# PHENOL

Data were last evaluated in IARC (1989).

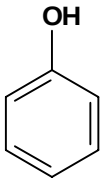
## 1. Exposure Data

### 1.1 Chemical and physical data

1.1.1 *Nomenclature*

*Chem. Abstr. Serv. Reg. No.*: 108-95-2
*Chem. Abstr. Name*: Phenol
*IUPAC Systematic Name*: Phenol
*Synonyms*: Carbolic acid; hydroxybenzene

1.1.2 *Structural and molecular formulae and relative molecular mass*




$C_6H_6O$ Relative molecular mass: 94.11

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless, acicular crystals with characteristic sweet and acrid odour (Budavari, 1996)
(*b*) *Boiling-point*: 181.8°C (Lide, 1997)
(*c*) *Melting-point*: 40.9°C (Lide, 1997)
(*d*) *Solubility*: Soluble in ethanol, water, diethyl ether, chloroform, glycerol, carbon disulfide, petrolatum and alkalis (Budavari, 1996)
(*e*) *Vapour pressure*: 47 Pa at 25°C; relative vapour density (air = 1), 3.24 (American Conference of Governmental Industrial Hygienists, 1991)
(*f*) *Flash point*: 79°C, closed cup (Budavari, 1996)
(*g*) *Explosive limits*: upper, 8.6%; lower, 1.7% by volume in air (American Conference of Governmental Industrial Hygienists, 1991)
(*h*) *Conversion factor*: $mg/m^3 = 3.85 \times ppm$

### 1.2 Production and use

The estimated worldwide synthetic phenol capacity in 1994 was approximately 5200 thousand tonnes; estimated capacities by region were reported as (thousand tonnes): Mexico and South America, 155; Europe, 1967; Japan, 800; Asia, 256; China, 126; and the United States, 1870 (Wallace, 1996). Production in the United States in 1993 was reported to be 1 544 222 tonnes (United States International Trade Commission, 1994).

Phenol has a wide range of uses, including in the preparation of phenolic and epoxy resins (bisphenol-A), nylon-6 (caprolactam), 2,4-D, selective solvents for refining lubricating oils, adipic acid, salicylic acid, phenolphthalein, pentachlorophenol and other derivatives; in germicidal paints; as a laboratory reagent and in dyes and indicators; and as a slimicide, biocide and general disinfectant (Lewis, 1993). The world demand for phenol by use in 1993 was reported as (%): phenolic resins, 35; bisphenol-A, 30; caprolactam, 15; alkylphenols, 7; aniline, 5; and others, 8 (Wallace, 1996).

### 1.3 Occurrence

#### 1.3.1 *Occupational exposure*

Data on levels of occupational exposure to phenol have been presented in a previous monograph (IARC, 1989).

#### 1.3.2 *Environmental occurrence*

Phenol is present in plant and animal organic wastes as a result of decomposition. The level of phenol present in poultry manure, for example, has been shown to increase as degradation proceeds. Phenol is an important industrial chemical and enters the environment in air emissions and wastewater connected with its use as a chemical intermediate, disinfectant and antiseptic (United States National Library of Medicine, 1997).

### 1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 19 mg/m$^3$ as the threshold limit value for occupational exposures to phenol in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for phenol in drinking-water has been established (WHO, 1993).

## 2. Studies of Cancer in Humans

### 2.1 Industry-based studies

In the nested case–control study among rubber workers in the United States (Wilcosky *et al*., 1984), described in greater detail in the monograph on dichloromethane (see this volume), one of the substances evaluated was phenol, which was analysed as a potential risk factor in relation to each of five cancer types. None of the odds ratios was

significant; the only one greater than 1.0 was that for stomach cancer (odds ratio, 1.4; *n* = 6) in white men. The odds ratio for lung cancer in white men was 1.0 (*n* = 13).

Dosemeci *et al*. (1991) reported results concerning phenol from a cohort study in the United States initiated to assess risks due to formaldehyde. This report concerned 14 861 workers employed before 1966 in five facilities producing or using phenol as well as formaldehyde. Subjects were traced to 1980. More than 360 000 person–years of follow-up accrued. Job history records were linked to extensive industrial hygiene data and expertise to assess possible exposure to formaldehyde and phenol. Relative risk estimates (standardized mortality ratios (SMRs)) for white male workers exposed to phenol were derived by comparison with the general United States population. The SMR for all causes of death combined was close to 1.0, as was the SMR for all cancers combined. Exposed workers had no excess of cancer at any of the following sites: buccal cavity and pharynx, stomach, colon, liver, pancreas, skin, prostate, testis, brain or leukaemia. There were slight, unremarkable excesses for cancers of the larynx (SMR, 1.1; 95% CI, 0.5–2.3; *n* = 7), lung (SMR, 1.1; 95% CI, 0.9–1.3; *n* = 146), urinary bladder (SMR, 1.1; 95% CI, 0.6–1.4; *n* = 13), kidney (SMR, 1.3; 95% CI, 0.7–2.1; *n* = 13) and rectum (SMR, 1.4; 95% CI, 0.8–2.2; *n* = 18). Only for oesophageal cancer (SMR, 1.6; 95% CI, 0.9–2.6; *n* = 15) and Hodgkin's disease (odds ratio, 1.7; 95% CI, 0.8–3.1; *n* = 10) were the excesses noteworthy, albeit not significant. Nor was there any stronger evidence of a cancer risk when the exposed group was compared with an internal comparison group of workers unexposed to phenol. When the phenol-exposed group was separated into subgroups by cumulative exposure, the SMRs were [2.1 (95% CI, 1.0–3.7; *n* = 11)] for oesophageal cancer, [1.1 (95% CI, 0.9–1.4; *n* = 78)] for lung cancer and [0.9 (95% CI, 0.1–3.3; *n* = 2)] for Hodgkin's disease for medium and high exposure combined. [The Working Group noted that workers typically had multiple exposures.]

Kauppinen *et al*. (1993) carried out a case–control study of respiratory tract cancer nested within a cohort of 7307 Finnish male woodworkers (IARC, 1995) from 35 plants (including plywood, particle-board, sawmill and formaldehyde (IARC, 1995) glue plants). Each case of respiratory tract cancer within the cohort identified in the Finnish Cancer Registry and diagnosed between 1957 and 1982 (*n* = 136) was matched by year of birth with three controls (*n* = 408) from the cohort. Job history records were supplemented by interviews with subjects or next-of-kin, and were linked to a specially devised plant- and period-specific job–exposure matrix which included 12 substances, one of which was phenol. The interview, achieved for 65% of subjects, also requested smoking data. Several logistic regression models were run, varying the treatment of induction period, smoking status and duration of exposure. Any exposure to phenol, without adjustment for induction period or smoking, gave an odds ratio of 3.2 (90% CI, 1.8–5.6; *n* = 14) for lung cancer. Estimates were slightly higher when a 10-year induction period was included in the model (odds ratio, 3.5; 90% CI, 1.8–7.0; *n* = 6). Adjustment for smoking did not eliminate the association (odds ratio, 2.5; 90% CI, 1.2–5.0; *n* = 9). Long-term workers (more than five years' exposure) (odds ratio, 1.4; 90% CI, 0.6–3.6; *n* = 7) had lower risk than short-term workers (one month to five years' exposure) (odds

ratio, 3.3; 90% CI, 1.0–11.0; *n* = 7). While workers exposed to phenol tended also to be exposed to other substances, none of those substances showed as strong an association with respiratory tract cancer as did phenol. In particular, although all phenol-exposed workers were also exposed to formaldehyde, workers exposed to formaldehyde but not to phenol had no excess risk of respiratory tract cancer (odds ratio, 1.0).

### 2.2 Community-based studies

In Siemiatycki's (1991) population-based case–control study of cancer in Montreal, Canada (see monograph on dichloromethane in this volume), phenol was one of the substances evaluated; 1% of the entire study population had been exposed to it at some time. Among the main occupations to which phenol exposure was attributed in this study were electric motor repairmen and foundry workers. The publication reported an association between phenol and pancreatic cancer (odds ratio, 4.8; 90% CI, 1.8–12.7; *n* = 4); for no other site was cancer risk associated with phenol exposure. [The Working Group noted that detailed results for other sites were not provided, because they were based on small numbers, and that workers typically had multiple exposures.]

## 3. Studies of Cancer in Experimental Animals

Phenol was tested for carcinogenicity by oral administration in drinking-water in one strain of mice and one strain of rats. No treatment-related increase in the incidence of tumours was observed in mice or in female rats. In male rats, an increase in the incidence of leukaemia was observed at the lower dose but not at the higher dose. Phenol was tested extensively in the two-stage mouse skin model and showed promoting activity (IARC, 1989).

### 3.1 Skin application

*Mouse*: Groups of five male TG.AC or FVB/N non-carrier mice, six to seven weeks of age, were administered 3 mg phenol (reagent grade) per animal in acetone by skin application twice per week for up to 20 weeks. A skin papilloma occurred in an exposed TG.AC mouse, whereas none occurred in controls (not considered to be significant) (Spalding *et al*., 1993).

### 3.2 Administration with known carcinogens

#### 3.2.1 *Mouse*

Groups of 22–24 female CC57 Br mice, weighing 12–14 g, were administered phenol ('chemically pure') twice a week orally [method not stated] for total doses of 0, 0.02 or 1.0 mg in three modes; phenol was given for 2.5 months and 1 mg per animal benzo[*a*]pyrene subsequently for 2.5 months; 1 mg per animal benzo[*a*]pyrene was given for 2.5 months followed by phenol for 2.5 months; or the two were given concurrently for 2.5 months. The high dose of phenol given in combination with benzo[*a*]pyrene pro-

duced a 27.2% incidence of malignant forestomach tumours ($p < 0.01$) compared with 4.6% when benzo[*a*]pyrene was given alone. In groups given 1.0 mg phenol either before or after the initiator, the incidence of malignant forestomach tumours was reduced from that in mice given only the initiator (Yanysheva *et al*., 1992).

Groups of 7–10 male Sprague-Dawley rats, weighing 200 g, were administered phenol (purity, > 99.5%) at doses of 0 or 100 mg/kg bw by gavage on five days per week for six weeks beginning one week after partial hepatectomy and intraperitoneal injection of 30 mg/kg bw *N*-nitrosodiethylamine to initiate liver carcinogenesis. Phenol did not increase the multiplicity of enzyme-altered (γ-glutamyltranspeptidase) foci compared with that in a group subjected only to initiation (Stenius *et al*., 1989).

## 4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

### 4.1 Absorption, distribution, metabolism and excretion

The major route of phenol metabolism is conjugation with sulfate and, at high dose, with glucuronic acid. In addition, hydroquinone (see this volume) is formed, which is excreted as a sulfate or glucuronide conjugate. Several glutathione conjugates can be formed from the reactive 1,4-benzoquinone formed from hydroquinone (Figure 1).

#### 4.1.1 *Humans*

In a case of lethal human phenol intoxication (a phenol-containing disinfectant was ingested), the phenol concentration in brain, kidney, liver and muscle was determined several hours after death. The concentration in the brain was highest, followed by the kidney; the concentrations in liver and muscle were half that in the brain (Lo Dico *et al*., 1989).

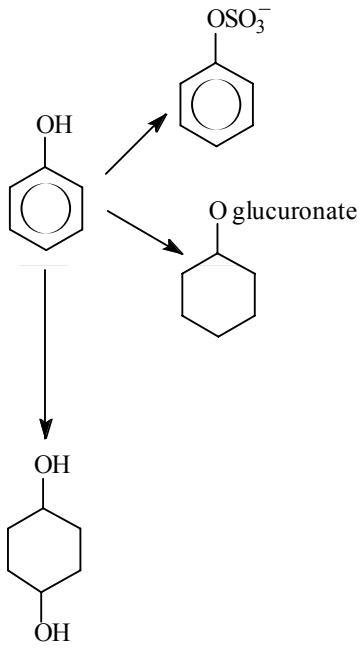
Studies in flow-through diffusion cells showed that full-thickness rat skin absorbed [$^{14}$C]phenol at a slightly faster rate than human skin (Hotchkiss *et al*., 1992), which absorbs phenol reasonably well (Bucks *et al*., 1990).

The sulfation of phenol and the glucuronidation of its hydroquinone metabolite were measured in human liver cytosols and microsomes, respectively. The rate of phenol sulfation varied between 0.31 and 0.92 nmol/mg protein/min; this is slightly higher than the rate for mice (0.46) and lower than that for rats (1.20). The rate of hydroquinone glucuronidation was between 0.10 and 0.28 nmol/mg protein/min, slightly higher than that for rats (0.08) and lower than that for mice (0.22). These enzyme-kinetic data were subsequently used to simulate phenol metabolism in mice, rats and humans *in vivo*, using a compartmental pharmacokinetic model with benzene as phenol precursor (Seaton *et al*., 1995).

#### 4.1.2 *Experimental systems*

Absorption of phenol in a flow-through diffusion cell *in vitro*, using full-thickness rat skin, indicated relatively rapid absorption through rat skin: 27% was absorbed in

**Figure 1. Metabolism of phenol**




Hydroquinone[a]

[a]For the metabolism of hydroquinone, see Figure 1 in the monograph on hydroquinone in this volume.

72 h; the rate for human skin was somewhat lower (19%) in the same system (Hotchkiss *et al*., 1992). Studies on the disposition of phenol after oral, dermal, intravenous and intratracheal administration to rats confirmed earlier results (Hughes & Hall, 1995): even after dermal application, phenol is rapidly excreted in urine, mainly as phenyl sulfate with smaller amounts of phenyl glucuronide. At higher phenol doses, biliary excretion of phenyl glucuronide in particular becomes more important, and a 2-*S*-glutathionylhydroquinone metabolite was observed (Scott & Lunte, 1993). The latter is probably formed from 1,4-benzoquinone (see this volume), the oxidized hydroquinone metabolite, which reacts spontaneously at a high rate with glutathione. The glutathione conjugate can undergo redox cycling, which may cause toxicity (Puckett-Vaughn *et al*., 1993). When phenol and hydroquinone are administered simultaneously to mice, their conjugation may be mutually decreased by competition for the same sulfotransferase enzyme, resulting in slower elimination, and possibly increased formation of 1,4-benzoquinone; the latter may be responsible for bone-marrow toxicity (Legathe *et al*., 1994). The formation and pharmacokinetics of phenol and hydroquinone during benzene exposure in rats, mice and humans have been simulated by Seaton *et al*. (1995).

Phenol is converted by rat liver microsomes to a reactive metabolite that binds covalently to protein; the most likely metabolites involved in this are hydroquinone and, at

a lower rate, catechol, the covalent binding of which does not require NADPH (Wallin *et al*., 1985). 1,4-Benzoquinone is responsible for the inactivation of CYP2E1; this does not require reactive oxygen species, but is a direct effect (Gut *et al*., 1996). Peroxidases (e.g., from macrophages), may also catalyse the formation of reactive products from phenol (Schlosser *et al*., 1989), in which 1,4-benzoquinone plays a critical role. The conversion of hydroquinone to 1,4-benzoquinone *in vitro* was stimulated by phenol (Smith *et al*., 1989). A small percentage of phenol is converted *in vitro* to trihydroxybenzene or, after ring opening, to muconic acid (Schlosser *et al*., 1993).

Incubation of mouse peritoneal macrophage lysate with bovine serum albumin and [$^{14}$C]phenol or [$^{14}$C]hydroquinone resulted in covalent binding of $^{14}$C to protein dependent on hydrogen peroxide and inhibited by the peroxidase inhibitor aminotriazole or by the –SH nucleophile antioxidant cysteine. The conversion of [$^{14}$C]phenol to protein- and calf thymus DNA-binding metabolite(s) was also catalysed by purified prostaglandin H synthase and was dependent on either hydrogen peroxide or arachidonic acid (Schlosser *et al*., 1989). Phenol (100 μmol/L) induced formation of 8-hydroxydeoxyguanosine in HL60 cell DNA *in vitro*, but not in bone-marrow cells of B6C3F$_1$ mice *in vivo* after a single intraperitoneal dose of 75 mg/kg (Kolachana *et al*., 1993).

#### 4.1.3 *Comparison of human and rodent data*

The metabolism of phenol in humans and in rats or mice is very similar: at low doses, mainly sulfate conjugates of phenol and hydroquinone are excreted in urine. Whether the reactive intermediate 1,4-benzoquinone plays an important role *in vivo* at low exposure is uncertain; as long as sufficient glutathione is available, this will probably rapidly trap the 1,4-benzoquinone and protect the cell from damage. Urinary excretion of mercapturates reflects formation of the glutathione conjugates. When at higher dose this protection fails, toxicity may become overt. Whether the covalent binding observed *in vitro* has relevance *in vivo* is uncertain.

### 4.2 Toxic effects

The toxicity of phenol has been reviewed (WHO, 1994).

#### 4.2.1 *Humans*

Phenol poisoning can occur in humans after skin absorption, inhalation of vapours or ingestion. Acute local effects are severe tissue irritation and necrosis. At high doses, the most prominent systemic effect is central nervous system depression (IARC, 1989).

#### 4.2.2 *Experimental systems*

Phenol causes irritation, dermatitis, central nervous system effects and liver and kidney toxicity in experimental animals (IARC, 1989).

Phenol induced fluorescence from 2′,7′-dichlorofluorescin in HL60 human leukaemia cells *in vitro* at concentrations that were not cytotoxic; this was interpreted to indicate generation of reactive oxygen species (Shen *et al*., 1996). When phenol was incu-

bated with hydrogen peroxide and horseradish peroxidase, disappearance of polyunsaturated *cis*-parinaric fatty acid was observed in a cell-free system, and also when *cis*-parinaric acid was incorporated into cellular lipids of HL60 cells; the reaction was inhibited by ascorbate and glutathione. The authors interpreted this to demonstrate the generation from phenol of phenoxy radicals capable of direct oxidation of polyunsaturated fatty acid (Ritov *et al*., 1996).

In contrast to catechol and hydroquinone, phenol was a weak inducer of apoptosis in HL60 human promyelocytic leukaemia cells, and had an apoptotic effect only at the highest concentration tested (0.75 mmol/L) (Moran *et al*., 1996). Phenol (≤ 10 mmol/L) had no effect on the colony formation of granulocytes/macrophages induced by a recombinant granulocyte/macrophage colony-stimulating factor of murine bone-marrow cells (Irons *et al*., 1992).

In a study on the immunotoxic effects of cigarette tar components, it was shown that phenol (≤ 1 mmol/L) had no effect on interleukin-2-dependent DNA synthesis or cell proliferation in cultured human lymphoblasts (Li *et al*., 1997).

Phenol (25, 50, 75 or 100 mg/kg, single intraperitoneal administration) decreased the incorporation of $^{59}$Fe by erythrocytes in a dose-dependent fashion in female Swiss mice, when administered with hydroquinone (50 mg/kg, single intraperitoneal administration) (Snyder *et al*., 1989). Phenol (≤ 40 μmol/L) had no consistent effect on the number of erythroid colony-forming bone-marrow cells from Swiss Webster or C57BL/J6 mice (Neun *et al*., 1992) and only inhibited the growth of bone-marrow cells from female C57 BL/6 × DBA/2 mice at millimolar concentrations (Seidel *et al*., 1991).

### 4.3 Reproductive and reproductive effects

#### 4.3.1 *Humans*

No data were available to the Working Group.

#### 4.3.2 *Experimental systems*

Phenol was toxic in cultured rat conceptuses at 10 μmol/L, the lowest concentration tested, and killed all embryos at 200 μmol/L (Chapman *et al*., 1994).

### 4.4 Genetic and related effects

#### 4.4.1 *Humans*

No data were available to the Working Group.

#### 4.4.2 *Experimental systems* (see Table 1 for references)

Phenol was mutagenic to *Escherichia coli* B/Sd-4 at highly toxic doses only (survival level, 0.5–1.7%; Demerec *et al*., 1951), but it did not induce filamentation in the *lon*$^-$ mutant of *Escherichia coli* (Nagel *et al*., 1982) and was not mutagenic to *Salmonella typhimurium* strains in most studies. In one study, it was weakly mutagenic to *S. typhimurium* TA98 in the presence of an exogenous metabolic system, but only when the assay was performed using a modified medium.

Phenol weakly induced mitotic segregation in *Aspergillus nidulans*.

Phenol did not increase the frequency of sex-linked recessive lethal mutations in *Drosophila melanogaster* following feeding or administration by injection.

Phenol did not induce DNA single-strand breaks in mouse lymphoma L5178Y cells. It was reported in abstracts that phenol induced DNA strand breaks in mouse lymphoma cells, as measured by the alkaline unwinding technique followed by elution through hydroxyapatite (Garberg & Bolcsfoldi, 1985), but that it did not induce strand breaks, as measured by the alkaline elution technique, in rat germ-cell DNA after either single or multiple dose treatments (Skare & Schrotel, 1984).

Phenol induced mutations at the *hprt* locus of Chinese hamster V79 cells in the presence of an exogenous metabolic system from the livers of phenobarbital-induced mice and *tk* locus mutations in mouse lymphoma L5178Y cells in the presence or the absence of an exogenous metabolic activation system. Micronuclei were induced by phenol in Chinese hamster ovary cells in one study and sister chromatid exchanges in mammalian cells were increased in several studies, including three with human lymphocytes.

Phenol was reported to induce DNA oxidative damage in human promyelocytic HL60 cells and to inhibit repair of radiation-induced chromosomal breaks in human leukocytes (Morimoto *et al.*, 1976). However, it only slightly inhibited DNA repair synthesis and DNA replication synthesis in WI-38 human diploid fibroblasts (Poirier *et al.*, 1975).

DNA oxidative damage was not found in bone marrow of mice given a single intraperitoneal injection of phenol. Administration of phenol did not induce micronuclei in bone-marrow cells in three studies; however, micronuclei were induced in the bone marrow of pregnant CD-1 mice after a single oral dose, but micronuclei were not seen in the liver of fetuses. As reported in an abstract, phenol induced micronuclei in male and female mice at doses of 150 and 200 mg/kg bw (Sofuni *et al.*, 1986). In one study, FISH probes for centromeres were used to demonstrate that the micronuclei in the bone-marrow cells of mice injected three times intraperitoneally with 160 mg phenol/kg bw were the result of chromosomal breakage and not aneuploidy. This result substantiates a similar finding reported as an abstract [details not given] (Lowe *et al.*, 1987). Inhibition of topoisomerase I *in vitro* was not found and inhibition of topoisomerase II *in vitro* was observed only if a peroxidase/hydrogen peroxide system was added to the reaction mixture. Covalent binding to DNA was not observed in rat Zymbal glands after in-vivo exposure. In Chinese hamster cells *in vitro*, phenol did not inhibit intercellular communication in two studies, but in a third study, inhibited intercellular communication in CYP1A1-, CY1A2- and CYP2B1-transfected cell lines as well as in the parental line.

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Phenol is a basic feedstock for the production of phenolic resins, bisphenol A, caprolactam, chlorophenols and several alkylphenols and xylenols. Phenol is also used in

**Table 1. Genetic and related effects of phenol**

| Test system | Results[a] | | Dose[b] (LED or HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 9140[c] | Contruvo *et al*. (1977) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 282 | Florin *et al*. (1980) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | NT | 2000 | Kinoshita *et al*. (1981) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 250 | Pool & Lin (1982) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 800 | Haworth *et al*. (1983) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 1500 | Kazmer *et al*. (1983) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | – | 9140[c] | Contruvo *et al*. (1977) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | – | 282 | Florin *et al*. (1980) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | NT | 50 | Gilbert *et al*. (1980) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | – | 250 | Pool & Lin (1982) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | – | 800 | Haworth *et al*. (1983) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation | – | – | 9140[c] | Cortruvo *et al*. (1977) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation | – | – | 282 | Florin *et al*. (1980) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation | – | – | 250 | Pool & Lin (1982) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation | – | – | 800 | Haworth *et al*. (1983) |
| SA8, *Salmonella typhimurium* TA1538, reverse mutation | – | – | 9140[c] | Cortruvo *et al*. (1977) |
| SA8, *Salmonella typhimurium* TA1538, reverse mutation | – | NT | 25 | Gilbert *et al*. (1980) |
| SA8, *Salmonella typhimurium* TA1538, reverse mutation | – | – | 250 | Pool & Lin (1982) |
| SA8, *Salmonella typhimurium* TA1538, reverse mutation | – | – | 800 | Haworth *et al*. (1983) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 9140[c] | Cortruvo *et al*. (1977) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 282 | Florin *et al*. (1980) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | (+) | 2350 | Gocke *et al*. (1981) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 250 | Pool & Lin (1982) |
| SAS, *Salmonella typhimurium* TA1536, reverse mutation | – | – | 9140[c] | Cortruvo *et al*. (1977) |
| ANN, *Aspergillus nidulans*, aneuploidy | (+) | NT | 1412 | Crebelli *et al*. (1987) |

**Table 1 (contd)**

| Test system | Results[a] | | Dose[b] (LED or HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| VFS, *Vicia faba*, sister chromatid exchange | + | NT | 10000 | Zhang *et al*. (1991) |
| PLS, *Hordeum vulgare*, sister chromatid exchange | + | NT | 10000 | Zhang *et al*. (1991) |
| PLS, *Secale cereale*, sister chromatid exchange | + | NT | 10000 | Zhang *et al*. (1991) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations | – | | 20000 µg/mL[d] | Sturtevant (1952) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations | – | | 4700 ppm feed | Gocke *et al*. (1981) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations | – | | 5250 µg/mL inj | Woodruff *et al*. (1985) |
| DIA, DNA strand breaks/cross-links, mouse lymphoma L5178YS cells *in vitro* | – | NT | 94 | Pellack-Walker & Blumer (1986) |
| G9H, Gene mutation, Chinese hamster V79 cells, *hprt* locus *in vitro* | NT | + | 250 | Paschin & Bahitova (1982) |
| G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro* | ? | (+) | 300 | McGregor *et al*. (1988) |
| G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro* | + | + | 5 | Wangenheim & Bolcsfoldi (1988) |
| SIM, Sister chromatid exchange, mouse spleen cells *in vitro* | + | NT | 10000 | Zhang *et al*. (1991) |
| MIA, Micronucleus test, Chinese hamster ovary CHO cells *in vitro* | (+) | (+) | 175 | Miller *et al*. (1995) |
| DIH, DNA oxidative damage, human promyelocytic HL-60 cells *in vitro* | + | NT | 9.4 | Kolachana *et al*. (1993) |
| SHL, Sister chromatid exchange, human lymphocytes *in vitro* | (+) | NT | 94 | Morimoto & Wolff (1980) |
| SHL, Sister chromatid exchange, human lymphocytes *in vitro* | + | + | 282 | Morimoto *et al*. (1983) |
| SHL, Sister chromatid exchange, human lymphocytes *in vitro* | + | NT | 0.5 | Erexson *et al*. (1985) |
| SHL, Sister chromatid exchange, human lymphocytes *in vitro* | – | NT | 188 | Jansson *et al*. (1986) |
| DVA, DNA oxidative damage, $B6C3F_1$ mouse bone-marrow cells *in vivo* | – | | 75 ip × 1 | Kolachana *et al*. (1993) |
| MVM, Micronucleus test, NMRI mouse bone-marrow cells *in vivo* | – | | 188 ip × 2 d | Gocke *et al*. (1981) |
| MVM, Micronucleus test, male CD-1 mouse bone-marrow cells *in vivo* | – | | 250 po × 1 | Gad-El Karim *et al*. (1986) |

**Table 1 (contd)**

| Test system | Results[a] | | Dose[b] (LED or HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| MVM, Micronucleus test, pregnant CD-1 mouse bone-marrow cells *in vivo* | + | | 265 po × 1 | Ciranni *et al*. (1988) |
| MVM, Micronucleus test, CD-1 mouse bone-marrow cells *in vivo* | – | | 160 ip × 1 | Barale *et al*. (1990) |
| MVM, Micronucleus resulting from chromosomal breakage, male CD-1 mouse bone marrow *in vivo* | +[e] | | 160 ip × 3 d | Chen & Eastmond (1995a) |
| AVA, Aneuploidy, male CD-1 mouse bone marrow *in vivo* | –[e] | | 160 ip × 3 d | Chen & Eastmond (1995a) |
| BID, Binding (covalent) to DNA, cultured rat Zymbal gland cells *in vitro* | + | NT | 750 | Reddy *et al*. (1990) |
| BVD, Binding (covalent) to DNA, female Sprague-Dawley rat Zymbal glands, liver, spleen and bone marrow *in vivo* | – | | 75 po × 4 d | Reddy *et al*. (1990) |
| ICR, Inhibition of intercellular communication, V79 Chinese hamster cells | – | NT | NG | Chen *et al*. (1984) |
| ICR, Inhibition of intercellular communication, V79 Chinese hamster cells | – | NT | 400 | Malcolm *et al*. (1985) |
| ICR, Inhibition of intercellular communication, V79 Chinese hamster cells | + | NT | 103 | Vang *et al*. (1993) |
| Inhibition of topoisomerase I activity *in vitro* | – | NT | 94 | Chen & Eastmond (1995b) |

**Table 1 (contd)**

| Test system | Results[a] | | Dose[b] (LED or HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| Inhibition of topoisomerase II activity *in vitro* | –[f] | NT | 47 | Chen & Eastmond (1995b) |

[a] +, positive; (+), weakly positive; –, negative; NT, not tested; ?, inconclusive
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw /day; NG, not given; inj, injection; ip, intraperitoneal; po, oral
[c] 4.1% of this dose was ozonated before testing
[d] Vaginal douche
[e] The origin of the bone-marrow micronuclei was determined by a multicolour FISH assay using mouse major and satellite probes. Results showed that micronuclei are a result of chromosome breakage and not loss of entire chromosome.
[f] Inhibitory effects were seen following bioactivation using a peroxidase/hydrogen peroxide system.

disinfectants and antiseptics. Occupational exposure to phenol has been reported during its production and use, as well as in the use of phenolic resins in the wood products industry. It has also been detected in automotive exhaust and tobacco smoke.

### 5.2 Human carcinogenicity data

A study of Finnish woodworkers found a high risk of lung cancer among those exposed to phenol, although the excess risk was stronger in short-term than in long-term workers. This result was not replicated in three other studies which reported results on phenol and lung cancer, although two of them had very low statistical power. In the three studies reporting associations with multiple cancer sites, a few elevated risks were reported, but not at any cancer site in two or more studies. The pattern of results fails to demonstrate a risk of cancer due to phenol exposure.

### 5.3 Animal carcinogenicity data

Phenol was tested for carcinogenicity by oral administration in rats in one study and in mice in one study. An increased incidence of leukaemia was reported in male rats treated with the lower dose but not in high-dose rats or in mice or female rats. Phenol was a promoter of mouse skin carcinogenesis in two-stage protocols.

### 5.4 Other relevant data

Phenol is well absorbed from the gastrointestinal tract and through the skin of animals and humans. It is metabolized principally by conjugation (by sulfation and glucuronidation) with a minor oxidation pathway leading to quinone-related reactive intermediates which bind covalently to protein and are detoxified by conjugation with glutathione. Topically applied phenol is a skin irritant and systemic toxicity is seen in liver and kidney after topical and oral dosing.

After in-vivo administration, phenol induced micronuclei in mice and chromosomal aberrations in rats. It also caused oxidative DNA damage in mice, and it bound covalently to rat DNA. 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. It did not induce recessive lethal mutations in *Drosophila melanogaster* and had only a weak effect in inducing segregation in *Aspergillus nidulans*. Phenol was not mutagenic in bacteria.

### 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of phenol.

There is *inadequate evidence* in experimental animals for the carcinogenicity of phenol.

### Overall evaluation

Phenol is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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