures are already being applied.

Corrosivity

Given the results from the skin and eye irritation studies, it is concluded that furfural is of no concern for workers with regard to corrosivity (**conclusion ii**).

Sensitisation

Given the results from the dermal sensitisation studies with guinea pigs, it is concluded that furfural is of no concern for workers with regard to skin sensitisation (**conclusion ii**).

There are no data from human experience or any other indications for respiratory sensitisation.

Repeated-dose toxicity – systemic effects

In the section on 'carcinogenicity', risk characterisation for carcinogenic effects is described.

Dermal exposure

Starting points for the risk characterisation for workers exposed by skin contact for systemic effects are (a) the NOAEL of 53 mg/kg bw/day from the 13-week oral toxicity study with rats of Jonker (2000b,c), and (b) the estimated dermal exposure levels for the different occupational scenarios (see chapter 4.1.1.2 and Table 4.7).

The oral toxicity studies with rats are taken as starting point for the risk characterisation as no systemic effects were observed up to relatively high concentrations in the relevant inhalation studies.

Given the estimated frequency of exposure (up to 225 d/year), chronic exposure is assumed for risk characterisation. The MOSs between the NOAEL and the dermal exposure levels are

mentioned in Table 4.24. The MOSs are evaluated by comparison with the minimal MOS of 55. The assessment factors used to establish the minimal MOS are given in Appendix 3 (table I-4). There is concern when the MOS is significantly lower than the minimal MOS. The conclusions are given in Table 4.24.

Table 4.24 Occupational risk assessment of furfural for repeated dose toxicity (systemic effects).

Scenario/subscenario	Risk characterisation for dermal exposure			Risk characterisation for inhalation exposure		
	Estimated dermal exposure (mg/day)	**MOS[A]**	**Conclusion[B]**	**Estimated inhalation exposure (mg/m^3)**	**MOS[C,]**	**Conclusion[D]**
1. Production						
- full shift	42	88	ii	30	11	iii
- cleaning & maintenance	650	5.7	iii	70	5	iii
2. Production of derivatives						
- full shift	42	88	ii	6	53	iii
3. Production of refractories, etc.						
- mix, mould, etc.	63	59	ii	40	8	iii
4. Use of furfural						
- refining, etc.	42	88	ii	25	13	iii
- cleaning & maintenance	21	177	ii			

[A]: calculation based on the oral NOAEL of 53 mg/kg bw/d and assuming a worker body weight of 70 kg; [B]: Based on comparison of the MOS with a minimal MOS of 55 (Appendix 3: Table I-4); [C]: based on a NOAEL of 320 mg/m^3; [D]: Based on comparison of the MOS with a minimal MOS of 112.5.

Given the MOSs for dermal exposure as mentioned in Table 4.24, it is concluded that systemic effects due to repeated dermal exposure cannot be excluded for the scenario: 'production - cleaning and maintenance'. Therefore, **conclusion iii** is reached for this scenario. It might be possible that in some industrial premises worker protection measures are already being applied.

Inhalation exposure

Starting-points for the risk characterisation for workers exposed by inhalation for systemic effects are (a) the NOAEL of 320 mg/m^3 from the 28-day inhalation study with rats of

Muijser (2001; Arts *et al.* (2004)), and (b) the estimated inhalation exposure levels for the different occupational scenarios (see chapter 4.1.1.2 and Table 4.7).
Given the estimated frequency of exposure (up to 225 d/year), chronic exposure is assumed for risk characterisation. The MOSs between the LOAEL and the inhalation exposure levels are mentioned in Table 4.24. The MOSs are evaluated by comparison with the minimal MOS of 112.5. The assessment factors used to establish the minimal MOS are given in Appendix 3 (table I-5). There is concern when the MOS is significantly lower than the minimal MOS. The conclusions are given in Table 4.24.

Given the MOSs for inhalation exposure as mentioned in Table 4.24, it is concluded that systemic effects due to repeated inhalation exposure cannot be excluded for all scenarios. Therefore, **conclusion iii** is reached for all scenarios. It might be possible that in some industrial premises worker protection measures are already being applied.

Combined exposure

Given the conclusions for scenario's 1-4 given above for the inhalation route, it is clear that uptake via both the dermal and inhalation route in these scenarios will give rise to adverse systemic health effects. It should be noted, though, that exposure to furfural vapour is not taken into account in the dermal exposure assessment.

Mutagenicity

From the results of the mutagenicity studies it is concluded that furfural is not genotoxic *in vivo*. Hence, this endpoint is not of concern: **conclusion ii**.

Carcinogenicity

Furfural induced tumours in the livers of male rats (cholangiosarcomas) and hepatocellular adenomas and carcinomas in female and male mice, respectively, after oral (gavage) administration. The mechanism by which these tumours are induced does not involve genotoxicity, as furfural is not genotoxic *in vivo*. Furfural is for that reason considered a threshold carcinogen.

As the liver tumours were observed at exposure levels that also induced liver toxicity, it is assumed that at levels at which no liver toxicity is induced, no tumours will arise. At the

repeated dose toxicity section it is proposed to select the application-method applied by Jonker (Jonker, 2000b). In this study a NOAEL for liver toxicity of 53 mg/kg bw/day is obtained.

A similar rationale as for the role of systemic toxicity in tumour-induction is proposed with respect to local toxicity at the site of entrance i.e. as long as no cytotoxicity occurs, it is not expected that locally tumours will be induced. In the repeated dose toxicity section the possible occurrence of systemic and local toxicity under worker exposure conditions is already evaluated (Table 4.24, and Table 4.23, respectively). However, as the true mechanism underlying these liver tumours is unclear so far, this uncertainty should be reflected in the final evaluation of the comparison between the MOS and minimal MOS. We, therefore, want the scenario-specific MOS to be clearly in excess of the minimal MOS value (in contrast to the criterion applied for repeated dose toxicity where it is stated that "There is concern when the MOS is significantly lower than the minimal MOS").

From Table 4.23 for local effects and Table 4.24 for systemic effects it can then be concluded that all scenarios are of concern, i.e. lead to conclusion iii. This applies to all inhalation exposure scenarios (local and systemic effects) as well as (for systemic effects) to the dermal exposure scenarios 1 ('production - cleaning and maintenance'), and, additionally, scenario 3 ('Production of refractories, etc.- mix, mould, etc.'). The latter scenario is included because of the low (MOS/minMOS) ratio, as well as the fact that exposure to furfural vapour is not taken into account in the dermal exposure assessments. Thus, for this latter scenario the (MOS/minMOS) ratio is considered insufficient for deriving a conclusion ii for this endpoint (while a conclusion ii was derived for this scenario for repeated dose toxicity). The dermal exposure scenarios 2 and 4 are considered to be without risk: i.e. a **conclusion ii** is derived.

For combined exposure, clearly there is concern for carcinogenic effects for all exposure scenarios: **conclusion iii**.

Reproductive toxicity

There are no indications for effects on fertility (**conclusion ii**).

Developmental studies by inhalation or dermal exposure are lacking. An oral developmental toxicity study (OECD 414) with furfural in rats is available. Developmental toxicity occurred only at maternally toxic levels. Furfural appeared to be not teratogenic. The NOAEL for developmental effects is 100 mg/kg bw/day (highest dose level that could be evaluated, because of low survival of parent female animals in the 150 mg/kg bw/day group (16/25

females died at this dose level)). In the 150 mg/kg bw/day dose group a not statistically significant reduction in mean foetal body weight was observed in one litter; it cannot be excluded that this effect is caused by maternal toxicity. The NOAEL for maternal toxicity was less than 50 mg/kg bw/day. The CMR Working Group concluded that furfural should not be classified for reproductive toxicity (November 2003).

The MOSs between the oral NOAEL and the respiratory and dermal exposure levels are shown in Table 4.25 and the MOSs are evaluated by comparison with the minimal MOS (55). The assessment factors used to establish the minimal MOS are given in Appendix 3 (table I-6). There is concern when the MOS is significantly lower than the minimal MOS. The conclusions are given in Table 4.25.

Table 4.25 Occupational risk assessment of furfural for developmental toxicity.

Scenario/subscenario	Risk characterisation for dermal exposure			Risk characterisation for inhalation exposure		
	Estimated dermal exposure (mg/day)	**MOS[A]**	**Conclusion [B]**	**Estimated inhalation exposure (mg/m^3)**	**MOS[A,C]**	**Conclusion[D]**
1. Production						
- full shift	42	167	ii	30	23	ii
- cleaning & maintenance	650	11	iii	70	10	iii
2. Production of derivatives						
- full shift	42	167	ii	6	117	ii
3. Production of refractories, etc.						
- mix, mould, etc.	63	111	ii	40	18	ii
4. Use of furfural						
- refining, etc.	42	167	ii	25	28	ii
- cleaning & maintenance	21	333	ii			

[A]: calculation based on the NOAEL for developmental effects of 100 mg/kg bw/d and assuming a worker body weight of 70 kg; [B]: Based on comparison of the MOS with a minimal MOS of 55. [C]: assuming a respiratory volume of 10 m^3 for a working day; [D]: Based on comparison of the MOS with a minimal MOS of 55.

Based on the finding that a developmental toxicity effects only occurred at maternally toxic dose levels, MOS values which are slightly lower (i.e. a factor 1-3) than the minimal MOS are not considered of toxicological relevance. Therefore, it is concluded that with regard to inhalation exposure in the occupational scenario 1 'production – full shift', scenario 3

'Production of refractories, etc. - mix, mould, etc.' and scenario 4 'Use of furfural- refining, etc.', there is no concern for workers with respect to developmental toxicity (**conclusion ii**). Though ADME studies do not directly support a possible risk for developmental effects after dermal and inhalation exposure, it is concluded that these effects cannot be excluded for scenarios 1 'production - cleaning and maintenance', given the low associated MOSs (as indicated in Table 4.25) i.e. a **conclusion iii** is derived for this scenario for both dermal and inhalation exposure. It might be possible that in some industrial premises worker protection measures are already being applied.

Occupational limit values

In Table 4.1 an overview of occupational limit values for furfural is given. In the United Kingdom an Occupational Exposure Standard (OES)-value of 8 mg/m^3, i.e. a 8-hour TWA value, and a Short Term Exposure Limit (15-minute STEL) of 20 mg/m^3 are established; also a skin notation applies for this substance (HSE, 2002).

ACGIH (2001) established a TLV of 7.9 mg/m^3 (2 ppm) for furfural on the basis of irritation to the eyes, mucous membranes and skin. A STEL is not recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The BEI-value (established in 1991 by ACGIH) of furfural is 200 mg/g creatinine (sampling time: end of shift) based on total furoic acid in urine. This determinant is not specific, i.e., it is observed after exposure to some other chemicals. Furthermore, it is usually present in non-occupationally exposed humans. Correction for this background is included in the BEI-value. A skin notation is assigned to furfural.

The current Maximum Accepted Concentration (2 ppm; 8 mg/m^3) of The Netherlands is under revision at the moment. Despite the lack of adequate inhalation carcinogenicity studies, the oral carcinogenicity studies with rats and mice were used to estimate the cancer risk in the draft report of Dutch Expert Committee on Occupational Standards. Additional cancer risk of 4.10^{-5} and 4.10^{-3} for a person of 70 kg, breathing 10 m^3 of air during an 8-hour workshift, 5 days a week for 40 years were calculated to be 0.4 and 40 mg/m^3 (DECOS, 1996).

The Swedish National Board of Occupational Safety and Health (1993) established a Level Limit value of 2 ppm (8 mg/m^3) and a short-term value (STV) of 10 ppm (40 mg/m^3). The substance can easily be absorbed percutaneously.

Since recent data indicate that furfural apparently is not genotoxic *in vivo*, any concerns about a non-threshold component in the observed carcinogenic effects, as indicated above, have been alleviated. Although guideline inhalation or dermal carcinogenicity studies are not available, any possible carcinogenic effects after exposure via these routes will probably result only after chronic tissue damage and inflammatory responses, i.e. effects with a clear threshold.
It should be considered whether the current occupational limit values are low enough for worker protection based on the additional tests performed.

4.1.3.3 Consumers

From the identified uses, attention has been paid to consumer exposure to furfural resulting from its use as fragrance material in perfume (scenario I) and as flavouring agent in food (scenario II). For consumers, dermal exposure is most relevant in scenario I, whilst in scenario II it is oral exposure. For both scenarios it is considered that exposure occurs frequently. Starting points for the risk characterisation are the dermal external exposure of 1 µg/kg bw/d for scenario I (cosmetics), the oral external exposure estimates of 9 and 136 µg/kg bw/d (the latter as worst case estimate) for scenario II (food flavouring substance), and absorption percentages of 100% and 90% for the dermal and oral route, respectively. It is noted that the use of furfural in fragrance materials and food flavouring substances is regulated by other EU legislation.

<u>Irritation (Scenario I)</u>

Depending on the concentration, furfural liquid can be irritating to the skin, and for this property the substance has been classified. For concentrations as low as 0.1 % (the reported maximum concentration in perfume) no skin irritation was observed. Hence, for consumers

there is no concern for skin irritation (**conclusion ii**). Furfural is considered to be an eye irritant and is classified/labelled accordingly (**conclusion ii**).

Sensitisation (Scenario I)

Furfural is not a skin sensitiser. Consumers are therefore not at risk after repeated dermal exposure (**conclusion ii**).

Repeated-dose toxicity (Scenario I and II)

Starting points for the risk assessment for consumers are the dermal and oral exposure estimates and the oral NOAEL of 53 mg/kg bw/d from the dietary 13-week oral toxicity study with rats. Studies to assess the systemic toxicity after repeated dermal exposure are lacking. Route-to-route extrapolation is applied for scenario I, taking into account the oral and dermal absorption percentages of 90 and 100%, respectively. The (external) NOAEL of 53 mg/kg bw/d, observed in the 13 week oral study, corresponds to an internal NOAEL for systemic effects of 47.7 mg/kg bw/d.

For scenario I: The calculated external dermal dose of 1 µg/kg bw/d corresponds to a systemic dose of 1 µg/kg bw /d. Comparing the internal NOAEL with this calculated systemic dose, a margin of safety of 47700 can be calculated.

For scenario II: Comparing the oral NOAEL with the oral exposure estimate of 9 µg/kg bw/day, a margin of safety of 5889 can be calculated. When taking into account the worst case estimate of 136 µg/kg bw/day a margin of safety of 390 can be calculated. Using assessment factors of 10 for intra- and interspecies (2.5 x 4) differences, the minimal MOS is 100. There is no need for a factor for duration extrapolation because furfural has been studied in a chronic bioassay and no effect of exposure duration was found in relation to the NOAEL, or the nature of the observed effects.

The MOSs for scenarios I and II do not indicate a concern for consumers for repeated dermal and oral exposure **(conclusion ii)**.

Mutagenicity (Scenario I and II)

Furfural is not genotoxic *in vivo*. Hence, this endpoint is not of concern (**conclusion ii**).

Carcinogenicity (Scenario I and II)

Furfural induced tumours in the livers of male rats (cholangiosarcomas) and hepatocellular adenomas and carcinomas in female and male mice, respectively, after oral (gavage) administration. The mechanism by which these tumours are induced does not involve genotoxicity, as furfural is not genotoxic *in vivo*. As the liver tumours were observed at exposure levels that also induced liver toxicity, it is assumed that at levels at which no liver toxicity is induced, no tumours will arise. Hence, as starting point for the risk characterisation for carcinogenicity the oral NOAEL for liver toxicity (i.e. 53 mg/kg bw/d, as established under 'repeated dose toxicity') is taken. Route-to-route extrapolation is applied for scenario I, taking into account the oral and dermal absorption percentages of 90 and 100%, respectively. The (external) NOAEL of 53 mg/kg bw/d corresponds to an internal NOAEL of 47.7 mg/kg bw/d.

For scenario I: The calculated external dermal dose of 1 µg/kg bw/d corresponds to a systemic dose of 1 µg/kg bw /d. Comparing the internal NOAEL with this calculated systemic dose, a margin of safety of 47700 can be calculated.

For scenario II: Comparing the oral NOAEL with the oral exposure estimate of 9 µg/kg bw/day, a margin of safety of 5889 can be calculated. When taking into account the worst case estimate of 136 µg/kg bw/day a margin of safety of 390 can be calculated. Using assessment factors of 10 for intra- and interspecies (2.5 x 4) differences, the minimal MOS is 100. There is no need for a factor for duration extrapolation because furfural has been studied in a chronic bioassay and no effect of exposure duration was found in relation to the NOAEL, or the nature of the observed effects.

Even in the light of the need for a slightly higher MOS than the required minimal MOS of 100, because of the unknown exact mechanism for carcinogenicity, the current MOSs of 47700 and 390-5889 for scenarios I and II do not indicate a concern for consumers with regard to carcinogenicity **(conclusion ii).**

Reproductive toxicity (Scenario I and II)

There are no indications for effects on fertility. Developmental studies by inhalation or dermal exposure are lacking. An oral developmental toxicity study with rats is available. Developmental toxicity occurred only at maternally toxic dose levels. Furfural is not teratogenic. The NOAEL for developmental effects is 100 mg/kg bw/d and the NOAEL for maternal toxicity was <50 mg/kg bw/d. This latter value is used to characterise the risk for the pregnant population. Route-to-route extrapolation is applied for scenario I, taking into account the oral and dermal absorption percentages of 90 and 100%, respectively. This results in internal NOAELs of 90 mg/kg bw/d for developmental effects and <45 mg/kg bw/d for maternal toxicity, respectively.

For scenario I: Comparing the internal NOAELs of 90 and <45 mg/kg bw/d with the calculated systemic dose of 1 µg/kg bw/d for scenario I, margins of safety of 90000 and <45000, respectively, can be calculated.

For scenario II: Comparing the oral NOAELs of 100 and <50 mg/kg bw/d with the oral exposure estimate of 9 µg/kg bw/d, margins of safety of 11100 and <5555, respectively, can be calculated. When taking into account the worst case estimate of 136 µg/kg bw/day, margins of safety of 735 and <368, respectively, can be calculated. Using assessment factors of 10 for intra- and interspecies (2.5 x 4) differences and 3 for the LOAEL for maternal toxicity, the minimal MOS is 100 for developmental effects and 300 for maternal effects.

Taking into account the magnitude of these MOSs and the worst case character of the highest exposure estimate, for both scenario I and II there is no concern for consumers for reproductive toxicity after repeated dermal and oral exposure **(conclusion ii**).

4.1.3.4 Human exposed indirectly via the environment

Local exposure

With EUSES, for local exposure the highest estimated daily intake dose via food and air was found for scenario Vb, formulation for manufacturing refractories, site 2 (11 µg/kg bw/day). The main exposure routes are air, drinking water and intake of leaf crops.

Repeated-dose toxicity

Starting points for the risk assessment for human exposed indirectly via the environment are the above mentioned (internal) exposure estimates from EUSES and the oral NOAEL of 53 mg/kg bw/d from the dietary 13-week oral toxicity study with rats. The (external) NOAEL of 53 mg/kg bw/d, observed in the 13 week oral study, corresponds to an internal NOAEL for systemic effects of 47.7 mg/kg bw/d.

The calculated intake of 11 µg/kg bw/d compared to the internal NOAEL results in a margin of safety of 4336. Using assessment factors of 10 for intra- and interspecies (2.5 x 4) differences, the minimal MOS is 100. There is no need for a factor for duration extrapolation because furfural has been studied in a chronic bioassay and no effect of exposure duration was found in relation to the NOAEL, or the nature of the observed effects.

The MOS does not indicate a concern for human exposed indirectly via the environment (local) for repeated exposure **(conclusion ii)**.

Carcinogenicity

Furfural induced tumours in the livers of male rats (cholangiosarcomas) and hepatocellular adenomas and carcinomas in female and male mice, respectively, after oral (gavage) administration. The mechanism by which these tumours are induced does not involve genotoxicity, as furfural is not genotoxic *in vivo*. As the liver tumours were observed at exposure levels that also induced liver toxicity, it is assumed that at levels at which no liver toxicity is induced, no tumours will arise. Hence, as starting point for the risk characterisation for carcinogenicity the oral NOAEL for liver toxicity (i.e. 53 mg/kg bw/d, as established under 'repeated dose toxicity') is taken. The (external) NOAEL of 53 mg/kg bw/d corresponds to an internal NOAEL of 47.7 mg/kg bw/d.

The calculated intake of 11 µg/kg bw/d compared to the internal NOAEL results in a margin of safety of 4336. Using assessment factors of 10 for intra- and interspecies (2.5 x 4) differences, the minimal MOS is 100. There is no need for a factor for duration extrapolation because furfural has been studied in a chronic bioassay and no effect of exposure duration was found in relation to the NOAEL, or the nature of the observed effects.

Even in the light of the need for a slightly higher MOS than the required minimal MOS of 100, because of the unknown exact mechanism for carcinogenicity, the current MOS does not

indicate a concern for human exposed indirectly via the environment (local) with regard to carcinogenicity **(conclusion ii).**

Reproductive toxicity (Scenario I and II)

There are no indications for effects on fertility. Developmental studies by inhalation or dermal exposure are lacking. An oral developmental toxicity study with rats is available. Developmental toxicity occurred only at maternally toxic dose levels. Furfural is not teratogenic. The NOAEL for developmental effects is 100 mg/kg bw/d and the NOAEL for maternal toxicity was <50 mg/kg bw/d. This latter value is used to characterise the risk for the pregnant women. The internal NOAELs are 90 mg/kg bw/d for developmental effects and <45 mg/kg bw/d for maternal toxicity, respectively.

Comparing the calculated intake of 11 µg/kg bw/d to the internal NOAELs margins of safety of 8182 and <4091, respectively, can be calculated. Using assessment factors of 10 for intra- and interspecies (2.5 x 4) differences and 3 for the LOAEL for maternal toxicity, the minimal MOS is 100 for developmental effects and 300 for maternal effects. Taking into account the magnitude of these MOSs, there is no concern for human exposed indirectly via the environment (local) for reproductive toxicity after repeated exposure **(conclusion ii**).

Regional exposure

For regional exposure, the total daily intake estimated by EUSES is 4 ng/kg bw/day. For the natural occurrence of furfural in food, FEMA calculated a total potential daily intake of approximately 300 µg/kg bw/day for furfural and precursors of furfural from natural occurrence in food. The total daily intake estimated by EUSES can be considered negligible compared to the natural occurrence.

Humans have been exposed to this source of furfural via the diet for many years. No formal risk characterisation will be performed for this natural occurrence of furfural. However, to have some indication of the margins between the estimated 'natural' exposure to furfural (and related compounds) of 300 µg/kg bw/d and the N(L)OAELs for the endpoints of concern, please see the table below.

	Repeated dose toxicity	Carcinogenicity	Reproductive toxicity	
			Developmental tox.	Maternal tox.
Oral NOAEL (mg/kg bw/d)	53	53	100	<50
Margin between NOAEL and estimated exposure of 300 µg/kg bw/d	177	177	333	<167

4.1.3.5 Combined exposure

In this combined exposure section the exposures in occupational settings are compared to the exposures resulting from other sources (i.e. consumer products, indirectly via the environment). In Table 4.26 an overview of all exposures is given.

The exposure of workers is higher than the other exposures, and the risk characterisation already resulted in concern for the endpoints repeated dose toxicity, carcinogenicity, and developmental toxicity for some or all scenarios. These have been indicated in the occupational sections and will not be further discussed here. Because conclusions iii were drawn, risk reductions measures will be taken in the occupational setting. The exposures resulting from consumer products and from natural occurrence in food are outside the scope of the Existing Substances Regulation (793/93/EC) and will not be included in a formal risk characterization for combined exposure.

From the table it is clear that exposure via the environment is negligible as compared to the occupational exposures. Therefore the risk characterization for combined exposure is completely driven by the risk characterization for the occupational settings (**conclusion iii**).

Table 4.26 Overview of the total exposure to furfural.

	Exposure in µg/kg bw/day*		
Workers exposure	oral	inhalatory	dermal
Production: - Full shift - cleaning and maintenance		4300 10000	600 9300
Production of derivatives Full shift		900	600

Production of refractories Mix, mould, etcetera		5800	900
Use of furfural - refining, etcetera - cleaning and maintenance		3600 -	600 300
Consumer exposure			
cosmetic products (fragrances)			1
food flavouring substances	9-136		
Indirectly exposed via the environment			
local (scenario Vb, highest exp.)	11		
regional (EUSES calculation)	0.004		
natural occurrence in food (estimation by FEMA)	300		

* Worker exposure estimates calculated from the data in table 4.25 assuming a worker body weight of 70 kg, a respiratory volume of 10 m^3 for a working day and 100% dermal and inhalation absorption.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES

Furfural does not need to be classified for explosive and flammability properties. Based on theoretical and structural considerations, furfural is not expected to have oxidising potential. Given these properties, there is no need for further information and/or testing with regard to physico-chemical properties (**conclusion ii**).

5 CONCLUSIONS / RESULTS

Environment:

(X) i) There is need for further information and/or testing

(X) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

(X) iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account

Conclusion i) is reached because:

- The PEC soil exceeds the PNEC soil in the scenarios 'formulation for manufacturing refractories Va, Vb' and 'use as intermediate in pesticide manufacture VI'. The terrestrial PNEC is derived through the equilibrium partitioning method and there is therefore scope to refine this PNEC through testing. However, no testing is proposed for the terrestrial compartment since for these scenarios also conclusion iii is drawn for the local aquatic compartment. The development of risk reduction measures for the aquatic compartment should take account of the conclusions for the terrestrial compartment for these three scenarios.

Conclusion iii) is reached because:

- The PEC water exceeds the $PNEC_{surface\ water}$ in the scenarios 'formulation chemical tracer in mineral oil and fuel industry IVb', 'formulation for manufacturing refractories Va, Vb' and 'use as intermediate in pesticide manufacture VI'. As no further refinement of the PECs and PNECs is possible, there is a need for limiting the risks.

For all remaining scenarios a conclusion ii is drawn for the environment.

Risks of 2-furaldehyde as a result of emissions by the pulp and paper industry (unintentional source):

The PEC_{STP} and the $PEC_{surface\ water}$ exceed the corresponding PNECs in the 'pulp and paper industry, scenario VII' (unintentional source). For the refinement of this scenario site-specific measured effluent or surface water concentrations are needed. Additionally, measured data from other pulp and paper industries in the EU are needed to refine this scenario. Since this

considers an unintentional source beyond the scope of this EU risk assessment, there will be no follow-up of this scenario in the context of Regulation 793/93/EC.

Human health

Workers:

(X) iii) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion (iii) is reached because:

- systemic effects and local effects on respiratory tract cannot be excluded after repeated inhalation exposure in all scenarios;
- systemic effects cannot be excluded after repeated dermal exposure in scenarios 1 'production – cleaning and maintenance';
- carcinogenic effects cannot be excluded after repeated dermal and inhalation exposure in all scenarios; and
- developmental effects due to repeated dermal and inhalation exposure cannot be excluded in scenario 1 'production – cleaning and maintenance'.

It might be possible that in some workplaces adequate worker protection measures are already being applied.

Consumers:

(X) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human via the environment:

(X) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Combined exposure:

(X) iii) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account.

The risk characterization for combined exposure is completely driven by the risk characterization for the occupational settings.

Risks arising from physico-chemical properties:

(X) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

6 REFERENCES

Abbott MG, McFee AF, Tice RR, Genotoxicity of four furan compounds tested in vivo, Environ. Mol. Mutag. Suppl., p. 5. (1991)

ACGIH (The American Conference of Governmental Industrial Hygienists) (2001). Furfural: Documentation of the threshold limit values and biological exposure, 5th edition. Cincinnati: ACGIH.

ACGIH (The American Conference of Governmental Industrial Hygienists) (2003) TLVs and BEIs, Threshold Limit Values for chemical substances and physical agents, Biological Exposure Indices, Cincinnati, p. 32, 90.

Adams, TB, Doull J, Goodman JI, Munro IC, Newberne P, Portoghese PS, Smits RL, Wagner BM, Weil CS, Woods LA, Ford RA, The FEMA GRAS assessment of furfural used as a flavour ingredient, Food Chem. Toxicol. 35: 739-751 (1997).

Appel MJ (2001a) Sub-acute (28-day) oral toxicity study with furfural in rats. TNO report V3155, TNO Nutrition and Food Research, Zeist, The Netherlands.

Appel MJ, Mommers C, Muijser H, and Arts JHE (2001b) Route-to-route extrapolation: sub-acute (28-day) toxicity of 1,4 dichlorobenzene and furfural after oral and inhalation exposure. TNO report V3591, TNO Nutrition and Food Research, Zeist, The Netherlands.

Arts JHE, Muijser H, Appel JA, Bessems JGM, Woutersen RA (2004) Sub-acute (28-day) toxicity of furfural in Fischer 344 rats: a comparison of the oral and inhalation route. Food and Chemical Toxicology, 42(9), 1389-1399.

Benjamin MM, Woods SL and Ferguson JF (1984): Anaerobic Toxicity and Biodegradability of Pulp Mill Waste Constituents. Water Res. 18 No. 5: 601-607

BGAA (1996)- Expositionsbeschreibung 2-furylmethanal (V.7.0325).

Borelli S (1988) Krankheiten der Haut und Schleimhaut durch Kontakte in Beruf und Umwet, *in* Dermatologischer Noxen-Katalog, Springer.

Bringmann, G and R Kühn, 1976. Vergleichende Befunde der Schadwirkung wassergefährender Stoffe gegen Bakterien (Pseudomonas putida) und Blaualgen (Microcystus aeroginosa) im Zellvermehrungstest. GWF-wasser/abwasser. 117 (1976) H.9, 410-413.

Bringmann, G and R Kühn, 1978. Grenzwerte der Schadwirkung wassergefährender Stoffe gegen Blaualgen (Microcystis aeruginosa) und Grünalgen (Scenedesmus quadricauda) im Zellvermehrungstest. Vom Wasser, 50, 45-60.

Bringmann, G and R Kühn, 1980. Bestimmung der biologischen Schadwirkung wassergefährender Stoffe gegen Protozoa (III. Saprozoische Flagellaten). Z. Wasser Abwasser Forsch 13, no.5, pp 170-173.

Bringmann, G and R Kühn, 1980. Bestimmung der biologischen Schadwirkung wassergefährender Stoffe gegen Protozoen (II. Bakterienfressende Ciliaten). Z. Wasser Abwasser Forsch 13, no.1, pp 26-31.

Bringmann, G and R Kühn, 1982. Ergebnisse der Schadwirkung wassergefahrender Stoffe gegen Daphnia magna in einem weiterentwickelten standardisierten Testverfahren. Z. Wasser Abwasser Forsch 15, no.1, pp 1-6.

Bringmann, G, 1978. Bestimmung der biologischen Schadwirkung wassergefährender Stoffe gegen Protozoen (I. Bakterienfressende Flagellaten; Modelorganismus). Z. Wasser Abwasser Forsch 11, no.9, pp 410-413.

Buck N (2000) Release of furfural from micro-encapsulation through solvating. Unpublished report from the Clinical Pharamacology Group, University of Southampton, United Kingdom [as cited in WHO, 2001].

Castellino N, Elmino O, Rozera G (1963) Experimental Research on Toxicity of Furfural.

Archives of Environmental Health 1963; 7: 574-582.

CEH (1994) Chemical Economics Handbook, Furfural by R. Will et al. March-April.

Chengelis CP (1997) A 28-day repeated dose oral toxicity study of furfural in rats, WIL Research Laboratories, Inc., Project number WIL-12367, Ashland.

CMR Working Group (2003), November Meeting.

Cocker J, Gregg N, Brown R, Rajan R, Topping M, Furfural, Draft criteria document for an occupational exposure limit, Health and Safety Commission, Working Group on the Assessment of Toxic Chemicals, United Kingdom (1992)

Company A (1980). Furfural, general information, applications, properties, handling, Bulletin 203-D.

Company B (2000). Exposure questionnaire Furfural, 27-1-2000.

Company C (2000). Exposure questionnaire Furfural, 30-3-2000.

Concawe (1999). Exposure data for furfural for the petroleum industry.

Connel DW, Markwell RD (1990) Bioaccumulation in the soil to earthworm system. Chemosphere 20, 91-100.

Cralley LV, Cralley LJ (1989) In: Plant practices for job related health hazards control, Volume 1, Production processes, Wiley Interscience, New York/Chichester/Brisbane/Toronto/Singapore, p. 892-893.

DECOS (1996) Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards. Health-based recommended occupational exposure limit for furfural, The Hague: Health Council of the Netherlands, draft report.

DEI (1994). Dutch Emission Inventory

Deneer JW, W Seinen and JLM Hermens, 1988. The acute toxicity of aldehydes to the guppy. Aquatic Toxicol. 12, 185-192.

Di Pede C, Viegi G, Taddeucci R, Landucci C, Settmi L, Paggiaro PO (1991) Biological monitoring of work exposure to furfural. Arch. Environm. Health 46, 125-126.

Dillon DM, McGregor DB, Combes RD, Zeiger E (1992) Detection of mutagenicity in Salmonella of some aldehydes and peroxides. Environm. Mol. Mutagen. suppl. p. 15.

Ecoserv (2001) Illova downstream products - Sezela. Occupational exposure assessment & occupational hygiene survey. Ecoserv PYT LTD (September 2001).

EFSA (2004) Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to furfural as a flavouring substance. (Question number EFSA-Q-2003-116) Opinion adopted by the AFC Panel on 2 June 2004 by written procedure.
http://www.efsa.eu.int/science/afc/afc_opinions/491/opinion_afc12_ej67_furfural_en1.pdf

Ettinger MB, Lishka RJ and Moore WA (1954): The Determination and Persistence of Furfural in River Waters. Proceedings of the eighth industrial waste conference: Purdue Univ Ext Ser.

European Commission (2002) Commission directive 2002/72/ec of 6 august 2002 relating to plastic materials and articles intended to come into contact with foodstuffs Official Journal of the European Union 13.2.2003 L 39/2.

European Commission (2003) “Synoptic Document” Provisional list of monomers and additives notified to European Commission as substances which may be used in the manufacture of plastics intended to come into contact with foodstuffs (updated to 25 july 2003). Document can be downloaded from http://cpf.jrc.it/webpack (legislative information).

Feron VJ (1972) Respiratory tract tumours in hamsters after intratracheal instillations of benzo(a)pyrene alone and with furfural. Cancer Research 32, 28-36.

Feron VJ, Kruysse A (1978) Effects of exposure to furfural vapour in hamsters simultaneously treated with benzo(a)pyrene or diethylnitrosamine. Toxicology 11, 127-144.

Feron VJ, Kruysse A, Dreef-van der Meulen H (1979) Repeated exposure to furfural vapour: 13-week study in syrian golden hamsters. Zbl. Bakt. Hyg., I. Abt. Orig. B 168, 442-451.

Feron VJ, Woutersen RA, Appelman LM (1984) Epithelial damage and tumours of the nose after exposure to four different aldehydes by inhalation. In: Crosdanoff P et al.; Problems of inhalatory toxicity studies. Munchen: MMV Medizin Verlag, 587-610.

Feron VJ, Til, HP, de Vrijer F, Woutersen RA, Cassee FR, van Bladeren PJ (1991) Aldehydes: occurrence, carcinogenic potential, mechanism of action and risk assessment. Mutation Research, 259, 363-385.

Finnish Environmental Institute (1997) Finnish exposure register.

Flek J, Sedivec V (1978) The absorption, metabolism and excretion of furfural in man. Int. Arch. Occup. Environ. health 41, 159-168.

Foussereau et al. (1982) Occupational Contact Dermatitis. Clinical and Chemical Aspects. 1st Ed. P.225.

Galloway SM, Bloom AD, Resnick M, Margolin BH, Nakamura F, Archer P, Zeiger E (1985) Development of standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7, 1-51.

Gomez-Arroyo S, Souza V (1985) In vitro and occupational induction of sister-chromatid exchanges in human lymphocytes with furfuryl alcohol and furfural. Mutat. Res. 156, 233-238.

Gorelick NJ (1995) Overview of mutation assays in transgenic mice for routine testing. Toxicol. **20** (suppl), 321-330.

Gorelick NJ, Mirsalis JC (1996) A strategy for the application of transgenic rodent mutagenesis assays. Environ.Mol.Mutagen., 28,434-442.

Gregg C, Rajan R, Cocker J, Groves J (1997) 2-Furaldehyde: Risk Assessment Document. Pub. HSE Books. P.O.Box 1999. Sudbury. Suffolk. United Kingdom.

Gudi R, Schadly EH (1996) In vitro mammalian cytogenetic test with an independent repeat assay. Microbiological Associates, Inc., Maryland, Laboratory Study Number G96AS33.335.

Gupta GD, Misra A, Agarwal DK (1991) Inhalation Toxicity of Furfural Vapours: an Assessment of biochemical Responses in Rat Lungs. Journal of Applied Toxicology 11 (5), 343-347.

Hadi SM, Shahabuddin, Rehman A (1989) Specificity of the interaction of furfural with DNA. Mutation Research 225, 101-106.

Hakkert BC, Stevenson H, Bos PMJ, Van Hemmen JJ (1996) Methods for the establishment of health-based recommended occupational exposure limits for existing substances. TNO Report V96.463.

Hansch L (1995) Exploring QSAR, Volume 2, ACS, Washington DC, p. 11.

Hazardous Substances Data Bank (HSDB) (Febr 1996). File Z960201A.1

Hazardous Substances Data Bank (1997). HSDB Accession number 542; update code: 9704; substance identification: furfural.

Hazardous Substances Data Bank (HSDB) (July 1998)

Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards (DECOS): Calculating cancer risk. The Hague: Health Council of the Netherlands, 1995; publication no. 1995/06 WGD.

HEDSET (1997). Existing Substances Regulation. Data submission for furfural. Exposure data sheet for furfural use(r)s.

Heil J, Reifferscheid G (1992) Detection of mammalian carcinogens with an immunological DNA synthesis-inhibition test. Carcinogenesis, 13, 2389-94.

Hessov Ib, 1975. Toxicity of 5-hydroxymethylfurfural and furfural to Daphnia magna. Acta Pharmacol. Toxicol.,37, 94-96.

Heukelekian H and Rand MC (1955): Biochemical Oxygen Demand of Pure Organic Compounds. J Water Pollut Contr Assoc 29: 1040-53.

Howard (1993) Handbook of environmental fate and exposure data for organic chemicals. Lewis Publishers. Volume I-IV

HSE (2002) EH40/2002 Occupational Exposure Limits 2002. ISBN 0 7176 2083 2.

IARC (1995). Volume 63. Dry cleaning, some chlorinated solvents and other industrial chemicals.

Illovo Sugar (2003) Skin sensitisation study of furfural in guinea pigs (guinea pig maximization test). Conducted by Jai Research Foundation, India. Report no. JRF Study no. 3953 (May 23). Gujarat, India.

INRS (1986) Valeurs limites pour les concentrations des substances dangereuses dans l'air des lieux de travail. Cah. Not. Doc. 125 (4e trimestre), 556.

IPCS (2000) Concise International Chemical Assessment Document 21, 2-furaldehyde. WHO, Geneve.

Irwin R (1990) NTP technical report on the toxicology and carcinogenesis studies of furfural in F344/N rats and B6C3F1 mice (gavage studies). NIH publication No. 90-2837. National Toxicology Program, Research Triangle Park, North Carolina.

Jonek JJ, Konecki J, Kaminski M (1975) Histoenzymatic changes in liver in acute poisoning with furfural. Rev. roum. Morphol. Embryol. Physiol., Morphol.-Embryol. 21, 47-51.

Jones RE (1979) Mutagenicity test. The Quaker Oats Company, Reference number TT-578, Chicago.

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.

Jonker D (2000c) Sub-chronic (13 week) oral toxicity study in rats with micro-encapsulated furfural. Unpublished TNO report V99.520, TNO Zeist, The Netherlands.

Juhnke, I and D Ludemann, 1978. Ergebnisse der Untersuchung von 200 chemische Verbindingen auf akute Fischtoxizitat mit dem Goldorfentest. Z.f. Wasser- und Abwasser Forschung 11, Jahrgang No.5, 161-164.

Kawasaki, M. (1980) Experience with the test scheme under the Chemical Control Law of Japan: An approach to Structure-Activity Correlations. Ecotoxicol. Environ. Saf. 4, 444-454.

Kern TG (1997) Skin sensitization study of furfural in Albino Guinea pigs, WIL Research Laboratories, Inc., WIL project no.: WIL-12376, Ashland.

Kirk-Othmer (1984) Encyclopedia of Chemical Technology, John Wiley & Sons, New York 3rd. ed., 501-510.

Koepel, v.d. Morton International, Amersfoort (1998). Personal Communication.

Konecki J, Jonek JJ, Kaminski M (1974) Histochemical changes in the small intestine in acute furfural poisoning; Folia Histochemica et Cytochemica, 12, 59-70.

Laham S, Potvin M (1989) Metabolism of furfural in the Sprague-Dawley rat; Toxicological and Environmental Chemistry; Vol. 24; p. 35-47.

Lake BG, Edwards AJ, Price RJ, Phillips BJ, Renwick AB, Beamond JA, Adams TB (2001).Lack of effect of furfural on DNA unscheduled DNA synthesis in the in vivo rat and mouse hepatocyte DNA repair assays and in precision-cut human liver slices. Food and Chemical Toxicology 39, 999-1011.

Laurson J, Selden C, HOdgson HJF (2005). Hepatocyte progenitors in man and in rodents - multiple pathways, multiple candidates, Intrenat. J. Experimental Pathology, 86 (1), 1-18.

Loquet C, Toussaint G, LeTalaer JY (1981) Studies on mutagenic constituents of apple brandy and various alcoholic beverages collected in western France, a high incidence area for oesophageal cancer. Mutation Research 88, 155-164.

Loquet C, Toussaint G, LeTalaer JY, Studies on mutagenic constituents of apple brandy and various alcoholic beverages collected in western France, a high incidence area for oesophageal cancer. Mutation Research 88, 155-164 (1981)

Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 7-4, 7-5, 8-12 (1990)

MAFF (1997) Food Safety Information Bulletin No. 81, January 1997.

McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, Caspary WJ, Responses of the

L5178Ytk^{+}/tk^{-} Mouse Lymphoma Cell Forward Mutation Assay II: 18 coded chemicals. Environ. molec. Mutag. 11, 91-118 (1988)

Merck Index 10th ed (1983), p. 614*ii.* Technical Bulletin Furfural - QO Chemicals.

Meyberg M, Kappler R, Kristen U (1987) Bestimmung der Cytotoxizitaet organischer Luftschadstoffe. VDI-Berichte 609, 507-512.

Ministerie van Sociale Zaken en Werkgelegenheid (SZW) (1996) Arbeidsinspectie, De nationale MAC-lijst 1996, The Hague, The Netherlands, SDU Service centrum Uitgeverijen, 35 (pub. no., P145).

Miyakawa Y, Nishi Y, Kato K, Sato H, Takahashi M, Hayashi Y (1991) Initiating activity of eight pyrolysates of carbohydrates in a two-stage mouse skin tumorigenesis model. Carcinogenesis 12 (7), 1169-1173.

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E (1986) Salmonella mutagenicity tests: II Results from the testing of 270 chemicals. Environ. Mutat. 8, suppl. 7, 1-119.

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

NAS (1987) In: Adams et al., 1997.

Nemec A (1997a) Dose range-finding developmental toxicity study of furfural in rats; WIL Research Laboratories, Inc., Laboratory study number WIL-12377, Ashland.

Nemec A (1997b) Developmental toxicity study of furfural in rats; WIL Research Laboratories, Inc., Laboratory study number WIL-12378, Ashland.

NIOSH (National Institute for Occupational Safety and Health) (1987) Guide to industrial respiratory protection, OHNS, Publication no. 87-116.

NIOSH (National Institute for Occupational Safety and Health) (1995) Health hazard evaluation report HETA 95-0147-2542 - North American Refractories Company - Cincinnati, Cincinnati.

Nishi Y, Miyakawa Y, Kato K (1989) Chromosome aberrations induced by pyrolysates of carbohydrates in Chinese hamster V79 cells. Mut. Res. 227, 117-123.

Nomeir AA, Silveira DM, McComish MF, Chadwick M (1992) Comparative metabolism and disposition of furfural and furfuryl alcohol in rats. Drug Metabolism and Disposition 20 (2), 198-204.

OFI (1995) In: Adams et al., 1997

Opdijke DLJ (1978) Furfural, Fragrance raw materials monographs, Food Cosmetic Toxicology, 16, p. 759-764.

Palmer SJ, Kendall TZ, Krueger HO, Furfural: A flow-through life-cycle toxicity test with the cladoceran (*Daphnia magna*) Final Report. Wildlife International, LTD. Project Number: 566A-105A (2005)

Parkash MK, Caldwell J (1994) Metabolism and excretion of [^{14}C]furfural in the rat and mouse. Fd. Chem. Toxic. 32 (10), 887-895.

Patty (1981) Industrial Hygiene & Toxicology, 3rd edition, Vol 2A, 2B, 2C 1981-82, p. 2663.

Pitter P. (1976): Determination of Biological Degradability of Organic Substances. Water Research 10, pp 231-235.

Reynolds SH, Stowers SJ, Patterson RM, Maronport RR, Aaronson SA, Anderson MW; Activated oncogens in B6C3F1 mouse liver tumours: Implications for risk assessment. Science 237, 1309-1316 (1987)

Rivard CJ, Grohmann K (1991) Degradation of furfural (2-furaldehyde) to methane and carbon dioxide by anaerobic consortium, Applied Biochemistry Biotechnology, 28(29), p. 285-295.

Rodriguez-Arnaiz R, Romas-Morales P, Zimmering S (1992) Evaluation in Drosophila melanogaster of the mutagenic potential of furfural in the mei-9a test for chromosome loss in germ-line cells and the wing spot test for mutational activity in somatic cells, Mutation Research, 280, p. 75-80.

Rorije, E., M. Muller and W.J.G.M. Peijnenburg. Prediction of environmental degradation rates for High Production Volume Chemicals (HPVC) using Quantitative Structure-Activity Relationships. RIVM, The Netherlands, Report No. 719101030 (1997).

Rowe EH, Tullos LFJR (1980). Lube solvents no threat to waste treatment. Hydrocarbon Process 59: 63-65.

Sabljic and Guesten (1995). QSARs for soil sorption. In: Overview of Structure-Activity Relationships for Environmental Endpoints. Hermens JLM (ed.).

Sax NI (1984) Dangerous Properties of Industrial Materials, 6th edition, New York: Van Nostrand Reinolds, p.1780.

Sax NI (1989) Dangerous Properties of Industrial Materials, 7th edition, p. 1780.

SCCNFP (2004). Opinion of the Scientific Committee on Cosmetic products and Non-Food consumer Products intended for consumers concerning FURFURAL. Adopted by the SCCNFP during the 28th plenary meetingof 25 May 2004. SCCNFP/0822/04.

SCF (1987) Reports of the Scientific Committe for Food, seventeenth series 1986. Commission of the European Communities, EU-10778 EN. Office for official publications of the European Community, Luxembourg.

SCF (1993) Summary on furfural prepared for the SCF Meeting Copenhagen May 1993. CS/FL/59.

SCF (1999) Opinion on a programme for the evaluation of flavouring substances. Document nr SCF/CS/FLAV/TASKF/11 Final; Annex I to the minutes of the 119th Plenary meeting.

Shibamoto T, Mutagen formation in browning model system. Journal of applied toxicology 4, vol. 2, 97-100 (1984)

Shimizu A (1986) Experimental study on hepatic cirrhosis and hepatocarcinogenesis, II. Influence of cirrhotic liver on 2-FAA hepatocarcinogenesis in rats, Acta Pathol. Jpn. 36 (7), 1039-1048.

Shimizu A, Kanisawa M (1986) Experimental studies on hepatic cirrhosis and hepatocarcinogenesis, I. Production of hepatic cirrhosis by furfural administration. Acta Pathol. Jpn., 36 (7), 1027-1038.

Shimizu A, Nakamura Y, Harada M, Ono T, Sato K, Inoue T, Kanisawa M (1989) Positive foci of glutathione-S-transferase placental form in the liver of rats given furfural by oral administration, Jpn. J. Cancer Res. 80, 608-611.

Shinohara K, Kim E-H, Omura H (1986) Furans as the mutagens formed by amino-carbonyl reactions. Developm. Food Sci. 13, 353-362.

Sittig and Marshall et al (1991) Handbook of toxic and hazardous chemicals and carcinogens, p.845.

Sleijffers A, Wolterink G, Zomer B, Hollestelle SCG, Van de Werken G, Vleeming W, Opperhuizen A, Van Amsterdam JGC (2006) The adverse health effects of aldehydes as tobacco ingredients. Part 1. Furfural, Benzaldehyde, Isobutyraldehyde, Ethylvanillin, Phenylacetaldehyde, and Salicylaldehyde. RIVM, Bilthoven The Netherlands, Report no 340630005/2006.

Soska J, Koukalova B, Ebringer L (1981) Mutagenic activities of simple nitrofuran derivates I. Comparison of related compounds in the phage inductest, chloroplast-bleaching and bacterial-repair and mutagenicity tests, Mutation Research 81, 21-26.

Steenwinkel M-JST, Krul CAM (2003) *In vivo* gene mutation study by use of *λlacZ*-transgenic mice with furfural. TNO report V3934, TNO Nutrition and Food Research, Zeist, The Netherlands.

Steinhagen WH, Barrow CS (1984) Sensory Irritation Structure-Activity Study of Inhaled Aldehydes in B6C3F1 and Swiss-Webster mice. Toxicology and Applied Pharmacology, 72, p. 495-503.

Stich HF, Rosin MP, Wu CH, Powrie WD (1981) Clastogenicity of furans found in food. Cancer Letters 13, p. 89-95.

Struijs J (1996): SimpleTreat 3.0: a model to predict the distribution and elimination of Chemicals by Sewage Treatment Plants, 49 p in English, RIVM report 719101025

Subramanyam A, Sailaja D, Rathnaprabba D (1989) Genotoxic assay of two dietary furans by some in vivo cytogenetic parameters, EMS Abstracts, p. 239.

Swedish Forest Industries Federation (2006). Letter on use of sulphite pulping process in Sweden from the Swedish National Inspectorate, 21-01-2006.

Swedish National Board of Occupational Safety and Health (1993) Occupational Exposure limit values, Ordinance (AFS 1993:9), Solna , Sweden.

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

Terrill JB, van Horn WE, Robinson D, Thomas DL (1989) Acute Inhalation Toxicity of Furan, 2-Methyl Furan, Furfuryl Alcohol, and Furfural in the Rat. Am. Ind. Hyg. Assoc. J.

50, p. 359-361.

Teta MJ, Ott MG, Schnatter AR (1987) Population based mortality surveillance in carbon products manufacturing plants. Br. J. Ind. Med. 44, p. 344-350.

TFC (TransFurans Chemicals bvba) (1980) Personal communication by company (until end of 1997 named QO Chemicals, Inc.)

TFC (TransFurans Chemicals bvba) (1996) Personal communication by company (until end of 1997 named QO Chemicals, Inc.)

TFC (TransFurans Chemicals bvba) (2000) Personal communication by company (April 22, 1999).

TFC (TransFurans Chemicals bvba) (2000) Personal communication by company (February 21, 2000).

TFC (TransFurans Chemicals bvba) (2003) Personal communication by company (October 2003).

TGD (2003) Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Chemicals.
European Commission, European Chemicals Bureau (ECB), Ispra, Italy.

TGD (1996). Technical Guidance Documents in support of the Commission Directive 93/67/EEC on risk assessment for New Notified Substances and the Commission Regulation (EC) 1488/94 on risk assessment for Existing Chemicals.
European Commision, European Chemicals Bureau (ECB, Ispra, Italy..

Turnbull, H, JG DeMann, RF Weston, 1954. Toxicity of various refinery materials to fresh water fish, Ind. Eng., 46 (2), 324-333

Ubaydullayev R (1970) Biological effects of low concentrations of furfural under experimental conditions. Journal of hygiene, microbiology and immunology, 14, 240-251.

Uddin S (1993) Effect of furfural on the secondary structure of DNA, Med. Sci. Res. 21(4), p. 545-546.

Uddin S, Hadi SM (1995) Reactions of furfural and methylfurfural with DNA; Biochemistry and Molecular Biology International, 35 (1), p. 185-195.

Veen, M. van (1977) Consexpo 2. Consumer Exposure and Uptake Models. RIVM report 612810005.

Veith GD, Defoe DL and Bergstedt BV (1979): Measuring and estimating the bioconcentration factor of chemicals in fish. J. Fish. Board Can. 36, 1040-1048.

Verschueren K (1983) Handbook of environmental data on organic chemicals, 2nd edition, Van Nostrand Reinolds, New York.

Vinogradova VK, Smirnova VG, Belyakov AA, Chernova LN, Osokina AP, Problems of labour hygiene and state of health of workers engaged in furfurol production. Gig. Tr. Prof. Zabol. 12, 7-10 (1968)

Volskay, VT and C.P. Leslie Grady, 1988. Toxicity of selected RCRA compounds to activated sludge microorganisms. J. Water Pollut. Control Fed., 60, 1850.

Wallen, IE, W.C Greer, R. Lasater, 1957. Toxicity to *Gambusia affinis* of certain pure chemicals in turbid waters. Sewage Ind. Wastes, 29 (6), 695-711.

Watanabe K, Matsuda M, Furuhashi S, Kimura T, Matsunaga T, Yamamoto I (2001). Skin reaction induced by aldehydes for food flavoring agents. Journal of Health Science 47 (3), 327-329.

WHO (1993) WHO Food additives Series, No. 30, 271-83, WHO, Geneve.

WHO (1999) WHO Food Additive Series, No. 42, Furaldehyde (p. 33- 56), WHO, Geneve.

WHO (2001) WHO Food Additive Series, No. 46, Furaldehyde (p. 3-6), WHO, Geneve.

Wilmer JWGM, Leeman WR, Splinter A, Feron VJ (1987) Induction of DNA repair in nasal epithelium by formaldehyde and other irritant aldehydes. In: Proc. 2nd Int. Conf. on the role of formaldehyde in biological systems. Tyhiak E, Gullner G (eds). Keszthely, Hungary, 79.

Witters H, Fish, short-term toxicity test on embryo and sac-fry stages of zebrafish, *Brachydanio rerio*. Test substance: furfural. Study report VITO FST 04001, Mol, Belgium, (2005)

Woodruff RC, Mason JM, Valencia R, Zimmering S (1985) Chemical mutagenesis testing in Drosophila. V. Results of 53 coded compounds tested for the National Toxicology Program. Environ. Mutat. 7, 677-702.

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

Zhang J, He Q, Lioy PJ (1994) Characteristics of aldehydes: concentrations, sources and exposures for indoor and indoor residential microenvironments. Environmental Science & Technology 28 (1); 146 -152. Abstract in Toxline plus.

Zienicka M, Ptotic B, Zielenska M, Szymczyk T (1978) Mutagenic activity of furfural in Salmonella typhimurium TA100. Mutation Research 58, 205-209.

Appendix 2

Reliability Index and usefulness of information in HEDSET*

Reliability Index	Description reliability	Usefulness	Description usefulness
1 valid without restrictions	the method and description are in accordance with test guidelines[1]	a useful	relevant for RA-report[5]
		b not useful	not relevant for RA-report[5]
2 valid with restrictions	the method **and/or** description are less in accordance with test guidelines[2,5]	a useful	relevant for RA-report[5]
		b not useful	not relevant for RA-report[5]
3 invalid	the method and/or description are **not** in accordance with test guidelines[3,5]	a useful	relevant for RA-report[5]
		b not useful	not relevant for RA-report[5]
4 not assignable	the orignal data are not available[4,5]	a useful	relevant for RA-report[5]
		b not useful	not relevant for RA-report[5]

* The reliability index and usefulness indication are also applicable for QSAR-data (e.g. log Kow). Usefulness is applicable after evaluating all tests for one endpoint.

1 for example: -complete test report available; GLP, Annex V; OECD, EU e.t.c.
See also chapter 2 Risk Assessment for Human Health of TGD (page 28)
-publications are not included

2 for example: -validity of data cannot be fully established
-some modifications or omissions in method and description
-acceptable publication (e.g. according to EU- or OECD guidelines)

3 for example: -method unknown and/or critical pieces of information are not available (e.g. identity of substance)
-documentation not sufficient for unequivocal assessment
-do not meet important criteria of today standard test methods

4 for example: -only abstract available
-secondary literature (reviews, tables etc..)

5 Motivation/justification should be given:
-when study is useful but as supporting data
-when study is not useful for the RA-report (e.g. chinese language)

Appendix 3

Establishment of the minimal MOSs used for occupational risk characterisation

In the table below calculations of the minimal MOS-values via assessment factors are given. The assessment factors are based upon the draft version of the TGD (2005).

Table I-1

Assessment factors applied for the calculation of the minimal MOS for lethality after acute inhalation exposure applicable on the acute inhalation toxicity study with rats

Aspect	**Assessment factors**
Interspecies differences[A]	2.5
Intraspecies differences	5
Differences between experimental conditions and exposure pattern of the worker	1
Dose-response curve / Type of critical effect[B]	10
Confidence of the database	1
Overall	125

[A] For inhalation studies only a factor 2.5 is used, and no correction is made for differences in body size, because extrapolation is based on toxicological equivalence of a concentration of a chemical in the air of experimental animals and humans; animal and humans breathe at a rate depending on their caloric requirements.

[B] It is noted that the MOS values are calculated for a severe effect (lethality). Therefore, an assessment factor of 10 is applicable.

Table I-2

Assessment factors applied for the calculation of the minimal MOS for lethality after acute dermal exposure applicable on the acute dermal toxicity study with rabbits

Aspect	**Assessment factors**
Interspecies differences[A]	2.4 x 2.5
Intraspecies differences	5
Differences between experimental conditions and exposure pattern of the worker	1
Dose-response curve / Type of critical effect[B]	10
Confidence of the database	1
Overall	300

[A] Extrapolation based on differences in caloric demands, together with a factor 2.5 for remaining uncertainties.

[B] It is noted that the MOS values are calculated for a severe effect (lethality). Therefore, an assessment factor of 10 is applicable.

Table I-3

Assessment factors applied for the calculation of the minimal MOS for local effects after chronic inhalation exposure applicable on a 28-day inhalation study with rats (Muijser, 2001; Arts et al., 2004)

Aspect	**Assessment factors**
Interspecies differences	2.5
Intraspecies differences	5
Differences between experimental conditions and exposure pattern of the worker[A]	3
Dose-response curve[B] **/ Type of critical effect**	3
Confidence of the database	1
Overall	112.5

[A] In case of systemic effects the default value for extrapolation from subacute to chronic exposure amounts 6. In case of local effects a smaller factor is indicated compared to systemic effects. Although it is assumed that the severity of effects will increase with longer exposure times, the height of the NOAEL for local effects will decrease to a lower extent than in the case of a systemic effect. A factor 3 is considered applicable.

[B] A default value of 3 is used, because a LOAEL instead of a NOAEL is used as starting point for the risk characterisation.

Table I-4

Assessment factors applied for the calculation of the minimal MOS for systemic effects after chronic dermal exposure applicable on a 13-week oral toxicity study with rats (Jonker, 2000b,c)

Aspect	**Assessment factors**
Interspecies differences	4 x 2.5
Intraspecies differences	5
Differences between experimental conditions and exposure pattern of the worker[A]	1
Dose-response curve / Type of critical effect	1
Route-to-route extrapolation[B]	1.1
Confidence of the database	1
Overall	55

[A] Normally a factor 2 is applied for extrapolation of subchronic to chronic exposure. A chronic diet study with micro-encapsulated furfural is not available, unfortunately. However, given the results of the oral subchronic and chronic gavage study, no effect of exposure duration was found on the NOAEL and the effects observed. Therefore, no correction for differences between experimental conditions and exposure pattern of the worker is

made.

[B] Route-to-route extrapolation correction is made for differences between dermal and oral exposure. Based on the information available for oral absorption 90% is taken into account and for the dermal route 100%.

Table I-5

Assessment factors applied for the calculation of the minimal MOS for systemic effects after chronic inhalation exposure applicable on a 28-day inhalation study with rats (Muijser, 2001; Arts et al., 2004)

Aspect	**Assessment factors**
Interspecies differences	2.5
Intraspecies differences	5
Differences between experimental conditions and exposure pattern of the worker[A]	3
Dose-response curve / Type of critical effect[B]	3
Route-to-route extrapolation	1
Confidence of the database	1
Overall	112.5

[A] A factor of 3 is applied for extrapolation of subacute to chronic exposure. A chronic inhalation study with rats is not available, unfortunately. However the results of the oral subchronic and chronic study in hamsters, show no effect of exposure duration on the NOAEL and the effects observed;

[B] As the critical effect at the next higher dose of 640 mg/m^3 is mortality, a factor of 3 is considered applicable here.

Tabel I-6

Assessment factors applied for the calculation of the minimal MOS for developmental toxicity after dermal and inhalation exposure (rats) applicable on an oral developmental toxicity study with rats

Aspect	**Assessment factors Dermal**	**Assessment factors inhalation**
Interspecies differences	4 x 2.5	4 x 2.5
Intraspecies differences	5	5
Differences between experimental conditions and exposure pattern of the worker	1	1
Dose-response curve / Type of critical effect	1	1
Route-to-route extrapolation[A]	1.1	1.1
Confidence of the database	1	1
Overall	55	55

[A] Route-to-route extrapolation correction is made for differences between dermal, inhalation and oral exposure.

Based on the information available for oral absorption 90% is taken into account and for the dermal and inhalation route 100%.

The report provides the comprehensive risk assessment of the substance 2-furaldehyde. It has been prepared by the Netherlands in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

Part I - Environment
This part of the evaluation considers the emissions and the resulting exposure to the environment in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined.

The environmental risk assessment concludes that there is a need for limiting the risks for the aquatic compartment as a consequence of exposure arising from formulation of chemical tracer in mineral oil and fuel industry, formulation for manufacturing refractories and use as intermediate in pesticide manufacture. In addition there is a need for better information to adequately characterise the toxic effects of 2-furaldehyde to the terrestrial ecosystems.
At present, there is no concern for the atmosphere, for macro-organisms in the sewage treatment plant.

Part II – Human Health
This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

There is concern for workers only, but not for consumers and humans exposed via the environment.

The conclusions of this report will lead to risk reduction measures proposed by the Commission’s committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.