

Phenol

Toxicological overview

Key Points

Kinetics and metabolism

- Phenol is rapidly absorbed following inhalation, ingestion and through the skin
- Following ingestion phenol undergoes first-pass metabolism and is conjugated with glucuronic acid and sulphate
- Phenol is predominantly excreted via the urine

Health effects of acute exposure

- Toxic, harmful and corrosive
- Acute ingestion and skin exposure can cause systemic effects such as anorexia, headache, dark urine, hypothermia, hypotension, arrhythmia and coma
- Local effects are observed following inhalation (wheezing, cough, dyspnoea), ingestion (gastrointestinal effects) and dermal exposure (inflammation, erythema)

Health effects of chronic exposure

- Chronic inhalation of phenol may cause anorexia, weight loss, salivation, muscle weakness, liver and kidney damage
- Following chronic ingestion nausea, vomiting, headaches, abdominal pain, sore throat, mouth ulcers and dark urine may occur, as well as respiratory and cardiovascular effects
- Chronic skin exposure may cause local effects such as skin irritation, inflammation and necrosis, as well as including anorexia, headache, vertigo and dark urine
- International Agency for Research on Cancer classified phenol as a category 3 carcinogen i.e. not classifiable as to the carcinogenicity to humans

Toxicological Overview

Summary of Health Effects

Following acute inhalation of phenol, respiratory effects such as wheezing, coughing, and dyspnoea may occur. Chronic inhalation of phenol may lead to gastrointestinal effects such as anorexia, weight loss, muscle weakness, liver and kidney effects. There does not appear to be cumulative health effects following chronic inhalation exposure.

Following acute ingestion of phenol systemic effects as seen following inhalation may occur, as well as burning of mouth and throat, necrosis of skin and mucous membranes, abdominal pain, nausea, vomiting, sweating, diarrhoea and cyanosis. Ingestion is commonly fatal. Chronic ingestion may cause mouth ulcers, sore throat, abdominal pain, nausea, vomiting, diarrhoea, headache and dark urine.

Following acute skin exposure to phenol local effects may include inflammation, erythema, corrosion and burns. Systemic toxicity may also occur, similar to that observed following inhalation or ingestion of phenol. Chronic skin exposure may cause skin irritation, inflammation, necrosis, anorexia, headache, vertigo, salivation and dark urine.

The international Agency for the Research on Cancer (IARC) concluded that phenol is not classifiable as to its carcinogenicity in humans (group 3).

No data were available regarding the reproductive or developmental effects of phenol in humans.

Kinetics and metabolism

Phenol is rapidly absorbed following inhalation and ingestion [1-3]. Approximately 70 – 80 % of the dose is absorbed following inhalation of phenol vapour, and 90 % of the dose was recovered in urine following oral exposure. Phenol vapour and aqueous solutions are also rapidly absorbed through the skin. Approximately 80 % of the dose was absorbed through the skin when volunteers placed their hands in phenol solutions for 30 minutes [4]. The skin is thought to be the primary route of entry during occupational exposure [3].

Once absorbed phenol is rapidly distributed to all tissues in animals [1-3]. The highest peak concentrations were found in liver although both phenol and metabolites were also detected in the lungs, CNS, spleen, kidney, adrenal gland and thyroid, depending on the animal species [4]. No data were found regarding the distribution of phenol in humans by any route of exposure [1-3].

Following absorption by the oral route, phenol undergoes first-pass metabolism as it is rapidly conjugated with glucuronic acid and sulphate [1, 2]. Hydroxylation to hydroquinone and catechol also occurs [2]. Quantitatively, the liver, lungs, kidney and gastrointestinal mucosa are the most important sites for phenol metabolism. The roles these organs play in metabolism depend on the route of exposure and the dose. The lack of first pass metabolism following skin absorption may contribute to the toxicity of phenol following dermal absorption [4].

The major route of excretion of phenol is via the urine. A minor part is excreted in faeces or expired air [1, 2]. The rate of excretion depends on route of exposure and dose. Following a single dose of phenol, the excretion rates during the first 24 hours are approximately 99 %, 90 % and 80 % for inhalation, oral and dermal routes, respectively [4].

Sources and route of exposure

The main route of exposure to phenol is via inhalation (products of combustion in air, cigarette smoke) or ingestion (smoked food) [2, 5].

Phenol is a constituent of coal tar and formed during the natural decomposition of organic materials. The majority of phenol in the atmosphere however is from anthropogenic activity. Residential wood burning, exhaust gases and degradation of benzene under light are all potential sources of phenol [2, 5].

The main emission of phenol occurs to air. Atmospheric levels in urban/suburban areas are estimated to be 0.1 – 8 $\mu\text{g m}^{-3}$ whereas concentrations near industrial areas may be higher. Ambient air levels in a highly industrialised region of Poland reached between 3.8 and 26.6 $\mu\text{g m}^{-3}$ [2, 5]. Phenol has also been detected in rain, surface and ground water, although data are scarce [2].

Workers may be occupationally exposed to phenol if working in the processing of phenolic resins, production of phenol derivatives, caprolactam, cokes or insulation materials. Wood workers and those working in plywood plants are also at risk of occupational exposure, as are those working in iron and steel foundries or synthetic fibre and fibrous glass wool factories [1, 2].

The main route of systemic exposure is predominantly via ingestion, inhalation or dermal absorption as phenol is readily absorbed from the GI tract, the lungs and the skin [1].

Health Effects of Acute / Single Exposure

Human Data

Inhalation

Only limited data are available on adverse effects following short term inhalation [2].

Phenol vapours are irritating to the upper respiratory tract, and wheezing may occur. Other effects associated with inhalation include anorexia, weight loss, headache, vertigo, salivation and dark urine indicative of nephrotoxicity [1].

Ingestion

Both local and systemic effects have been reported following ingestion of phenol, including cardiovascular effects, respiratory distress, metabolic acidosis, renal failure, neurological effects, shock, coma and death [1, 2, 5].

Intense burning of the mouth and throat may occur following swallowing a significant concentrated dose of phenol, leading to necrosis of the skin and mucous membranes of the throat, as well as abdominal pain and gastrointestinal irritation including nausea, vomiting, sweating and diarrhoea. Skin may be pale and sweaty, and pupils may be constricted or dilated. Cyanosis is usually evident. Respiratory and pulse rates are initially increased then decreased. Excitation may occur which may be rapidly followed by unconsciousness. Ingestion at such level is usually fatal [1, 5].

Respiratory effects, often characterised by an initial increase in respiratory rate followed by decrease in both rate and magnitude leading to respiratory failure are the most common cause of death following acute ingestion of phenol [2, 3]. Death has been reported to have occurred within 10 minutes of ingestion of 4.8 g. Other cases have been reported in which death has occurred within hours of ingestion of 10 – 20 g phenol. In the latter case, tachypnoea was initially observed, followed by dyspnoea. On autopsy pulmonary oedema was reported [3]. The lowest dose at which death has occurred in humans was 140 mg kg⁻¹ bw. [4].

Cardiovascular effects have been reported following phenol ingestion such a bradycardia [1, 2, 5]. However, following ingestion of one ounce of 89 % phenol one casualty was in respiratory arrest within 30 minutes and within 60 minutes had developed ventricular tachycardia, subsequently developing supraventricular and ventricular dysrhythmias. The same casualty also showed signs of GI irritation as esophagitis and GI bleeding occurred within one week of exposure [3].

Dark urine may be produced following ingestion of phenol. Acute renal failure may occur [1].

Dermal / ocular exposure

Local effects after dermal exposure include dermal inflammation, erythema, and, due to it being a local anaesthetic, painless blanching. However, once pain becomes evident serious burns, corrosion and necrosis may have already occurred. Effects are worse if affected sites

are bandaged [1-3]. A 5 – 10 % phenol solution used on dressings has been reported to cause necrosis of the skin and underlying tissues, in some cases necessitating amputation. A white, brown or red discolouration of the skin may also occur [1, 2]. Dermal exposure to 40 % phenol in dichloromethane resulted in severe burns [3].

Systemic toxicity may occur rapidly following dermal absorption, and approximately 50 % of reported cases are fatal [1, 2]. Cardiovascular shock, cardiac arrhythmias and bradycardia, as well as metabolic acidosis have been reported within 6 hours of skin peeling procedures with phenol [2, 3]. Hyperventilation, acute renal failure, and methaemoglobinaemia have also been reported [2].

Gastrointestinal effects such as nausea and vomiting have been reported in cases where casualties were exposed to phenol-water solution. In one case, following phenol exposure (concentration not stated) hepatic effects such as an increase in bilirubin concentration were also observed. In another case (casualty exposed to 40 % phenol in dichloromethane) acute renal failure was reported [3].

Fumes of phenol are irritating to the eyes and may cause miosis or mydriasis. Phenol is corrosive and can cause severe ocular damage including corneal opacification [1].

Animal and In-Vitro Data

General toxicity

The clinical effects following phenol exposure are independent of the route of exposure. The acute effects are generally attributed to the depression of the CNS, leading to symptoms such as neuromuscular hyperexcitability (twitching and convulsions), increased heart rate followed by slow and irregular heart rate), hypertension followed by hypotension, salivation, dyspnoea and hypothermia [2].

Inhalation

Phenol is a respiratory irritant in laboratory animals. Female rats exposed to 234 ppm phenol for one hour showed signs of nasal irritation during exposure. Slight loss of coordination with spasm of the muscle groups was also reported after four hours and frank tremors with severe coordination after eight hours. All symptoms had ceased after one day. Ocular irritation also occurred [3]. In addition, mice exposed to phenol vapour (concentration not stated) showed an increase in reflex apnea (an index for respiratory irritation) with increased phenol concentration [3].

Inhalation of phenol also caused hyperaemia, bronchopneumonia and purulent bronchitis in a number of animal species [2].

Ingestion

After oral ingestion of phenol the mucous membranes of the throat and oesophagus may become inflamed and necrotic [2].

Female rats treated with 0 – 224 mg kg⁻¹ bw showed signs of neurotoxicity (tremours) 1 – 2 minutes after administration of the 120 and 224 mg kg⁻¹ bw dose. After 24 hours, miosis was significantly inhibited at all dose levels and locomotor activity was decreased in rats exposed to 224 mg kg⁻¹ bw [2]. Necrosis or atrophy of the spleen was also observed in rats given single doses of phenol (224 mg kg⁻¹) by gavage [3].

Haematological effects were reported in pregnant mice given a single dose of phenol (265 mg kg⁻¹) on gestation day 13 [3].

Neurological symptoms were observed in rabbits and rats following acute phenol exposure. Tremors starting at the head then spreading to the rest of the body, loss of coordination and convulsions preceded death after exposure to 300 – 940 mg kg⁻¹. Similarly, rats given 120 mg kg⁻¹ phenol orally displayed tremors, followed by convulsions and coma [3].

Dermal / ocular exposure

Following dermal exposure to phenol erythema, inflammation, oedema, skin irritation, discolouration, eczema and necrosis was reported in a number of laboratory animal species. Many effects are dose related and in some cases, resulted in death [2, 3].

Dyspnea and death was observed in pigs following exposure to a single dose of 500 mg kg⁻¹ undiluted phenol over 35 – 40 % of the body surface area. Cardiac arrhythmia was also noted in rabbits treated with 50 % phenol solution [3].

Renal effects such as haemoglobinuria and haematin casts in the distal convoluted tubules were observed in rats exposed to an acute dermal exposure to 107.1 mg kg⁻¹ liquid phenol [3].

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

Few data were found regarding adverse effects following chronic inhalation exposure to phenol. There does not appear to be cumulative health effects following chronic inhalation exposure [1, 2].

A cohort study of individuals working in the rubber and tyre industry revealed a significant increase in mortality from ischemic heart disease in phenol-exposed workers compared with controls. In contrast, those working in phenol-formaldehyde resin plants had a decreased mortality due to heart disease [3].

Gastrointestinal effects such as anorexia, progressive weight loss and excess production of saliva may occur following chronic exposure to phenol liquid and vapour. Muscle pain and weakness have also been reported, as have hepatic effects such as enlarged liver and elevated concentrations of liver enzymes. In addition, dark urine and glucose were present in the urine [3].

Ingestion

Chronic ingestion of phenol causes severe GI irritation, cardiovascular, CNS and respiratory effects and decreased body weight [1, 2].

Local drinking water wells were contaminated following a phenol spill and resulted in individuals being exposed to phenol. Individuals that had ingested water containing $>0.1 \text{ mg L}^{-1}$ had mouth sores, sore throats, diarrhoea and dark urine. An increase in the prevalence of skin rashes was also reported, although dermal exposure cannot be ruled out. The average daily intake of those showing health effects over the period of concern (a few weeks) were estimated to be in the range of $10 - 240 \text{ mg day}^{-1}$. No residual effects were observed after six months [1-4].

People living near a river contaminated with phenol reported headaches, nausea, vomiting, diarrhoea and abdominal pain. The concentration of phenol in the reservoir used for drinking water was 0.05 mg L^{-1} . The chlorination process may have converted phenol to chlorophenol that may be responsible for causing such effects [3].

Dermal / ocular exposure

Repeated skin exposure may result in onychomycosis (yellowing of the skin), skin irritation and skin eruption, as well as dermal inflammation and necrosis [1, 3].

Phenol may also cause symptoms such as anorexia, headache, vertigo, salivation, dark urine suggestive of haemoglobinuria, and increased skin pigmentation [1, 3].

Genotoxicity

Few data are available on the genotoxicity of phenol in humans [3].

Carcinogenicity

Four epidemiological studies were considered by IARC [6].

A case-control study of approximately 7000 men working in the rubber industry showed a non-significant increase in stomach cancer. In another case-control study of 136 patients with lung cancer within a cohort of 7300 men working in the plywood industry, exposure to phenol was associated with an increased risk of lung cancer. The risk was higher in short-term rather than long-term workers. A cohort of 15000 workers in five US companies occupationally exposed to phenol showed increased mortality ratios for cancer of the oesophagus, kidney and Hodgkin's disease, but decreased ratios for cancer of the stomach, brain, buccal cavity and pharynx. None of the mortality ratios were related to dose and were non-statistically significant. In a small population based, case control study, exposure to phenol was associated with an increased risk of pancreatic cancer (odds ratio = 4.8) although this was based on only four cases [6].

Overall, IARC stated that "the pattern of results fails to demonstrate a risk of cancer due to phenol exposure" and concluded that there was inadequate evidence in humans for the carcinogenicity of phenol and therefore it cannot be classified as to its carcinogenicity to human i.e. group 3 [6].

Reproductive and developmental toxicity

Few data were available regarding the reproductive or developmental effects of phenol in humans [3, 7]. Three small epidemiological studies have been carried out and have shown no clear association between occupational exposure to phenol and adverse pregnancy outcome. However, such studies, due to their design, may not have been sensitive enough to identify any adverse effects. Moreover, most women included in the studies were exposed to a mixture of solvents as well as phenol, and no data regarding exposure levels, frequency and duration of exposure were reported [7].

Animal and In-Vitro Data

Inhalation

Guinea pigs exposed to 26 -52 ppm phenol via inhalation for 41 days showed signs of inflammation, cellular infiltration, pneumonia, bronchitis, endothelial hyperplasia and capillary thrombosis. Myocardial injury, characterised by myocardial inflammation, degeneration, necrosis, interstitial fibrosis and lymphocyte infiltration, was also reported. Guinea pigs also had centrilobular degeneration and necrosis of the liver as well as renal proximal tubule and glomerular injury. Rabbits showed qualitatively similar, but less severe effects after 88 days. Neurological effects (hindlimb paralysis) were seen in guinea pigs, but not in rabbits [3].

Elevated liver enzymes were measured in rats exposed to 26 ppm phenol for 15 days. Such rats also showed signs of neurological impairment such as muscle tremors, twitching and movement disturbances [3].

Ingestion

Pregnant rats exposed to phenol (40 – 53.3 mg kg⁻¹ day⁻¹) by gavage showed signs of dyspnoea [3].

Rats exposed to 16 – 1694 mg kg⁻¹ day⁻¹ and mice exposed to 25 – 2642 mg kg⁻¹ day⁻¹ phenol in drinking water for 13 weeks showed no adverse effects on the respiratory, cardiovascular, endocrine, immune, neurological or reproductive system. In addition, the GI tract, bone, liver, kidney and skin were unaffected. A decreased body weight of rats and mice was reported at higher doses, which was associated with a decrease in water intake [3].

In the National Cancer Institute drinking-water study rats and mice were dosed with 2500 ppm or 5000 ppm phenol for 103 weeks, which corresponds to doses of approximately 260 – 280 or 585 – 630 mg kg⁻¹ day⁻¹ for rats, and 450 or 660 mg kg⁻¹ day⁻¹ for mice. There were no adverse effects on the respiratory, cardiovascular, endocrine, immune, neurological or reproductive system, nor the GI tract, bone, liver, kidney and skin. Decreased body weight of both rats and mice was observed, which was related to the decreased water intake [3, 4, 8].

Higher toxicity was observed in a rat study in which phenol (0 – 120 mg kg⁻¹ day⁻¹) was administered by gavage for 14 days. All rats dosed with 120 mg kg⁻¹ day⁻¹ died within 11 days. Kidney and liver pathology occurred in some rats administered 40 mg kg⁻¹ day⁻¹ phenol as well as thymus necrosis or atrophy. One rat showed such effects after administration of 12 mg kg⁻¹ day⁻¹ [4].

Dermal / ocular exposure

Skin crusts were reported on mice exposed to 5 mg phenol (5 % (w/v) solution) for 32 weeks, whereas skin ulceration occurred in mice exposed to 5 mg phenol (20 % (w/v)) [3].

Genotoxicity

Several bacterial mutagenicity studies reported negative results regarding the mutagenic activity of phenol [4]. However, several *in-vitro* mammalian systems have reported positive data. Using the bone marrow micronucleus test, a significant increase in micronuclei was reported in mice orally administered 265 mg kg⁻¹ bw [2]. Phenol gave a positive result in the V79/HPRT mutation test with metabolic activation. Conflicting results were obtained using the mouse lymphoma/ TK mutation test, as statistically significant and dose-related increases in mutation frequency were reported in the presence and absence of metabolic activation. However, such data could not be repeated by other laboratories [2].

The International Programme on Chemical Safety (IPCS) Environmental Health Criteria stated “the available data suggest that phenol may be genotoxic” [2].

Phenol has been considered on a number of occasions by the Committee on Mutagenicity of Chemicals in Food, Consumer products and the Environment (COM). The COM agreed that phenol should be considered an *in-vivo* somatic cell mutagen, based on positive results at high doses in the bone marrow assays for clastogenicity. The Committee concluded that,

following the oral route, there was potential for a threshold of activity as there was evidence of good protective mechanisms (rapid conjugation and detoxification of phenol in humans via the glutathione pathway) that would substantially reduce the systemic exposure to any active metabolites formed. However, there were insufficient data on inhalation and dermal exposure hence it was not possible to assume a threshold for inhalation or skin exposure [9].

In 1999 new data were presented and the COM concluded that overall, the *in-vitro* mutagenicity data were of poor quality and results were difficult to interpret, but *in-vivo* data showed phenol to be a somatic cell mutagen following intraperitoneal doses of approximately 100 – 160 mg kg⁻¹. No conclusions were drawn from the transgenic animal study on site-of-contact mutagenicity following inhalation or dermal exposure. Overall, the COM concluded that “the available data showed that occupational exposure to phenol was associated with a mutagenic hazard but it was not possible to quantify the risk” [9].

More recent data have been made available to provide a plausible mechanism to support the hypothesis that the positive data obtained in the bone-marrow test were due to a secondary threshold toxic effect, namely hypothermia, occurring at dose levels associated with positive results in the micronucleus assay, rather than a direct mutagenic effect. It was argued that the induction of micronuclei at the maximal tolerated dose is threshold related and may be causally related to hypothermia. The Committee agreed that if additional data on the dose-response of phenol-induced hypothermia could be provided then phenol could be regarded as having no significant *in-vivo* mutagenic potential at dose levels that do not produce any significant toxic effects [10].

Carcinogenicity

The IARC concluded that there is inadequate evidence in experimental animals for the carcinogenicity of phenol.

Reproductive and developmental toxicity

Phenol can cross the rat placenta into fetal circulation. In animal studies, the most reliable findings at non-maternally toxic doses have been a reduction in fetal weight and viability. There is consistent data on congenital malformations [7].

In a multigeneration study, rats were exposed to 100 – 12000 mg L⁻¹ drinking water (10 – 1200 mg kg⁻¹ bw) for three to five generations. Stunted growth was reported in the offspring of rats exposed to 7000 mg L⁻¹. At 8000 mg L⁻¹ offspring died due to maternal neglect, at 10000 mg L⁻¹ offspring died at birth and at 12000 mg L⁻¹ no reproduction occurred. No adverse effects were seen on growth, general appearance or fecundity in rats exposed to 100 – 100 mg L⁻¹ for five generations, or to 3000 – 5000 for three generations [2].

Pregnant rats given phenol (0 – 120 mg kg⁻¹ bw) by gavage during pregnancy (day 6 – 15) showed no signs of toxicity but the average fetal body weight per litter was significantly decreased at the highest dose. In this developmental toxicity study no convincing signs of fetotoxicity were seen at 140 mg kg⁻¹ day⁻¹ or below [2].

In a similar study Swiss albino mice were administered phenol (0 – 280 mg kg⁻¹ bw) by gavage during gestational day 6 – 15. Maternal toxicity was observed in the highest dose group, including ataxia and tremor, reduced body weight and reduced body weight gain. No dose related changes were reported for prenatal mortality, live litter size or morphological abnormalities [2].

In a two generation study male reproductive study, no significant changes were reported in fertility or reproductive function, with the exception of significant increased in testicular sperm counts and production rates in F₁ males exposed to 5000 ppm [7].

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.