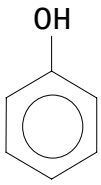
Recommendation from the Scientific Expert Group on Occupational Exposure Limits for Phenol

8 hour TWA:	2 ppm (8 mg/m^3)
STEL (15 min):	4 ppm (16 mg/m$^{3)}$
Additional classification:	"skin"
BLV:	120 mg phenol/g creatinine

Substance:

Phenol



Synonyms : Benzenol, carbolic acid, hydroxybenzene
EINECS No : 203 632-7
EEC No : 604-001-00-2
CAS No : 108-95-2
MWt : 94.11

Conversion factor (20°C, 101 kPa) : 3.91 mg/m^3 = 1 ppm

EU Classification : Muta. Cat. 3; R68 Possible risk of irreversible effects
T; R23/24/25 Toxic by inhalation, in contact with skin and if swallowed.
Xn; R48/20/21/22 Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed
C; R34 Causes burns

Occurrence/use:

Phenol is a white crystalline mass with a MPt of 40.6°C, BPt of 181.8°C and vapour pressure of 0.027 kPa at 20°C. The odour threshold is 0.05 ppm (0.2 mg/m^3). Phenol occurs naturally in coal tar and is produced synthetically from benzene with production levels in the EEC in excess of 1 000 000 tonnes per annum. It is used primarily in the production of phenolic resins, with lesser amounts used for manufacture of caprolactam, alkyl phenol and as a disinfectant and antiseptic.

Occupational exposure levels are generally reported to be less than 1 ppm (4 mg/m^3), although levels up to 4.4 ppm (17 mg/m^3) have been reported in a plant manufacturing synthetic fibres.

Health significance:

Phenol is readily absorbed through all routes, including human skin, either as vapour or as aqueous solution (Piotrowski, 1971; Baranowska-Dutkiewics, 1981). After absorption by any route, phenol reaches a peak in blood within minutes and is rapidly conjugated and distributed. Human and animal phenol metabolites are distributed in liver, kidney, adrenal gland and lung and further in the heart, thymus, testes, spleen and brain. (Liao and Oehme, 1981; Lo Dico *et al.*, 1989, Deichmann, 1944; CMA, 1994; Hughes and Hall, 1995). In the rat, more than 94% of the absorbed dose is eliminated in the urine in 24 hours (CMA, 1994).

The metabolic profile of phenol in humans is dose-dependent, similarly to rats or mice: at low doses, sulphate conjugates of phenol and hydroquinone are predominant, whereas saturation of the sulphate conjugation results in the predominance of glucuronide conjugates at higher doses. Saturation of the conjugation pathways is a key feature, since toxicity has been associated to free phenol in blood; sensitivity across species depends therefore on the metabolic conjugation efficiency.

The importance of the reactive intermediate 1,4-benzoquinone *in vivo* at low levels is unknown, as long as sufficient glutathione is available, this will probably rapidly trap the 1,4-benzochinone and protect the cell from damage (IARC, 1999).

Whether the covalent binding of radioactive metabolites of phenol with proteins of rat liver microsomes observed *in vitro* (Sawahata and Neal, 1983) actually has any relevance *in vivo* is uncertain (IARC, 1999).

The acute toxicity of phenol has been most extensively studied following oral administration in rats and mice; LD50 values have been estimated at 340-530 mg/kg for rats and 300 mg/kg for mice, reporting primary CNS effects (Deichmann and Witherup, 1944; von Oettingen and Sharpless, 1946). High oral gavage doses of phenol produced significant concentrations of free phenol in blood associated with neurobehavioural effects; saturation point occurred at doses greater than 15 mg/kg but less than 150 mg/kg (CMA, 1994).

It is corrosive to skin and eyes, and inhalation of phenol vapour leads to irritation of the respiratory tract. De Ceaurriz *et al.* (1981) determined the RD50 (the concentration leading to a 50% decrease in respiratory rate in mice (Alarie, 1973)) as 166 ppm (650 mg/m^3).

Phenol was not a skin sensitiser in a standard experimental animal study (Itoh, 1982, Descotes, 1988) and there are no indications that phenol possesses skin or respiratory sensitising properties in humans.

In relation to the effects of long-term exposure, continuous inhalation exposure of rhesus monkeys, rats and mice to 5 ppm (20 mg/m^3) phenol for 90 days resulted in no significant pathological effects (Sandage, 1961). Although this was a well-designed and wide-ranging study, the SCOEL felt that limited reporting of results, especially regarding irritation of the upper respiratory tract, was a difficulty. However, no significant systemic toxicity seems likely to have been produced in any of the three species at this level.

Intermittent inhalation exposure (7 hours/day, 5 days/week for 74 days) to 26–52 ppm phenol (100–200 mg/m^3) resulted in severe degeneration and necrosis in lung, liver, kidney and heart in rabbits after 63 exposures and guinea pigs after 29 exposures. No effects were seen in rats after 53 exposures (Deichmann *et al.*, 1944).

In a recent, well-conducted study, repeated inhalation exposure to 25 ppm phenol (6 hours/day for 8 consecutive days) did not result in the detection of free phenol in blood, nor in any evidence of neurobehavioural response in rats (CMA, 1994). The authors interpret the findings as indicating that metabolic conjugating capacity was not exceeded under these conditions and that there is a significant capacity for first-pass conjugation of phenol by the lung, as shown by Cassidy and Houston, 1980. Similar results were obtained in this study following low oral gavage doses of phenol (1.5 and 15 mg/kg bw).

Although only reported in an abstract, a recent study of male and female rats exposed nose-only to 0, 0.5, 5 or 25 ppm phenol for 6 hours/day, 5 days/week for two weeks supports previous negative findings on mortality, clinical signs of toxicity, food consumption, body weights, clinical chemistry, haematology, organ weights or gross or microscopic pathology, including upper respiratory tract up to the top dose (SOT annual report 1999).

On the other hand, continuous inhalation exposure of rats to 26 ppm (100 mg/m^3) phenol for 15 days resulted in slight CNS toxicity (impaired balance, disordered walking rhythm and involuntary muscle twitches in the neck) and a non-significant increase of liver enzymes, although haematological parameters were not affected and no free phenol was detected in plasma (Dalin and Kristofferson, 1974).

Subchronic and chronic oral exposure to high concentrations of phenol in drinking water produced no evidence of systemic toxicity, including tumorigenicity (NCI, 1980). 100 and 10 000 ppm phenol were administered in the 13-week study on F344 rats and BC6C3F1 mice (10 animals per group). 100, 2 500 and 5 000 ppm phenol were administered in a 103-week study on rats and mice (highest dose being equivalent to 630 mg/kg bw/day for female rats and 585 for male rats: 660 mg/kg bw/day for both sexes of mice).

In rats receiving oral doses of up to 120 mg/kg/day phenol in deionised water for 14 days, no histopathological effects were seen in the 4 mg/kg/day dose group (Berman *et al.*, 1995). However, kidney, spleen, thymus and CNS were evidenced as the main target organs in the higher dose groups.

A dose-related reduction in red blood cells in mouse was seen after administration of 5-95 mg phenol/l drinking water during 28 days, corresponding to 2-34 mg/kg/day (Hsieh, 1992). No spleen cellularity or white blood cell count changes were found. In the same study, in comparison with the control group, suppressed performance in various immunological assays and reduced levels of various neurotransmitters in brain tissue were found in the phenol-treated animals, particularly at the two higher concentrations of 19.5 and 95 mg/l. The significance of these findings for human health is questionable, particularly as the surrounding database on repeated exposure studies by the inhalation or oral routes does not provide consistent and convincing evidence of appreciable immunotoxicity or neurotoxicity.

In a 13-week neurotoxicity study rats were administered 200, 1 000 or 5 000 ppm phenol in drinking water. At 5 000 ppm lower body weight, reduced food and water consumption and abnormal clinical signs including dehydrated appearance were observed. No effects were observed at 200 ppm. Neurobehavioural evaluations did not show any findings of neurological significance at any concentration. No histopathological lesions in nervous tissue caused by phenol were detected. Other tissues were not examined (CTRR, 1998).

Few data are available on the effects of repeated exposure in humans. In a study of long-term occupational exposure to 21mg/m^3 (5.4ppm) of phenol (corresponding to 3mg/kg/day), chemical workers presented slight biochemical, haematological and [.....?] alterations (Shamy *et al.*, 1994). This study has some shortcomings, as only 20 workers were examined, it is not clear whether the exposure was only to phenol and how the exposure was measured. The results of another study indicate that long-term occupational exposure to phenol may lead to increased risk of ischaemic heart disease (Wilcosky and Tyroler, 1983) In this study workers were exposed to many different solvents in a rubber factory. Furthermore, according to the authors there are numerous problems with the interpretation of the results of this study, especially because hypertension and high serum cholesterol were uncontrolled confounders.

An investigation has been reported of 13 Japanese workers exposed to phenol and catechol vapours (Hirosawa *et al.*, 1976). However, for a number of reasons the data are of little value. The air concentrations cited relate to static samples, not to personal exposures. Both substances were present and the study was aimed at better understanding the toxicity of catechol rather than phenol. No data are presented for the reported subjective symptoms of upper respiratory tract irritation. Overall, it is not possible to use this study to derive a limit value.

The genotoxicity of phenol has been extensively studied, especially from the perspective of it being a benzene metabolite. There is general agreement on the overall lack of mutagenicity of phenol tested in bacterial systems (IARC, 1999), although sporadic positive results in non-conventional bacterial assays (Gocke *et al.*, 1981) and at high, toxic doses in such systems (Demerec *et al.*, 1951) have been published.

In cultured mammalian cells, phenol caused mutations, sister chromatid exchanges and micronuclei. It bound to cellular protein (but not to DNA) and inhibited intercellular communication (IARC, 1999, Morimoto *et al.*, 1983).

Inhibition of topoisomerase I *in vitro* was not detected and inhibition of topoisomerase II was only observed if a peroxidase/hydrogen peroxide system was added to the reaction mixture (Chen and Eastmond, 1995) .

Micronuclei assays *in vivo* have shown phenol to act as a clastogen; positive findings have been seen after single or repeated exposures corresponding to 90-180 mg/kg bw at 24h after i.p. application (Shelby *et al.*, 1993; Marrazini, 1994). However, the clastogenic effect of phenol is weak because the number of induced micronuclei was never twice as high as that of the control animals. High oral doses corresponding to 265 mg/kg bw induced micronuclei in male and pregnant female CD-1 mice, but not in the liver of the foetuses (Ciranni *et al.*, 1988).

DNA adduct formation in the liver of rats is shown after Arochlor induction and i.p. application at levels around the corresponding LD50 reported in other studies (Liu *et al.*, 1996), but not after repeated oral doses representing 0.2 LD50 (Reddy *et al.*, 1990). DNA adducts in the bone marrow of rats were only produced by the concurrent application of phenol and hydroquinone (Heddli *et al.*, 1991), which have been further shown to act synergistically as clastogens (Barale *et al.*, 1990).

Chromosomal aberrations in spermatogonia of mice were also produced at doses evidenced as toxic in another study (Bulsiewicz, 1977). No strand breaks could be detected in testicular DNA of rats after i.p. injection of phenol up to 79mg/kg bw.

Thus, genotoxic effects of phenol *in vivo* have been seen; however, they have been shown to be markedly dose-dependent. Glutathione levels should provide cellular protection by rapid conjugation of the most critical metabolites (e.g. 1,4-benzoquinone).

Carcinogenicity, particularly a potential leukaemogenic effect of phenol, has been raised as a concern, because of its metabolic relationship to benzene and because in the case of benzene, carcinogenic potential in animals was difficult to show until recently. Nevertheless, owing to the lipophilic properties of benzene and its distribution, it would easily reach the bone marrow to be metabolised, accumulating *in situ* more unconjugated, potentially clastogenic metabolites than would be achieved by administering phenol or any other polar metabolite. Phenol was considered non-carcinogenic in an oral study in rats or mice (NCI, 1980, see Annex I). In Finnish woodworkers the risk of lung cancer due to phenol exposure was not related to exposure time (Kaupinnen *et al.*, 1986) and the risk of stomach cancer was non-significant in a study in the rubber industry (Wilcosky *et al.*, 1984).

Phenol was a promoter of mouse skin carcinogenesis in two-stage protocols (IARC , 1989).

In terms of reproductive toxicity, no effects on fertility were caused by phenol in a two-generation unpublished study on rats. 5 000 ppm phenol was administered in drinking water (corresponding to 301 and 321 mg/kg/day in males and females of F1; and to 320 and 380 mg/kg/day for males and females of F2) for ten weeks prior to mating, during

the 2-week mating period and for females further during gestation, lactation and sacrifice (CMA, 1999).

Developmental studies , but not standard regulatory tests, in mice and rats have shown effects at doses which also cause severe maternal toxicity (HSE, 2000).

In a recent two-generation study phenol was administered to rats in drinking water at concentrations of 0, 200, 1 000 or 5 000 ppm. In this study additional endpoints such as sperm count and mobility, histological evaluation of liver, kidneys, spleen and thymus and an immunotoxicity screening plaque assay were performed. At 5 000 ppm no evidence of immunotoxicity was observed. The NOAEL for reproductive toxicity in this study was determined to be 1 000 ppm, which is equivalent to about 70 mg/kg/day for males and 93 mg/kg/day for females (Ryan *et al.*, 2001).

Recommendation:

The briefly reported inhalation study by Sandage (1961) suggests that no systemic toxicity was produced in three experimental species (rat, mouse, Rhesus monkey) continuously exposed to 5 ppm phenol for 90 days. However, because of its irritant/corrosive properties, there is concern that repeated inhalation exposure to phenol could produce local effects in the upper respiratory tract and it appears that this issue was not explored in this study. Nevertheless, a recent abstract indicates that no respiratory tract pathology (or other evidence of toxicity) was seen in rats repeatedly exposed to up to 25 ppm phenol for two weeks. Hence it might be predicted that 5 ppm would not have produced local respiratory tract effects in the earlier study. Assuming 100% retention and absorption of the inhalation dose, continuous exposure of rats to 5 ppm would equate to a body burden of approximately 15 mg/kg/day.

Earlier inhalation studies have reported toxicity in rats and rabbits exposed repeatedly or continuously to 26-52 ppm phenol. There is no reliable information on the effects of repeated exposure to airborne phenol in humans.

The findings of repeated oral dosing studies in animals have been conflicting, so that the overall picture is confused. Some studies have indicated no effects in rats and mice receiving hundreds of mg/kg/day; others have reported adverse effects in mice receiving as little as 2 mg/kg/day. In the opinion of the SCOEL, the quality and reliability of the overall repeated oral exposure database is inadequate for use in the derivation of an OEL proposal.

Hence, the SCOEL concluded that repeated daily exposure to 5 ppm phenol would probably produce no local or systemic toxicity in experimental animals. An uncertainty factor of 2 was applied to allow for the absence of human data. Taking into account the preferred value approach, an 8-hour TWA of 2 ppm (7.8 mg/m3) is recommended. The genotoxic potential of phenol *in vivo* is weak and probably metabolism-dependent, so that at low concentrations no genotoxic potential is expected and a threshold mechanism can be assumed.

It was judged that a STEL is required to protect agaist upper respiratory tract irritation. There are no human data to suggest a particular value for the STEL, but on the basis of animal data a STEL of 4 ppm was recommended.

Skin penetration may make a substantial contribution to the total body burden, so a skin notation is also required. No sensitisation notation is required.

At the level recommended, no measurement difficulties are foreseen.

Biological monitoring may be useful to assess occupational exposure to phenol. 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 (Piotrowski, 1971; Ohtsuji and Ikeda, 1972; Ogata *et al.*, 1986).

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ANNEX I

Groups of 50 F344 rats and B6C3F1 mice of each sex were given drinking water containing 2,500 or 5,000 ppm phenol for 103 weeks. As matched controls, groups of 50 rats and 50 mice of each sex received tap water. A dose-related depression in mean body weight gain occurred in rats and mice of each sex. Rats and mice given water containing phenol drank less than did the corresponding controls. A dose-related decrease in water consumption was observed for mice.

An increased incidence of leukaemia or lymphoma was detected in male rats and may have been associated with the administration of phenol (table 1). Although the incidence of these tumours in the low-dose group was significantly higher than that in controls, the incidence in the high-dose group was not. Thus, an association with administration of phenol was not established.

In male rats, the incidences of pheochromocytomas in the adrenal and C-cell carcinomas in the thyroid are higher in the low-dose group than in the control groups.

The historical incidences of male F344 rats in the bioassay programme with pheochromocytomas in the adrenal and C-cell carcinomas in the thyroid are 200/2,300 (9%) and 42/2,230 (2%), respectively.

Under the conditions of this bioassay, phenol was evaluated by the US National Institute of Health as being not carcinogenic for either male or female F344 rats or male and female B6C3F1 mice (NCI 1980).

table 1 Tumour incidence in male F344 rats administered phenol in the drinking water for 103 weeks (NCI, 1980)

Primary tumours	phenol in the drinking water		
	0 ppm (matched control)	2500 ppm	5000 ppm
Hematopoetic system:			
Leukaemia or lymphoma	18/50 (36%)	**31/50 (62%)***	25/50 (50%)
Adrenal:			
Pheochromocytoma	13/50 (26%)	**22/50 (44%)***	9/50 (18%)
Thyroid:			
C-cell adenoma	4/50 (8%)	2/49 (4%)	0/50 (0%)
C-cell carcinoma	0/50 (0%)	**5/49 (10%)***	1/50 (2%)
C-cell adenoma+carcinoma	4/50 (8%)	7/49 (14%)	1/50 (2%)

*) significantly different from the control group