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Phenol

Toxicological Overview

Key Points

Kinetics and metabolism

- phenol is readily absorbed following inhalation, ingestion and through the skin
- following ingestion, phenol undergoes first-pass metabolism
- phenol is predominantly excreted in the urine

Health effects of acute exposure

- may cause toxicity at the site of contact and systemically, by all routes of exposure
- following acute ingestion, gastrointestinal tract irritation and pain, pale and sweaty skin, constricted or dilated pupils, cyanosis, excitation, unconsciousness, cardiovascular and respiratory effects, respiratory failure and death may occur
- acute inhalation of phenol leads to wheezing, respiratory tract irritation, anorexia, weight loss, headache, vertigo, salivation and dark urine
- acute skin exposure leads to inflammation, blanching, discoloration of the skin, erythema, corrosion, necrosis and burns which may be painless

Health effects of chronic exposure

- chronic inhalation may lead to weight loss, muscle weakness and liver effects
- chronic ingestion may cause mouth sores, gastrointestinal tract irritation, cardiovascular, CNS and respiratory effects and decreased body weight
- chronic skin exposure may result in ochronosis, skin irritation, skin eruption, inflammation and necrosis
- the International Agency for Research on Cancer (IARC) classified phenol as a category 3 carcinogen, ie not classifiable as to the carcinogenicity to humans

Summary of Health Effects

Phenol may cause irritation and burns by any route of exposure. Phenol vapours are irritating to the respiratory tract and ingestion of phenol can cause corrosive damage to the entire gastrointestinal (GI) tract. Dermal exposure to phenol causes inflammation, erythema, discolouration of the skin, burns and necrosis. Ocular exposure can cause irritation and corneal opacification.

Phenol is readily absorbed following inhalation, ingestion and dermal exposure, resulting in systemic toxicity. Following absorption, phenol is rapidly distributed throughout the body. The major route of excretion of phenol is in the urine.

Cardiovascular, respiratory, renal and central nervous system (CNS) effects may occur following acute exposure by any route. Chronic inhalation of phenol may lead to effects including weight loss, muscle weakness and liver effects. Chronic ingestion may cause mouth sores, GI tract irritation, cardiovascular, CNS and respiratory effects, and decreased body weight. Systemic effects may also occur following chronic dermal exposure to phenol.

There is limited data available on the carcinogenicity of phenol in humans. The International Agency for Research on Cancer (IARC) concluded that phenol is not classifiable as to its carcinogenicity in humans (group 3). In long-term animals studies a carcinogenic effect was not reported in rodents orally administered phenol.

Phenol is considered to be an in-vivo somatic mutagen. It is assumed that there is a threshold for genotoxicity for oral exposure due to first-pass metabolism and detoxification of phenol. However, this is not applicable to inhalation and dermal routes of exposure.

Owing to limited data it is not possible to assess the reproductive and development effects of phenol in humans. In experimental animals adverse effects on the fetus have generally been observed at doses that cause maternal toxicity.

Kinetics and Metabolism

Phenol is readily absorbed following inhalation, ingestion and dermal exposure [1]. Following inhalation of phenol vapour at various concentrations, between 60 and 88% of the doses were retained by volunteers [2]. A mean 24-hour urinary recovery of 90% was reported in three volunteers following ingestion of a single dose of 0.01 mg/kg bw phenol [2]. Phenol vapour is also readily absorbed through the skin [2]. The skin is thought to be the primary route of entry during occupational exposure [1].

Following absorption, phenol is rapidly distributed throughout the body in animals [1, 3]. There is limited data on the distribution of phenol in humans. Following one case of fatal ingestion, phenol has been detected in the blood (130 µg/mL), urine (47 µg/mL), bile (187 µg/mL), brain (486 µg/g), muscle (204 µg/g), liver (228 µg/g), stomach contents (668 µg/g) and kidney (331 µg/g) (it has also been detected in the lungs in other cases) [1]. Following a fatal case of dermal exposure where an individual was painted with benzyl benzoate with a brush that had been soaked in 80% phenol, phenol was detected in the blood (4.7 µg/mL) and liver (3.3 and 7.1 µg/g phenol in unhydrolysed and hydrolysed samples, respectively), but not in the lungs, urine or stomach contents [1].

Following absorption by the oral route, phenol undergoes extensive first-pass metabolism, it is rapidly conjugated with glucuronic acid or sulphate [3–6].The remaining phenol may undergo oxidative metabolism to form hydroquinone and catechol (to a lesser extent) [6]. Phenol metabolism is saturable; data from humans and experimental animals suggests that conjugation with sulphate is the predominant metabolic pathway at lower doses but, as the dose increases, glucuronic acid conjugation and oxidative metabolism increase [6]. Metabolism of phenol takes place mainly in the liver, kidney and gut [2].

The major route of excretion of phenol is in the urine. A minor part is excreted in faeces or expired air [3, 4]. The rate of excretion depends on the 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 the inhalation, oral and dermal routes, respectively [2].

Sources and Route of Human Exposure

The major use of phenol is in the manufacture of bisphenol A and phenolic resins [2]. It is also used in the manufacture of caprolactam, aniline and other organic chemicals [2]. Phenol is used as a disinfectant, in chemical skin-peelers, nerve injections and in topical anaesthetics [2, 7]. It is also present in low concentrations in a number of over-the-counter preparations including antiseptics, lozenges, lotions, salves and ointments [5, 8]. Phenol is found in small quantities in cosmetics, paints, polishes, adhesives, lacquers, varnishes and solvents [2, 5]. Phenol may be found in consumer products up to 2.5%; it is allowed in soaps and shampoos up to 1% in the EU [9]. It may also be found in smoked meat and fish products, and as a constituent of smoked flavourings [6].

Phenol is a constituent of coal tar and is formed during the natural decomposition of organic materials [2]. It is also found as a normal constituent of human tissue and is found in urine, faeces, saliva and sweat [8].

The main emission of phenol occurs to air [3]. Residential wood and municipal solid waste burning, coal-fired power stations, cigarette smoking, exhaust gases and the natural degradation of benzene are all potential sources of phenol [1, 3, 10]. Phenol in the environment is largely of anthropogenic origin [3]. Atmospheric levels in urban/suburban areas are estimated to be 0.1–8 $\mu g/m^3$, 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 $\mu g/m^3$ [3, 10]. Phenol has a half-life of approximately 15 hours in air [1].

Phenol has also been detected in rain, and surface and ground waters, although data is scarce [3].

Phenol may be released to soil by the spreading of animal manure or sewage sludge, and may be present from historical manufacture of coal gas and coke [5]. The physicochemical properties of phenol suggest that it would weakly bind to soil and organic matter, and readily leach into surface and ground waters [5]. Phenol is readily biodegraded in aerobic and anaerobic conditions, and has a half-life in soil of typically less than 5 days [1]. However, it may persist in contaminated soils and coal tar sites where conditions may not be suitable for degradation due to ecotoxicity [5].

The general population may be exposed to phenol in food, food contact materials and other consumer items such as floor waxes, cosmetics and disinfectants [6]. Dermal contact at work or through the use of products containing phenol is the most likely route of exposure [1].

Workers may be occupationally exposed to phenol if employed in the processing of phenolic resins, or 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 [3, 4]. Workplace exposure limits (WEL) have been set in the UK, to protect workers from the harmful effects of phenol. The long-term exposure limit (LTEL) is 7.8 mg/m^3 (8-hour time weighted average exposure (TWA) reference period). The short-term exposure limit (STEL) for vapour is given as 16 mg/m^3 (15-minute reference period) [11].

Health Effects of Acute/Single Exposure

Human data

General toxicity

Irritation, burns and systemic toxicity may arise following exposure by any route [7]. Target organs for toxicity include nervous system, kidneys, heart and lungs [2]. Systemic effects following exposure to phenol include nausea, vomiting, diarrhoea, hypotension, tachycardia, cardiac arrhythmias, metabolic acidosis, pallor, sweating and shock [7]. Initially CNS stimulation may arise, followed by drowsiness, respiratory depression, cyanosis, convulsions, bronchospasm, rapid onset pulmonary oedema and death [7].

Inhalation

Only limited data is available on adverse effects following short-term inhalation.

Phenol vapours are irritating to the upper respiratory tract, and wheezing may occur. Other effects associated with inhalation include anorexia (leading to progressive weight loss), headache, vertigo, salivation and dark urine, indicative of nephrotoxicity [4].

Ingestion

Ingestion of phenol can cause irritation of the mucosal membranes and GI tract pain [7]. Ingestion of large quantities may result in painless (as phenol destroys nerve endings), discoloured burns [7]. Corrosive damage caused on ingestion may involve the entire GI tract [4]. Laryngeal oedema may occur and oesophageal stricture formation may follow as a late complication [7]. Skin may be pale and sweaty, and pupils may be constricted or dilated; cyanosis is usually evident. Excitation may occur, which may be rapidly followed by unconsciousness [4, 10].

Respiratory effects, often characterised by an initial increase in respiratory rate followed by a decrease in both rate and magnitude, leading to respiratory failure, are the most common cause of death following acute ingestion of phenol [1, 3]. The lethal dose in humans may be as low as 1–15 g phenol (equivalent to 14–214 mg/kg bw/day) [2]. In one fatal case death occurred within hours of ingestion of 10–20 g phenol; tachypnoea was initially observed, followed by dyspnoea [1]. At post-mortem pulmonary oedema was reported [1].

Cardiovascular effects (such as bradycardia) have been reported following phenol ingestion [3, 4, 10]. Following ingestion of one ounce (28.4 g) 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 tract irritation as oesophagitis and GI bleeding, within 1 week of exposure [1].

Dark urine may be produced following ingestion of phenol. Acute renal failure may occur [4].

Dermal/ocular exposure

Phenol is a strong irritant in humans [2]. Local effects after dermal exposure include inflammation, erythema and blanching and it may be painless, owing to phenol's anaesthetic properties [4]. A white, brown or red discolouration of the skin may also occur [3, 4]. Once pain becomes evident, serious burns, corrosion and necrosis may have already developed. Phenol causes coagulation necrosis by denaturing and precipitating proteins [1]. Necrosis has occasionally been reported following contact with phenol solutions as dilute as 1% [9].

Systemic toxicity may occur rapidly following dermal absorption; approximately 50% of reported cases were fatal where exposure was sufficient to cause systemic toxicity [3, 4]. Cardiovascular shock, cardiac arrhythmias, vomiting, lethargy, metabolic acidosis, hyperventilation, acute renal failure and methaemoglobinaemia have also been reported [1, 3].

GI 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 (with the casualty exposed to 40% phenol in dichloromethane) acute renal failure was reported [1].

Fumes of phenol are irritating to the eyes and may cause miosis or mydriasis. Phenol can cause severe ocular damage including corneal opacification [4].

Animal and in-vitro data

General toxicity

The effects following phenol exposure are largely independent of the route of exposure. For example, oral LD_{50} values in experimental animals are of a similar magnitude to the 24-hour LD_{50} for skin exposure in rats [2]. Acute effects are generally attributed to the depression of the CNS, leading to symptoms such as neuromuscular hyper-excitability (twitching and convulsions), increased heart rate followed by slow and irregular heart rate, hypertension followed by hypotension, salivation, dyspnoea and hypothermia [3].

Inhalation

Phenol is a respiratory irritant in experimental animals. Female rats exposed to 234 ppm (900 mg/m^3) phenol for 1 hour showed signs of nasal irritation during exposure. Slight loss of coordination with spasm of the muscle groups was also reported after 4 hours and frank tremors with severe coordination after 8 hours. All symptoms had ceased after 1 day. Ocular irritation also occurred [1]. In addition, mice exposed to phenol vapour (concentration not stated) showed an increase in reflex apnoea (an index for respiratory irritation) with increased phenol concentration [1].

Inhalation of phenol also caused hyperaemia, bronchopneumonia and purulent bronchitis in a number of animal species [3].

Ingestion

Phenol is more toxic when given by gavage than in drinking water, ie a single dose by gavage is more toxic than the same dose consumed in drinking water over a day. As such, adverse effects are observed at lower doses when administered by gavage than in studies where it is given in drinking water [1].

After oral ingestion of phenol the mucous membranes of the throat and oesophagus may become inflamed and necrotic [3].

The oral LD_{50} in various animal species ranges from 340–620 mg/kg bw/day [2].

Female rats treated with 0–224 mg/kg bw by gavage showed signs of neurotoxicity (tremors) 1–2 minutes after administration of the 120 and 224 mg/kg bw dose. After 24 hours, miosis (pupil response to light) was significantly inhibited at all dose levels and locomotor activity was decreased in rats exposed to 224 mg/kg bw [3].

Renal tubular necrosis with protein casts and papillary haemorrhage, necrosis or atrophy of the spleen or thymus and liver effects (changes in histopathology and serum markers of effect) were observed in 60% of animals exposed to a single gavage of 224 mg/kg phenol in water [1].

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

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. Similarly, rats given 120 mg/kg phenol orally displayed tremors, followed by convulsions and coma [1].

Dermal/ocular exposure

Following dermal exposure to phenol, erythema, inflammation, oedema, skin irritation, discolouration, eczema and necrosis were reported in a number of experimental animal species. Systemic effects have also been reported in animals exposed to phenol by dermal contact [1]. Lethality following dermal exposure to phenol is dependent on the concentration and surface area exposed [1, 3]. There are a number of studies which demonstrate higher mortality in animals exposed to lower concentrations of phenol [1]. It has been theorised that concentrated or neat solutions produce coagulative necrosis which reduces further penetration of the solution, resulting in less absorption of phenol than with more dilute solutions [1].

Tremors and convulsions were observed in rats on application of 107 mg/kg phenol to an unspecified surface area [1].

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

Renal effects such as haemoglobinuria and haematin casts in the distal convoluted tubules were observed in rats exposed to 107 mg/kg liquid phenol [1].

Health Effects of Chronic/Repeated Exposure

Human data

Inhalation

Data on health effects following chronic exposure to phenol is limited.

There is conflicting data on the cardiovascular effects of long-term exposure to phenol. A cohort study of individuals working in the rubber and tyre industry revealed a significant increase in mortality from ischaemic heart disease in phenol-exposed workers compared with controls. In contrast, those working in phenol-formaldehyde resin plants had a slight reduction in mortality due to heart disease [1].

GI effects such as anorexia, progressive weight loss and excess production of saliva may occur following chronic exposure to phenol vapour. Muscle pain and weakness have also been reported, as have hepatic effects such as enlarged liver and elevated concentrations of liver enzymes [1].

Workers exposed to concentrations of around 21 mg/m^3 phenol for about 13 years showed changes in haematological and clinical chemistry parameters indicative of liver toxicity [2].

Ingestion

Chronic ingestion of phenol causes severe GI tract irritation, cardiovascular, CNS and respiratory effects, and decreased body weight [3, 4].

A significant increase in GI symptoms (including mouth sores, nausea and diarrhoea) was reported in 17 out of 39 of the most highly exposed (>0.1 mg/L, and an estimated intake of 0.14–3.4 mg/kg bw/day) individuals in a retrospective study of 158 people exposed to drinking water for a number of weeks from wells contaminated by phenol [1]. Dark urine was observed in 17.9% of the most highly exposed individuals, compared to 3.4% in the controls [1]. An increase in the prevalence of skin rashes was also reported, although dermal exposure cannot be ruled out [1].

Dermal/ocular exposure

Repeated skin exposure may result in onychronosis (yellowing of the skin), skin irritation and skin eruption, as well as dermal inflammation and necrosis [1, 4].

Phenol may also cause symptoms such as anorexia, headache, vertigo, salivation, dark urine and increased skin pigmentation [4].

Genotoxicity

Little data is available on the genotoxicity of phenol in humans.

Carcinogenicity

Four epidemiological studies were considered by IARC [12].

A case–control study of approximately 7,000 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 7,300 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 15,000 workers in five US companies occupationally exposed to phenol showed increased mortality ratios for cancer of the oesophagus and kidney and Hodgkin's disease, but decreased ratios for cancer of the stomach, brain, buccal cavity and pharynx. None of the mortality ratios was related to dose and none was 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 [12].

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. IARC concluded that phenol cannot be classified as to its carcinogenicity to humans, ie group 3 [12].

Reproductive and developmental toxicity

Little data was available regarding the reproductive or developmental effects of phenol in humans [1, 13]. Three small epidemiological studies have been carried out and have shown no clear association between occupational exposure to phenol and adverse pregnancy outcomes. However, such studies, owing 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 was reported [13].

Animal and in-vitro data

Inhalation

No significant histological abnormalities were observed in monkeys, rats or mice exposed continuously to 5 ppm (19.25 mg/m^3) phenol for 90 days (although incomplete reporting suggests there may have been some pathology in the lung, liver and kidneys) [1].

Guinea pigs exposed to 26–52 ppm (100–200 mg/m^3) phenol by 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 [1].

Elevated liver enzymes (at termination) were measured in rats exposed whole body, continuously to 26 ppm (100 mg/m^3) phenol for 15 days. These rats also showed signs of neurological impairment such as muscle tremors, twitching and movement disturbances in the first 3–5 days of exposure [1]. However, rats exposed nose only to up to 25 ppm (96 mg/m^3) for 6 hours a day, 5 days a week for 2 weeks, showed no adverse effects by histopathology, haematology and clinical chemistry [1].

Exposure to 100–200 mg/m^3 for 7 hours a day, 5 days a week for 6–13 weeks, caused effects on the respiratory system, heart, liver and kidneys in guinea pigs and mice; in addition, neurological effects and mortality were observed in the guinea pigs [2].

Ingestion

A significant dose-dependent decrease in erythrocyte count was observed in CD-1 mice exposed for 28 days to phenol in drinking water; at the lowest dose of 4.7 mg/L (equivalent to an intake of 1.8 mg/kg bw/day) a 32% reduction was seen [9]. At the next highest dose of 19.5 mg/L (an intake of 6.2 mg/kg bw/day) suppressive effects were observed on T- and B-cells [9]. In the same study a statistically significant, dose-related decrease in a number of neurotransmitters was observed in mice exposed to doses up to around 34 mg/kg bw/day [2]. Significant limitations in study design and reporting have been noted, with successive studies having failed to replicate the effects observed in this study [6]. Histological examination following an immunotoxicity screening study in which rats were exposed to doses up to 300 mg/kg bw/day in drinking water for 13 weeks found no evidence of any treatment-related effects [2].

Rats exposed to 16–1,694 mg/kg bw/day and mice exposed to 25–2,642 mg/kg bw/day phenol in drinking water for 13 weeks showed no adverse effects on the respiratory, cardiovascular, endocrine, immune, neurological or reproductive systems. 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 [1].

In a National Cancer Institute drinking-water study, rats and mice were dosed with 2,500 or 5,000 ppm phenol for 103 weeks, which corresponds to doses of approximately 260–280 or 585–630 mg/kg bw/day for rats, and 450 or 660 mg/kg bw/day 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 [1, 2, 14].

As discussed in the acute exposure section, phenol appears to be more toxic following exposure by drinking water than by gavage. In contrast to the studies above on exposure by drinking water, all rats administered 120 mg/kg bw/day phenol in a 14-day gavage study died within 11 days [2]. Liver and kidney damage, and spleen or thymus necrosis or atrophy, was observed in a number of animals in the 40 mg/kg bw/day group [2]. Effects on the spleen or thymus were also observed in one of eight animals receiving 12 mg/kg bw/day [2]. Pregnant mice exposed also by gavage to 70 mg/kg bw/day have displayed neurotoxicity [2].

Pregnant rats exposed to phenol (40–53.3 mg/kg bw/day) by gavage showed signs of dyspnoea and rales [1].

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)] [1].

Tremors were observed in rabbits receiving 18 dermal applications (contact was equivalent to 5 hours a day, 5 days a week) of a 2.4% aqueous solution of phenol [2]. No effects were observed when a 1.2% solution was applied in the same manner [2].

Genotoxicity

Phenol does not appear to be mutagenic in standard bacterial assays; however, it is mutagenic to mammalian cells in vitro [15]. Increased sister chromatid exchange in human lymphocytes has also been observed on exposure to phenol in vitro [2]. Exposure of mammalian cells in vitro results in gene mutations and chromosomal damage in the presence and absence of metabolic activation [2]. There is some evidence to suggest that the effects may partly be due to oxidative DNA damage [15]. Negative results have been reported in rodents from in-vivo tests for chromosomal aberrations, DNA strand breaks and DNA adducts [6]. Results from the mouse bone marrow micronucleous test were negative or weakly positive following oral or intraperitoneal administration at doses that were equivalent to the LD_{50} [6].

Phenol has been considered on a number of occasions by the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM). In 1994 and 2000 COM concluded that phenol was an in-vivo somatic cell mutagen, based on positive results at high doses in the bone marrow assays for clastogencity. COM noted that, following the oral route, there was the potential for a threshold of activity as there was evidence of good protective mechanisms (rapid conjugation and detoxification of phenol in humans by the glutathione pathway) that would substantially reduce the systemic exposure to any active metabolites formed. However, there was insufficient data on inhalation and dermal exposure, hence it was not possible to assume a threshold following inhalation or skin exposure [16].

In 2008 COM considered data investigating the potential mode of genotoxic action of phenol and whether a threshold effect approach could be used in a risk assessment approach of the genotoxicty of phenol. COM reviewed results from a study that suggested that the in-vivo mutagenicity of phenol in the micronucleus assay was as a result of transient hypothermia caused by high doses of phenol. COM concluded that data from the studies suggests a role, but not necessarily causality, for phenol-induced hypothermia in the formation of micronuclei. COM confirmed that phenol was an in-vivo somatic cell mutagen and that there was insufficient evidence to support the use of a threshold approach for the assessment of systemic phenol. The threshold mode of action is route specific, ie detoxification in the GI tract before systemic absorption [15].

The European Food Safety Authority Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids considered phenol in a recent (2013) evaluation. The Panel

considered that the increased micronuclei in rodents administered high doses of phenol may be an indirect effect of phenol-induced hypothermia. For oral administration, a threshold for genotoxicity can be assumed due to the first-pass metabolism and detoxification of phenol. This conclusion is not applicable to inhalation and dermal routes of exposure for which there are concerns regarding genotoxicity, particularly at the site of contact. The Panel concluded that "orally administrated phenol is devoid of biologically relevant genotoxicity in vivo" [6].

Carcinogenicity

Phenol did not appear to have a carcinogenic effect on either rats or mice after long-term oral exposure [6]. IARC concluded that there is inadequate evidence in experimental animals for the carcinogenicity of phenol [12].

Reproductive and developmental toxicity

In a two-generation study, rats consuming phenol in drinking water at the highest dose (equivalent to doses of 300–380 mg/kg bw/day) showed reduced litter survival and a slight delay in offspring development [2]. Maternal toxicity was also present at this dose, as indicated by decreased maternal bodyweight [6].

In a multigenerational study, rats were exposed to 100–12,000 mg/L phenol in drinking water (resulting in an exposure of 10–1,200 mg/kg bw) for three to five generations. Stunted growth was reported in the offspring of rats exposed to 7,000 mg/L. At 8,000 mg/L offspring died due to maternal neglect, at 10,000 mg/L offspring died at birth and at 12,000 mg/L no reproduction occurred. No adverse effects were seen on growth, general appearance or fecundity in rats exposed to 100–1,000 mg/L for five generations, or to 3,000–5,000 mg/L for three generations [3].

Swiss albino mice were administered phenol (0–280 mg/kg bw/day) by gavage during gestational days 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 [3]. Fetotoxicity, including reduced body weight and a possible decrease in bone ossification, was observed in the presence of maternal toxicity when female rats were given phenol at 360 mg/kg bw on gestational days 6–15, three times daily by oral gavage [2].

In a two-generation study with exposures of up to 301 or 321 mg/kg bw/day phenol in drinking water for male or female rats, respectively, significant decreases in absolute seminal vesicle and ovary weights were observed at the highest dose, but no significant changes in the appearance of the parental and F_1 generation reproductive organs [1].

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