Compound	**Phenol**	***Data collection sheet (1/1)***
N°CAS 108-95-2	**CLP:** H301: Acute tox. 3(oral), H311: Acute tox. 3 (dermal), H331: Acute tox. 3 (inhal.), H314: Skin corr. 1B, H341: Muta. 2, H373: STOT RE 2	
1 ppm = 3.873 mg/m^3		

Organisation name	**OEHHA**	**RIVM**	**SCOEL**	**German Committee on Indoor Guide Values**	**EU-RAR**	**REACH Registrants**
Risk value name	REL	TCA provisonal (lack of data)	OEL	IA guide value I/II (RW I/II)		DNEL
Risk value (µg/m^3)	200	20	8000	20/200		1320
Risk value (ppb)	52	5.2	2078	5.2/52		342.9
Reference period	Chronic	Chronic	8 hours	Chronic	chronic	Chronic
Year	2000	1999 ; 2000	2003 (2009)	2011	2006	2011
Key study	Sandage, 1961; Dalin and Kristofferson, 1974	Sandage, 1961	Sandage, 1961	Shamy, 1994; Dalin and Kristofferson, 1974	Shamy, 1994	Route to route extrapolation
Study type	90-day and 15-day; continuous inhalation	90-day inhalation study	90-day inhalation study	90-day and 15-day; continuous inhalation		
Species	Mice, Sprague Dawley rats and rhesus monkeys	Mice, Sprague Dawley rats and rhesus monkeys	Mice, Sprague Dawley rats and rhesus monkeys	a) Human (Shamy) and b) rats (Dalin and Kristofferson)	Human workers	
Duration of exposure in key study	a) 90 days continuously to 5 ppm phenol b) 15 days cont. to 26 ppm	90 days continuously to 5 ppm phenol	90 days continuously to 5 ppm phenol	b) 15 days to a concentration of 26 ppm		
Critical effect	systemic effects including liver and nervous system effects : alimentary system, cardiovascular system, kidney, nervous system : twitching, muscle tremors,	effects on liver enzymes, lungs, kidneys, and the cardiovascular system in rats	effects on liver enzymes, lungs, kidneys, and the cardiovascular system in rats	Dalin and Kristofferson: neurotoxicity in rats; Shamy: systemic hepatotoxic effects	Systemic effects elevated activities for serum aminotransferases (especially ALAT) and increased	

	neurological impairment; elevated serum liver enzymes in rats			in exposed workers	clotting time indicating hepatotoxicity	
Critical dose value	NOAEL: 20 mg/m^3 (5 ppm) (Sandage, 1961)	NOAEL: 20 mg/m^3 (5 ppm)	NOAEL: 20 mg/m^3 (5 ppm)			NOAEC
	LOAEL: 100 mg/m^3 (26 ppm); (Dalin and Kristofferson, 1974)	LOAEL: 100 mg/m^3 (26 ppm)	LOAEL: 100 mg/m^3 (26 ppm)	rats: LOAEL: 100 mg/m^3; workers: LOAEL: 21 mg/m^3	LOAEL: 21 mg/m^3 (5.45 ppm)	
Adjusted critical dose	NOAEL ADJ: 20 mg/m^3 (5 ppm)				POD: LOAEL x8/24x5/7 = 5 mg/m^3	
Single assessment factors (see table R.8.6)	interspecies 3 x intraspecies 10 x subchronic-chronic 3 = 100	interspecies 10 x intraspecies 10 x subchronic-chronic 10 = 1000		intraspecies 10 x children 2 exposure 4.2 = 84	LOAEL-NOAEL 10 x intraspecies 10 x subchronic 3 = 300	2
Other effects						
Confidence						

Compound	**Phenol** C_6H_6O		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	70
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2017
General information			
CLP-INDEX-No.	4	INDEX	604-001-00-2
EC-No.	5	EINECS – ELINCS - NLP	203-632-7
CAS-No.	6	Chemical Abstracts Service number	108-95-2
Harmonised CLP classification	7	Human health risk related classification	Acute tox. 3(oral), Acute tox. 3 (dermal), Acute tox. 3 (inhal.), Skin corr. 1B, Muta. 2, STOT RE 2
Molar mass and conversion factor	8	[g/mol] – [ppm – mg/m³]	94.11 1 ppm = 3.873 mg/m³
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Sandage (1961)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	rats, monkeys, mice
Route/type of study	12	Inhalation, oral feed, etc.	inhalation
Study length	13	Days, subchronic, chronic	subchronic
Exposure duration	14	Hrs/day, days/week	24h/d; 7 d/w; 90 days
Critical endpoint	15	Effect(s), site of	Elevated organ-pathology at monkeys and rats (liver, kidneys) and mice (liver, lungs)
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	NOAEC
POD value	17	[mg/m³] or [ppm] or [mg/kg$_{BW}$×d]	4.72 ppm (time weighted average)
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	1
Study length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		1
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	1
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	1
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10

AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	5
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	250
POD/TAF	28	Calculated value (µg/m³ and ppb)	73.12 µg/m³ and 18.88 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	70
Additional comments	31		

Absolute odour threshold of phenol is 0.0056 ppm (22 µg/m³ at 23°C) according to Nagata (2003).

REACH registrants have derived a DNEL (inhalation, systemic effects, general population) of 1.32 mg/m³, POD was a NOAEC exposition (no further explanations were given), the applied TAF was 2.

In Germany, indoor air quality (risk) value of 0.2 mg/m³ (RWII) was derived based on the study by Shamy et al., 1994, using a TAF of 84, the recommended (precautionary) value is 0.02 mg/m³ (RWI).

Most OELs (8h) in Europe are 2 ppm (8mg/m³), in Denmark and Sweden 1 ppm (4 mg/m³).

Rationale section	32		

Phenol is well absorbed via the gastrointestinal and respiratory tracts and the dermis. Volunteers exposed to phenol concentrations of 6–20 mg/m³ via inhalation absorbed 60 to 88 % of the substance (ECB, 2006). Based on studies of humans exposed to phenol in air, it was estimated that percutaneous absorption of vapours is about half of that through the lungs. A half-life of 3.5 hours is reported after inhalation by humans (RIVM, 2001).

Limited data are available on the chronic effects of phenol in humans from oral, dermal or inhalation exposure. Effects are reduced spontaneous activity, muscle weakness, pain and disordered cognitive capacities. In animals, dysfunctions of the nervous system have been reported, including tremors, convulsions, loss of coordination, paralysis, reduced motor and spontaneous activity and reduced body temperature.

Phenol demonstrates various mutagenic effects in mammalian cell cultures. In general, effects are relatively weak. In vivo, phenol is a weak inducer of micronuclei in mouse bone marrow cells and of chromosomal aberrations in rats; the effect is bound to high doses which are equivalent to, or near, the maximum tolerable dose. Phenol is therefore classified as a category 2 mutagen. The IARC considers that there is inadequate evidence to classify phenol as a group 3 carcinogen (IARC, 1999).

Human data

A study by Shamy et al., 1994 was used in the EU-RAR (ECB, 2006) and the derivation of the German Indoor Guide Values (RW I values) (Ad hoc AG IRK, 2011). According to the authors, workers (n=20) were exposed to phenol alone (extraction medium for oil refining) at an average exposure concentration of 5.4 ppm (21 mg/m³) (time-weighted average, factory records) for a mean exposure duration of 13.5 years. Haematological and clinical chemistry parameters were examined only once at the end of the final shift at the end of the week, and compared with a control cohort (n=30). Exposed workers showed statistically significant higher transaminase levels (ALT, $p < 0.05$, AST $p < 0.01$) and clotting time ($p < 0.01$), and lower levels of serum creatinine ($p < 0.01$) than control subjects. Furthermore, workers exposed to phenol showed statistically significant higher levels of haemoglobin ($p < 0.05$), haematocrit, colour index, MCH (each $p < 0.01$), MCV ($p < 0.05$), basophils ($p < 0.01$), and neutrophils ($p < 0.05$), and lower levels of monocytes ($p < 0.01$). Statistically significant higher levels ($p < 0.01$) of Mg, Mn and Ca were also found. Local effects in the respiratory tract were not investigated. Elevated activities for liver enzymes, increased clotting time and increased concentration of metal ions are indicators for hepatotoxicity, and are consistent with the toxic effects of phenol observed at higher doses.

Urinary phenol concentrations in the exposed group were significantly ($p < 0.01$) elevated (68.60 ± 47.06 mg phenol/g creatinine) in comparison with the background levels in the control group (11.54 ± 4.7 mg phenol/g creatinine, verification of external exposure). Comparison with available literature shows that an 8-hour

exposure to 2 ppm phenol would correspond to a urine concentration, measured at the end of the shift, of 120 mg phenol/g creatinine (SCOEL, 2003). This provides some evidence that the reported phenol excretion in the worker study is the result of lower exposure.

The EU-LCI working group ultimately decided not to rely on the study by Shamy (1994) to derive the EU-LCI value, for several reasons:

- the exposure of the workers was not well described;
- exposure in the oil refining plant was probably not to phenol alone;
- the study is characterised by rather poor reporting of exposure conditions (e.g. there are no details of the analytical method and its validity);
- the results of only a single blood sample from the workers were reported.

Animal data

In an inhalation study (15 days, continuous exposure, 26 ppm), elevated serum liver enzymes in rats (n=7) demonstrated the systemic effects of phenol on the liver. 26 ppm (100 mg/m^3) produced neurotoxic effects: twitching, muscle tremors and neurological impairment. Levels of K^+ and Mg^{2+} and LDH, GOT, GPT and GLDH were markedly increased. While the elevated Mg^{2+} has to be regarded as an important factor in the depression and weakening of motor functions, the increased levels of K^+ and plasma enzymes can be regarded as indicators of cellular liver damage. No organ pathology was reported (Dalin and Kristofferson, 1974) (LOAEC 26 ppm).

Deichmann et al. (1944) exposed 12 guinea pigs, 15 rats, and six rabbits to concentrations of phenol in air between 26 and 52 ppm (100 and 200 mg/m^3) for 28–88 days, depending on the species. Guinea pigs appeared to be the most susceptible. Myocardial degeneration and inflammation, lobular purulent pneumonia, and similar lesions of the liver and kidneys were reported for the guinea pigs. Treatment of the guinea pigs had to be stopped prematurely because of respiratory disturbances and the sudden deaths of five animals, beginning after 20 days of exposure during a treatment period of 28 days. Rabbits did not exhibit any signs of discomfort, but showed similar findings on necropsy at 88 days. Rats exposed over a period of 74 days did not show any clinical symptoms or any morphologic abnormality. The study is of limited validity because of the absence of data on phenol purity, growth, haematology, clinical chemistry, organ weights and list of organs examined microscopically. The data from the rabbits and guinea pigs was considered to have low reliability because purulent bronchopneumonia may also indicate a primary infectious disease (reviewed in ECB, 2006).

A Russian study (Mukhitov, 1964) exposed groups of 15 male white rats to phenol (whole body) at 0, 0.01, 0.1, or 5 mg/m^3 (0.0026, 0.026, or 1.3 ppm) for 24 hours/day for 61 days. Analytic concentrations were obtained once or twice daily using a colorimetric assay. Although the behaviour of the rats at the two lower exposure concentrations was not different from controls, the animals in the highest exposure group were somewhat sluggish and sleepy. Motor chronaxy of right hind leg muscle antagonists was measured once every 10 days in five rats from each exposure group. Statistically significant motor chronaxy (mostly seen as shortened extensor chronaxy) was observed in rats exposed at 0.1 or 5 mg/m^3, starting after 30 days of exposure (cited from NRC, 2009). The reliability of this study cannot be evaluated, since the original study is not available.

A 14 day-inhalation study (similar to OECD Test Guideline 412) (Hoffman, 2001) specifically designed to examine effects on the respiratory tract was conducted in F344 rats. Phenol vapour was administered by nose-only exposure for ten exposures (5 days/week, 6 hours/day) at target concentrations of 0 (air control), 0.5, 5.0 and 25 ppm. Based on the conditions of this study, no adverse effects were seen at phenol concentrations up to 25 ppm in the respiratory tract or in any other organ system (reviewed in ECB, 2006). It has to be taken into account that no saturation of the metabolic conjugation capacity will occur under these study conditions (NOAEC local and systemic 25 ppm).

The animal study of the longest duration (Sandage, 1961) was conducted using three species (rat n=50, mouse n=100, rhesus monkey n=10; all animals were males). Exposure to 0 or 5 ppm phenol (measured at 4.72 ppm) continuously for 90 days did not result in any significant pathological effects. No significant systemic toxicity seems to have been produced in any of the exposed animals. Local effects in the upper respiratory tract due to the irritating/corrosive potential of phenol were not explored in this study. No further concentrations were tested. The study seems well conducted, but the reporting has some limitations. Additionally, only four animals were tested for haematology parameters and only half of the animals underwent examination for histological/organ pathology at the end of the exposure. Although the report indicates that there were no significant histological alterations in organs and tissues, incomplete reporting of the results suggests that there

may have been some lung, liver, and kidney pathology. In addition, no data were presented to support the assertion that there were no effects on haematology (three species), blood chemistry (monkeys only), urinalysis (three species), or kidney function tests (monkeys and rats). According to the author's interpretation, pathology results in phenol-exposed animals were essentially negative. However, it is reported that liver damage was observed in 30 % of the mice and kidney damage in 10–20 % of the rats and monkeys exposed to phenol. Lung damage was also reported to be 2–3 times higher in phenol-exposed mice compared to controls. The author noted that there are doubts concerning the significance of observations. As no detailed pathology data is presented in the study, the author's interpretation was followed, but the uncertainty has to be taken into account when applying the assessment factors. Therefore, the exposure concentration of 4.72 ppm (measured value, mean) is considered as the NOAEC.

In a weight-of-evidence approach, it can be concluded that liver toxicity is the adverse effect of concern. Sandage (1961) defined a NOAEL of 4.72 ppm with doubtful pathological results in the liver after subchronic exposure. LDH, GOT, GPT and GLDH levels – indicating liver toxicity – were markedly increased in a subacute study by Dalin (1974) resulting in a LOAEL of 26 ppm. A well-conducted and well-documented subacute study by Hoffman (2001) using intermittent exposure derived a NOAEL of 25 ppm (without saturation of the metabolic conjugation). Liver toxicity was also seen in the available human study (Shamy, 1994), but was not considered further due to the limitations of the study. No liver toxicity was seen in oral studies, which may be due to a high rate of first-pass metabolism.

Since the toxicity of phenol is the result of an overload of the metabolic conjugation capacity, the NOAEL of 4.72ppm and LOAEL of 26 ppm were considered for the derivation of an EU-LCI value.

The NOAEL of 4.72 ppm (18.17 mg/m^3) was used as the POD.

Rationale for assessment factors (AF):

- adjustment of exposure duration: continuous exposure → no AF
- interspecies difference: no allometric scaling for inhalation study, 2.5 for remaining differences → 2.5
- duration extrapolation (90d): subchronic to chronic → 2
- intraspecies differences → 10 (variability of metabolism in population)
- quality of whole database → 5 (no dose response, limitations in reporting, number of animals investigated pathologically, only male animals tested)

Based on a total assessment factor (TAF) of 250, a calculated EU-LCI value of 73.12 µg/m^3 was derived based on animal data. After rounding, the final EU-LCI value is 70 µg/m^3.

An alternate derivation based on the LOAEL of 26 ppm (100.698 mg/m^3) and a TAF of 1350 (LOAEL-NOAEL 3; interspecies 2.5, sa-c 6, intraspecies 10, quality of data 3) would also result in a rounded value of 70 µg/m^3, which supports the EU-LCI derivation above.

References:

Ad hoc-AG IRK/AGLMB (2011) Indoor air guide values for phenol. Bundesgesundheitsbl 54: 1262–1268.

ATSDR (2008) Toxicological profile for phenol. Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services Public Health Service, http://www.atsdr.cdc.gov/ToxProfiles/tp115.pdf (last retrieved on 4.12.2019).

Bruce RM, Santodonato J, Neal MW (1987). Summary review of the health effects associated with phenol. Toxicol Ind Health. 1987 Dec;3(4):535-68. Review.

Dalin NM, Kristofferson R (1974) Physiological effects of a sublethal concentration of inhaled phenol on the rat. Ann Zool Fennici 11:193–199

ECB (2006) Phenol. European Union Risk Assessment Report. Revised Edition. European Chemicals Bureau, Joint Research Center, Ispra. European Commission. Vol. 64.

EFSA (2008). Flavouring group evaluation 88. Consideration of phenol and phenol derivatives evaluated by JECFA (55th meeting). Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials.

Hoffman GM, Dunn BJ, Morris CR, Butala JH, Dimond SS, Gingell R, Waechter JM (2001) Two-Week (Ten-Day) Inhalation Toxicity and Two-Week Recovery Study of Phenol Vapor in the Rat International Journal of Toxicology, 20:45–52. Corresponding study report: CMA (1998) Two-week (ten day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. Study Nr. 96-6107, CMA Reference No. PHL-4.0-Inhal-HLS, Chemical Manufacturers Association, Phenol Panel, Arlington, VA 22209.

Institut für Arbeitsschutz der deutschen gesetzlichen Unfallversicherung (BGIA), Gestis, Stoffdatenbank,

IARC (1999) Phenol. IARC monographs on the evaluation of carcinogenic risks to humans. 71:749-768. International Agency for Research on Cancer, Lyon

IARC (1999): Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. Chapter Phenol. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71 (1999):749–768

Mukhitov, B. 1964. The effect of low phenol concentrations on the organism of man or animals and their hygienic evaluation. Pp. 185-199 in USSR Literature on Air Pollution and Related Occupational Diseases, Vol. 9, B.S. Levine, ed. NTIS PB 64- 11574. Springfield, VA: U.S. Department of Commerce, National Technical Information Service.

Nagata (2003) Measurement of Odor Threshold by Triangle Odor Bag Method. Odor measurement review. Office of Odor, Noise and Vibration, Environmental Management Bureau, Ministry of Environment, Tokyo, Japan, pp. 118–127

NRC (National Research Council (2009). Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 7. https://www.ncbi.nlm.nih.gov/books/NBK214900/pdf/Bookshelf_NBK214900.pdf (last retrieved on 4.12.2019).

RIVM (2001). Re-evaluation of human-toxicological maximum permissible risk levels. RIVM report 711 701 025

Sandage C (1961) Tolerance criteria for continuous inhalation exposure to toxic material. I. Effects on animals of 90-day exposure to phenol, CCl4, and a mixture of indole, skatole, H2S and methyl mercaptan. Wright-Patterson Air Force Base, OH. U.S. Air Force systems command, Aeronautical Systems Division. ASD technical report 61-519(I)

Shamy MY, El Gazzar RM, El Sayed MA, Attia AM (1994) Study of some biochemical changes among workers occupationally exposed to phenol, alone or in combination with other organic solvents. Industr Health 32:207–214

SCOEL (2003) Recommendation from the Scientific Expert Group on Occupational Exposure Limits for Phenol. European Commission. SCOEL/SUM/16