Resorcinol

(CAS No: 108-46-3)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

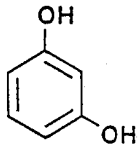
The present document contains the assessment of the health hazard of resorcinol by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by C de Heer, Ph.D. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of resorcinol has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG98). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in December 1998, literature was retrieved from the on-line databases Medline, Toxline, and Chemical Abstracts starting from 1966, 1965, and 1990, respectively, and using the following key words: resorcinol, 3-hydroxyphenol, 1,3-benzenediol, and 108-46-3.

In July 2000, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: P Ashford (Resorcinol Task Force).

An additional search in Toxline and Medline in September 2004 did not result in information changing the committee's conclusions.

2 Identity

name	:	resorcinol
synonyms	:	1,3-benzenediol; *m*-benzenediol; m-dihydroxybenzene; 1,3-dihydroxybenzene; *m*-hydroquinone; *m*-hydroxyphenol; 3-hydroxyphenol; *m*-dioxybenzene; resorcine
molecular formula	:	$C_6H_6O_2$
structural formula	:	
CAS number	:	108-46-3

3 Physical and chemical properties

molecular weight	:	110.11
boiling point	:	276-280°C (volatilises at lower temperature)
melting point	:	109-111°C
flash point	:	127°C (closed cup); 165°C (closed cup)
vapour pressure	:	at 25°C: 0.03 Pa
solubility in water	:	very soluble (at 20°C: 140 g/100mL)
log $P_{octanol/water}$	:	0.80-0.97 (experimental); 0.79-1.03 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 ppm = 4.59 mg/m^3 1 mg/m^3 = 0.22 ppm

Note: Most processes involving resorcinol involve elevated temperatures, at which resorcinol is a vapour. In other cases, it almost immediately becomes a resorcinol-water aerosol, because of its hygroscopic nature.

Data from ACG98, BUA93, NLM04, http://www.syrres.com/esc/est_kowdemo.htm.

The white crystals of resorcinol have a sweetish taste and may turn pink on exposure to air and light or on contact with iron (ACG98).

4 Uses

Resorcinol is used primarily in the manufacture of tyres and other rubber goods. Likewise, it is used in the manufacture of resorcinol-formaldehyde resins used in tyre building as well as in adhesives used for bonding structural wood laminates. To a lesser extent, resorcinol is used as a medical ingredient in various over-the-counter pharmaceutical skin creams, as a bacterial and fungicidal ointment, and in cosmetics (hair tonics and dyes).*

5 Biotransformation and kinetics

In F344 rats, resorcinol is quickly absorbed by the gastrointestinal tract and then rapidly metabolised and excreted. There was no significant sex difference. Twenty-four hours following an oral dose of 112 mg/kg bw containing ^{14}C-labelled resorcinol, 91-93% of the administered dose was excreted in the urine and 1-2% was detected in the faeces. The remaining radioactivity was distributed among various tissues with no indication of bioaccumulation in any single tissue.

* P Ashford, Resorcinol Task Force, personal communication.

Much of the material excreted in bile underwent enterohepatic circulation to be eventually excreted in the urine. The major metabolite present in the urine was the monoglucuronide conjugate (approximately 70%). Additional metabolites included a monosulphate conjugate, a mixed sulphate-glucuronide conjugate, and a diglucuronide conjugate (a minor metabolite). Essentially the same results were obtained after a single dose of 225 mg/kg bw or daily doses of 225 mg/kg bw for 5 consecutive days (Kim87).

Following subcutaneous administration of a single dose of 50 or 100 mg/kg bw ^{14}C-labelled resorcinol to male CD rats, radioactivity was rapidly lost from plasma with approximately 90% being cleared in the first 2 hours. Elimination was biphasic with half-lives of 18-21 minutes and 9-11 hours, respectively. Twenty-four hours after dosing of 10 mg/kg bw, 94% was excreted in the urine and <0.5% in the faeces, primarily (84%) as a glucuronide conjugate. Resorcinol equivalents were rapidly distributed to major tissues, but showed no tendency to accumulate. Daily subcutaneous administration of 100 mg/kg bw for 14 or 30 days did not affect the kinetics of resorcinol (Mer82).

After a 2-week daily topical application of 20 mL 2% resorcinol in a hydroalcoholic vehicle to 3 human volunteers (2 times/day, 6 days/week, 150 µg/cm^2 per application) to 2600 cm^2 of the body surface, 0.5-2.9% of the applied dose was detected in 24-hour urine as glucuronide or sulphate conjugates. No information was provided on the remaining part of the dose. Based on the urinary excretion in humans, the flux was calculated to be 0.37 µg/cm^2/h. In *in vitro* tests using excised full-thickness human skin, a flux of 0.86 µg/cm^2/h was established after application of 390 µg/cm^2 (Yeu83). In another study, skin uptake of resorcinol (1.2-2% in solution) by human skin was found to be 0.02 µg/cm^2/h (Lun92). Because of the limited validation of *in vitro* studies on dermal absorption, the committee considers the flux value of 0.37 µg/cm^2/h established in the human volunteer study the most relevant for the assessment of the health hazard.

Trace amounts of resorcinol equivalents were detected in the liver of female hairless Wistar rats 4 days after a single dermal application of 1.5% resorcinol in hair dye solution, whereas no resorcinol was detected in the thyroid gland. No other organs were examined for the presence of resorcinol (Tso92).

In *in vitro* experiments, the steady state permeability coefficient (K_p) was found to be 0.00024 cm/h for resorcinol in aqueous solutions through human skin (Rob77).

6 Effects and mechanism of action

Human data

A survey of 180 men employed in work involving resorcinol revealed that none complained of irritation or discomfort at exposure levels of 10 ppm (Fli76).

The lowest oral dose reported to be lethal for humans was 29 mg/kg bw (NIO04).

In a study on 42 workers in a tire-manufacturing plant, the presence of dermatitis has been directly correlated with exposure to the processes involving resorcinol use (Abb89). With positive results reported in 0.1 to 2.1% of patch-tested patients, resorcinol sensitisation appeared to be rare despite the widespread use of resorcinol in acne preparations, hair tonics, cosmetics, dyeing, and printing (Bar96, Fis82, Fro93, Gue92, Ket70, Lan87, Mar78, Mas93, Pec92, Ser92, Sus79, Tar95, Vil91, Wad81).

Upper and lower respiratory tract inflammatory disease and conjunctivitis developed in 210 out of 600 repeatedly exposed workers, following introduction of a new resorcinol-containing thermosetting resin into a rubber tire carcass stock formulation. The respiratory tract disease resulted from delayed hypersensitivity reactions. doPico et al. did not identify the aetiological chemical agent (doP75). Rubber workers (n=52) reported no adverse effects following prolonged exposure to concentrations of resorcinol of 0.3 mg/m^3 (Gam76).

In humans, resorcinol affected (observed primarily after clinical use of resorcinol- containing ointments) the central nervous system (with symptoms such as dizziness, trembling, cramps, and shortness of breath) as well as on red blood cells (methaemoglobinaemia, haemolytic anaemia, haemoglobinuria). Effects on the thyroid have also been reported after prolonged exposure. In addition, exogenous ochronosis, chronic myxoedema, and cyanosis have been associated with resorcinol exposure (ACG98, Blo85, Bon95, Kat77, Lun92, Pas78, Tus96, Wüt70). Human pathology reports from poisoning include siderosis of the spleen and kidney tubule damage (All94, Ric92).

Cutaneous application may result in local hyperaemia, dermatitis, oedema, corrosion, and loss of superficial layers of the skin. This may also be associated with enlargement of regional lymph nodes (NLM04).

In a case-control study in ordnance(munition)-factory workers, exposure histories of 32 (out of 33) previously diagnosed as haematologically abnormal (criteria: neutropenia, decreased platelet count, macrocytosis MCV, and increased percentage macrocytosis) were compared with 322 (out of 345)

controls with normal values. An odds ratio of 2.9 (95% confidential interval: 0.9-9.2; not statistically significant) was observed for haematological abnormalities based on 4 cases with 'low' (not further specified) levels of resorcinol exposure out of 29 male workers with 'abnormal' blood values compared with 15 males with resorcinol exposure out of 282 males with normal blood values (Wes97). The number of cases was very small, 25/29 cases were exposed to trinitrotoluene, which is known to induce haematology effects, and the apparently low (but not specified) levels of exposure to resorcinol. Therefore, the committee cannot assess whether resorcinol is capable of inducing haematology effects.

Some occupational groups (e.g., embalmers, rubber workers, and oil refinery workers) appear to have an elevated risk of brain tumours (Tho86). Although exposure to phenolic compounds (including resorcinol) is indicated, the committee cannot adequately evaluate risks due to any single exposure because of the small number of tumours observed and the occurrence of combined exposures.

Topical application of 20 ml 2% resorcinol (2 times/day, 6 days/week; equal to 150 µg/cm^2 per application) for 4 weeks to 2600 cm^2 of the body surface (daily dose 12 mg/kg bw/day) to 3 human volunteers did not result in significant changes in any thyroid function examined (T_3, T_4, T_7, and TSH) or haematological parameters (Yeu83).

Animal data

Irritation and sensitisation

Dermal application of 0.5 g resorcinol moistened with saline to the intact and abraded skin of rabbits for 24 hours resulted in no perceptible to moderate irritation and no perceptible irritation to necrosis, respectively (primary irritation index of 4.4). In an acute dermal toxicity test, high dermal doses (1-7.95 g/kg or 2.5-19.3 g total dose; amount per cm^2 not specified) resorcinol caused irritation and necrosis in a dose-related response (Fli76). In another study, no response was observed during the 72-hour observation period following topical application of a 2.5% (w/v) resorcinol preparation (volume not indicated) (Llo77). Aqueous solutions of 0.1-10% resorcinol were not irritating to guinea pigs in a screening study (Bra86).

Instillation of 0.1 g resorcinol into the eyes of rabbits caused discomfort, conjunctivitis, and corneal ulcerations that were not reversible (BUA93, Fli76). A 2.5% (w/v) resorcinol preparation instilled into the eyes of New Zealand

White rabbits resulted in transient mild conjunctival inflammation, not persisting for more than 24 hours (Llo77).

Throat sprayings with 1% resorcinol in water in rats and guinea pigs (3 times/ day for 2 weeks) resulted in irritation of the throat during spraying. Recovery was seen after cessation of exposure, and no gross evidence of respiratory damage was observed after a 10-week observation period (Fli76).

Resorcinol was sensitising when tested in the guinea pig maximisation test performed according to OECD guideline 406, but not in the open epicutaneous test (BUA93). Resorcinol was not photoallergenic to guinea pigs (Bra86).

Acute and subacute toxicity

In an inhalation toxicity test in female Wistar rats, resorcinol-water aerosol concentrations up to 7800 mg/m^3 for a 1-hour period and up to 2800 mg/m^3 for an 8-hour period caused no deaths or lesions attributable to inhalation of the aerosol at gross autopsy (Fli76). In contrast, 1-hour exposure to 160 mg/m^3 was reported to be lethal to rats (not further information) (NIO04). The dermal LD_{50} for (male) rabbits was 3360 mg/kg (Fli76). Rat oral LD_{50} values ranged from 202 to 980 mg/kg bw (All94, BUA93, Fli76, Llo77, Woo51). Oral LD_{50} values for mice and guinea pigs were found to be 200-500 mg/kg bw and 370 mg/kg bw, respectively (All94, NIO04, Woo51). The primary signs of resorcinol intoxication include initial stimulation of the central nervous system followed by depression, renal glomerular and tubular degeneration, central hepatic necrosis, myocardial depression, pruritis, and reddening of the skin (ACG98, Fli76). The subcutaneous LD_{50}s were 450 and 213 mg/kg bw in rats and mice, respectively (BUA93). Dogs died following intravenous injections of 0.7-1.0 g/kg bw (All94). The intraperitoneal LD_{50} in mice was 215 mg/kg (BUA93).

In subacute inhalation studies, no toxic effects (not further specified) were noted in rats, guinea pigs, and rabbits exposed to resorcinol concentrations of 34 mg/m^3 (8 ppm), 6 hours/day, for 2 weeks, and then maintained for several months with periodic sacrifices (Fli76).

Daily topical application of 1 or 3% resorcinol in vaseline to the ears and flanks of male Pirbright guinea pigs for up to 14 days resulted in concentration-dependent acanthosis, hypergranulosis, hyperkeratosis, and in the ear epidermis also in papillomatosis. Keratinocyte proliferation was induced in treated skin areas (Win77). Toxicity to rats was not observed after dermal application of an ointment containing 12.5% resorcinol, 2 times daily for 3 weeks (not further specified) (Bra86).

In rats, intravenously injected resorcinol (24.5 mg) led to a decrease in thyroidal radioiodine uptake and labelled iodothyronine/iodotyrosine ratio. A 2-week study in rats revealed increased thyroid weights, decreased T_4 plasma levels, and a decreased T_4 half-life after dietary exposure to 5% resorcinol (estimated intake 5 g/kg bw/day assuming a 150 g body weight) (Ber79). After F344/N rats (n=5/sex/group) received 12 daily oral (gavage) doses of resorcinol (vehicle: water) of 0, 27.5, 55, 110, 225, or 450 mg/kg bw, 5 days/week, over 17 days, tachypnoea and hyperexcitability ensued within 30 minutes of dosing and resolved within 2 hours in those animals given 55 mg/kg bw/day and higher (NTP92). Exposure of $B6C3F_1$ mice (n=5/sex/group) to 0, 37.5, 75, 150, 300, or 600 mg/kg bw/day by intubation, 5 days/week, over 17 days, resulted in death of 4/5 males and 5/5 females in the highest dose group and death of 1/5 males in the 300-mg/kg dose group. Clinical signs, including prostration and tremors, started within 30 minutes after dosing of 150 mg/kg bw and lasted 1-2 hours (NTP92). Feeding of 0-260 mg/kg bw/day for 4 weeks did not induce mortality, clinical abnormalities, histological changes, or body weight effects in resorcinol-exposed rats (n=10). Relative adrenal weights were decreased in all exposed animals (Bra86).

Thyroid uptake of labelled iodine was not affected in rats given a single subcutaneous dose of resorcinol (not further specified). Daily subcutaneous administration of 15 mg/kg bw resorcinol for up to 69 days resulted in moderate thyroid hyperplasia (Bra86).

Subcutaneous exposure of CD rats to 55, 88, 140, 220, and 350 mg/kg bw resulted in slight tremors, progressing to moderate to marked tonic clonic convulsions within 10 minutes after dosing of 140 mg/kg bw or more. Complete recovery of these symptoms occurred within 1-1.5 hours. No gross signs of toxicity were observed after exposure to 55 and 88 mg/kg bw (Mer82). In another study, subcutaneous injection of 154 mg/kg bw resorcinol in rats produced myxoedema and goitre. A similar injection of 50 mg/kg bw failed to produce any such disturbance in rat thyroid. In contrast, a temporary reduction of iodine uptake in the thyroid was noted in rats subcutaneously exposed to 5 mg/kg bw resorcinol (ACG98, Lun92).

The dose producing myoclonic convulsions in 50% of urethane-anaesthetised male Sheffield mice following intraperitoneal administration of resorcinol, was 101 mg/kg bw (Ang72).

Subchronic toxicity

When F344/N rats (n=10/sex/group) were given oral (gavage) doses of 0, 32, 65, 130, 260, or 520 mg/kg bw resorcinol, 5 days/week, for 13 weeks, 10/10 females and 8/10 males given the highest dose died. All male dose groups displayed increased absolute and relative adrenal weights, albeit without a clear dose-response relationship. Increased absolute and relative liver weights were seen at doses $\geq$65 mg/kg bw/day in females and at $\geq$130 mg/kg bw/day in males. There was no clear dose-response relationship. No other clinical signs, macroscopic or microscopic lesions, or changes in clinical chemistry parameters were seen in those rats that survived to the end of the study (NTP92). When $B6C3F_1$ mice (n=10/sex/group) were given oral (gavage) doses of 0, 28, 56, 112, 225, or 420 mg/kg bw/day, 5 days/week, for 13 weeks, 7/10 mice of each sex given the highest dose experienced dyspnoea, prostration, tremors, and then died. Absolute and relative adrenal gland weights were reduced significantly in all dose groups, although no dose-response relationship was observed. No other changes were recorded (NTP92). Effects on the thyroid gland were not addressed in the 13-week NTP studies in rats and mice.

Exposure of cross-bred rats (F1 from 1.0 BD IX x 0.1 WELS/Fohm) to 0.004% resorcinol in drinking water for 12 weeks (calculated intake: 0.04 mg/mL x 35 mL/day x 0.275 kg bw = 5 mg/kg bw/day), resulted in significantly increased mean epithelial cell height and significantly decreased mean follicle diameter upon histometrical evaluation of the thyroid gland. Seffner et al. interpreted these findings as a precursor phase of goitre. No other effects were studied. In these experiments, resorcinol was added as a control whilst studying humic acid effects on the thyroid (Sef95). In another study, similar exposure (5 mg/kg bw/day) for 30 days had resulted in significant enlargement of the thyroid gland and decreased T_3 and T_4 levels in Wistar rats (Coo85).

Multiple subcutaneous daily doses of 100 mg/kg bw (2x50) for 14 or 30 days to male Sprague-Dawley rats did not result in overt signs of toxicity or adverse changes in body weight gain, organ weights, thyroid function (serum T_3, T_4), several haematological parameters (number of red blood cells, haemoglobin, haematocrit) and clinical chemistry parameters examined, and histology (Mer82).

Topical application of hair dye solutions containing 2% resorcinol (and 23 other ingredients) and mixed with 6% H_2O_2 to male and female New Zealand rabbits for 13 weeks (1 hour, 2 times/week, 0.5 mL/kg bw) did not result in toxic effects (normal body weight gain, normal urinalysis). The only observation was a slight thickening of treated skin (Bra86, review, original report not available).

Thus, the adrenals, the liver, and the thyroid were identified as the target organs for subchronic exposure to resorcinol. Exposure of rats to resorcinol at 5 mg/kg bw/day through drinking water for 12 weeks resulted in histopathological changes in the thyroid (considered to be a precursor phase of goitre). No NOAEL for these effects was derived.

Chronic toxicity and carcinogenicity

The National Toxicology Program has completed and peer-reviewed a gavage study of resorcinol. The substance, dissolved in water, was administered at oral (gavage) doses of 0, 112, or 225 mg/kg bw/day to rats (F344/N; n=60/sex/group) and mice ($B6C3F_1$; n=60/sex/group), 5 days/week, for 104 weeks. Because of high mortality in the high-dose female rats (16 by week 22), the female rat study was restarted using doses of 0, 50, 100, or 150 mg/kg bw/day. At 15 months, interim evaluations were performed on 10 animals/species/sex/group. In rats, clinical signs, including ataxia, prostration, salivation, and tremors, started shortly after exposure, lasted for 0.5-1 hour, and became more pronounced at the end of each 5-day treatment period. They were seen in the 2 male dose groups and in females given 100 and 150 mg/kg bw. Due to high early mortality in the high-dose males, animals from this group were not evaluated at 15 months. Instead, 10 high-dose males that died or were killed moribund near month 15 were considered part of the 15-month interim evaluation. As in the female animals dying following administration of doses of 225 mg/kg bw, no gross or microscopic lesions were observed in these high-dose male animals. In male rats, body weights were decreased in the high-dose group throughout the study, being 10-15% lower than those in controls from week 87 to study termination. The survival rate in the high-dose group was decreased as well. Survival rate and body weights of low-dose males were similar to those of controls. In female rats, body weights in the high-dose group were lower than those of controls during most of the study, being 11-14% lower from week 95 to study termination. Mean body weights of the mid-dose females were slightly lower (4-7%) than those of controls in the final ca. 20 weeks of the study while those of the low-dose group were similar to those of controls. Survival rates were decreased in high-dose female rats, because of early deaths occurring between weeks 30 and 60, while in the mid- and low-dose female groups, they were similar to those in controls. At the interim evaluation, there were no treatment-related changes in absolute and relative organ weights, in haematology or clinical chemistry values, or in the incidences of neoplastic or non-neoplastic gross and microscopic lesions in any of the treated groups, when compared to controls, apart from a statistically

significantly increased relative liver weight in high-dose females. At the terminal evaluation, no increase in the incidence of any neoplastic or non-neoplastic lesion was found in any of the treated rat groups when compared to controls. In mice, clinical signs of toxicity including recumbency and tremors occurred for a short period after dosing in all treated mice groups. Survival rates in the treated groups were similar to the survival rate of the control mice. Apart from decreased body weights in high-dose female mice (by 10-15% from week 85 to study termination), no effects on body weights were observed. When compared to controls, there were no treatment-related changes in absolute and relative organ weights or in haematology or clinical chemistry values at the interim evaluation and no increases in the incidence of any neoplastic or non-neoplastic gross and microscopic lesion in any of the treated groups at the interim or terminal evaluation (NTP92). Based on this study, the committee concludes that resorcinol was not carcinogenic in rats or mice following long-term exposure to oral doses of 225 mg/kg bw/day. Based on clinical signs observed after administration of doses of 100 mg/kg bw and more, the committee concludes that 50 mg/kg bw is a NOAEL. For mice, the committee could not establish a NOAEL since clinical signs were seen in both males and females at 112 mg/kg bw, the lowest dose tested.

Skin painting of female Swiss mice (n=50/dose) with 0.02 ml of 5%, 25%, or 50% solutions of resorcinol in acetone twice weekly for 100 weeks did not result in statistically significant increased numbers of skin or other tumours when compared to untreated or vehicle-treated controls (Ste74).

A twice-weekly topical application of 0.02 mL 5% to 50% resorcinol to the inner ear of New Zealand White rabbits for 180 weeks failed to induce local or distant tumours or to cause any compound-related toxicity (Ste77).

Long-term toxicity and carcinogenicity studies on hair dyes containing 0.4-2% resorcinol in mice and rats did not reveal overt toxicity or carcinogenic effects following lifetime dermal application (Bra86, Bur75, IRDC79).

Oral (gavage) administration of doses of resorcinol of 225 mg/kg bw/day, 5 days/week, for 24 weeks to heterozygote p53-deficient mice (n=15/sex) did not induce increased tumour incidences (Eas98).

In 18-month studies performed in two laboratories (in the USA and Japan, respectively) under identical test conditions, oral (gavage) administration of doses of 225 mg/kg bw, 5 days/week, to $CB6F_1$ and hemizygote $CB6F_1$-Tg rasH2 mice, which carry 5 to 6 copies of the intact human c-Ha-*ras* gene, induced small, not statistically significant increases in the incidence of lung tumours in both wild-type and transgenic animals in both experiments. Taken the

results together, the incidences of carcinomas were 0/50 and 2/55 in transgenic males and females, respectively (vs. 1/24 and 0/25, respectively, in controls), while none was found in treated and control wild-type animals; incidences of adenomas were 4/50 and 4/55 in transgenic males and females, respectively (vs. 1/24 and 0/25, respectively) and 3/51 and 1/56 in wild-type males and females, respectively (vs. 1/24 and 1/25, respectively). In the US, but not in the Japanese study, signs of hyperactivity and sporadic tremors were seen primarily in resorcinol-treated mice throughout the study. Lower body weights and body weight gains were seen in treated mice in the US study and in treated wild-type males in the Japanese study (Mar00).

Dermal application of resorcinol doses of 225 mg/kg bw/day, 5 days/week, for 24 weeks, to the clipped skin of hemizygote Tg.AC mice (n=15/sex), which carry an activated H-*ras* oncogene, resulted in an increase in the incidence of squamous cell papillomas (males: 10/15 vs. 3/30 in controls, $p \leq 0.05$; females: 12/15 vs. 1/30, $p \leq 0.05$). Further, the incidences of hyperplasia (in males and females) and of hyperkeratosis, inflammation, and sebaceous gland hyperplasia were statistically significantly increased when compared to controls. No systemic treatment-related lesions were observed. Eastin et al. could not discern whether the non-neoplastic skin lesions were secondary to the papillomas or had contributed in some way to their development. However, with another compound, viz., rotenone, non-neoplastic but no neoplastic skin reactions were observed (Eas98).

Neither an increase in forestomach or urinary bladder epithelial cell turnover nor any treatment-related histological change could be detected in male Syrian golden hamsters (n=15) fed 0.25% resorcinol for 20 weeks (estimated intake 375 mg/kg bw/day based on 100 g body weight and 15 mg/day food consumption). The thyroid was not studied (Hir86).

Resorcinol failed to induce proliferative or pre-neoplastic lesions in stomach mucosa of male F344 rats upon dietary exposure to 0.8% resorcinol for 8 weeks. There were no effects of resorcinol treatment on body weight gain, food and water consumption (Shi90).

Female ICR/Ha Swiss mice, simultaneously or sequentially exposed to benzo[*a*]pyrene and resorcinol (10 mg) by topical application on clipped dorsal skin for up to 55 weeks, revealed a partial (>50%) inhibition of benzo[*a*]pyrene carcinogenicity by resorcinol. It was concluded that resorcinol did not show cocarcinogenic or tumour-promoting activity in mouse skin (Duu76).

Groups of male Syrian hamsters received either saline or subcutaneous injections of 70 mg/kg bw *N*-nitrosobis(2-oxopropyl)amine (BOP), twice with a 2 week interval, followed by a standard diet or diet containing 1.5% resorcinol from week 4 for a period of 16 weeks. At week 20, resorcinol-fed BOP-treated animals showed decreased numbers of pancreatic lesions (comprising carcinomas, atypical ductal hyperplasias, and ductal hyperplasias) when compared to those animals treated with BOP and fed a basal diet. There was no effect of resorcinol on the incidence of (pre)neoplastic lesions in the gall bladder or liver (nodules, adenomas, carcinomas). In the forestomach and glandular stomach a higher frequency of epithelial hyperplasias, but not of neoplastic lesions (such as papillomas, adenomas, carcinomas), was observed in resorcinol-treated and initiated animals when compared to initiated controls. Animals only treated with resorcinol for 16 weeks (not treated with BOP) displayed no effects on body weight gain or relative pancreas weights, but had significantly decreased relative liver weights (Mar91).

In a study designed to evaluate the potential of resorcinol to act as a promoter of urinary bladder carcinogenesis, 6-week-old male F344 rats were given drinking water containing 0.05% *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN) for 2 weeks. The rats were then fed diets containing 0.2% resorcinol for 21 additional weeks. No hyperplastic or papillomatous lesions were found in the bladders of BBN-initiated and resorcinol-fed rats (Miy85). In a comparable experimental setting, tumour initiation with 0.05% BBN in drinking water for 4 weeks was followed by dietary exposure to 0.8% resorcinol for 32 weeks. Also in this study, no hyperplastic lesions, papillomas, or carcinomas were detected in the urinary bladder (Kur90).

Tumour-promoting activity in the liver was studied in male F344 rats initiated with diethylnitrosamine (single intraperitoneal injection). Two weeks after initiation, animals were given a diet containing 20,000 ppm resorcinol for 6 weeks (calculated intake 1.2 g/kg bw/day based on body weight of 250 g and food consumption of 60 g/kg/day). At 3 weeks after initiation, a 2/3 partial hepatectomy was carried out. Resorcinol did not induce an increase in glutathione *S*-transferase placental form positive foci in the regenerating liver, indicative of the absence of tumour-promoting activity in the liver (Has92).

In another study, 6-week-old F344 rats were given a single gavage dose of 150 mg/kg of *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG). A week later, the rats were administered diets containing 0.8% resorcinol for an additional 51 weeks. Resorcinol exhibited no tumour-promoting activity in the forestomach and glandular stomach (Hir89). In male F344 rats, the incidence of lung tumours, initiated by a 2-weeks treatment with 0.1% *N*-bis(2-hydroxypropyl)nitrosamine

(in drinking water), was not affected by supplementation of the diet with 0.8% resorcinol for 30 weeks. Quantitative analysis of numbers and areas of lesions per unit area of lung section revealed an inhibitory effect of resorcinol. Resorcinol did not affect the incidence of neoplastic lesions in the thyroid gland, urinary bladder, and kidney (Has90).

In contrast, male F344 rats initiated with 3 intraperitoneal injections of methyl-*N*-amylnitrosamine over a 2-week period, followed a week later by administration of a diet containing 0.8% resorcinol for 49 weeks, showed significantly increased incidences of oesophageal squamous cell carcinomas (59%) and lingual squamous cell papillomas (50%) when compared to controls receiving the nitrosamine alone (incidence: 0 and 9%, respectively) (Yam89).

In summary, resorcinol did neither induce tumours in mice and rats following oral exposure nor in mice and rabbits following dermal exposure. Tumour-promotion activity was concluded in 1 out of 7 studies. In this study, resorcinol exposure significantly increased the incidence of oesophageal squamous cell carcinomas initiated by methyl-*N*-amylnitrosamine. In experiments in which doses of 225 mg/kg bw were administered by gavage or dermally to various types of genetically altered mice for 24 weeks or 18 months, there were only small, not statistically significant increases in the incidence of lung adenomas in male and female $CB6F_1$-Tg rasH2 mice orally dosed for 18 months.

The committee concludes from the NTP-study that the overall NOAEL for chronic toxicity of resorcinol in rats was 50 mg/kg bw/day. At the higher doses (100 and 150 mg/kg bw/day), acute clinical signs indicative of an effect on the central nervous system occurred.

Mutagenicity and genotoxicity

- *In vitro* tests:
  - Gene mutation assays. Resorcinol (tested up to 5 mg/plate) did not induce gene mutations in any of several strains of *S. typhimurium* and *E. coli*, with or without metabolic activation (Bra81, BUA93, Cre81, Cre85, Flo80, Haw83, NTP92, Pro81, Sha80). However, in the presence of S9 mix, a pH-dependent positive response was observed in the SD510 strain of *S. typhimurium* TA98 and in *E. coli* B/r WP2 trp^-hcr^-. Mutagenicity was highest at pH 3.0, decreased with increasing pH, and was no longer observed at pH>5.0 (Hos91). Gocke et al. produced positive results in *S. typhimurium* TA1535 (with S9; without S9 negative) and TA100 (without S9; with S9 negative) but only on a so-called ZLM medium, but not on a

Vogel-Bonner medium. Tests in strains TA1537, TA1538, and TA98 were negative (Goc81).
Tested in the absence of metabolic activation only, resorcinol induced a significant increase in the number of trifluorothymidine-resistant colonies of L5178Y mouse lymphoma cells (McG88, NTP92).
No induction of sex-linked recessive lethal mutations was observed in germ cells of adult male *D. melanogaster* given resorcinol in the feed, whereas equivocal results were obtained following injection (Fou94, NTP92). Feeding of 55 mM in sucrose did not induce sex-linked recessive lethal mutations in the Basc test with *D. melanogaster* (Goc81).

- Cytogenicity assays. Resorcinol (only tested in the absence of metabolic activation) failed to induce SCE in cultured hamster V79 cells (Wil81) or human peripheral blood lymphocytes (BUA93, Dar83, Jan86).
  Contradictory results were obtained with resorcinol in the SCE assay in CHO cells (BUA93, Gal85, Gal87, NTP92). It was also positive, with and without S9, in tests for induction of chromosomal aberrations in Chinese hamster lung fibroblasts (Sak85) and Chinese hamster ovary (CHO) cells (Sti81, Gal85, Gal87, NTP92, Sti91), although negative results in CHO cells were also reported (Dar83). Chromosomal aberrations were not found after treatment of human diploid fibroblasts with resorcinol (Dar83), but resorcinol was reported to induce chromosomal aberrations in cultured human amniotic cells and peripheral blood lymphocytes (Dar83, Sch82).
- Other assays. Resorcinol was negative in an unscheduled DNA synthesis test with primary rat hepatocytes (Pro81).
  Resorcinol did not induce an SOS response in *S. typhimurium* strain TA1535/pSK1002, with or without S9 (Nak87).
  It failed to induce DNA strand breaks in mammalian cells or in isolated DNA (Kaw89, Miu00, Yam85, Wal92).

- *In vivo* tests:
  Despite the positive responses observed with resorcinol *in vitro*, results from all reported *in vivo* tests for genotoxicity were negative. Treatment of mice with resorcinol did not induce micronuclei in bone marrow cells (tested up to 300 mg/kg bw) (Bra86, Dar83, Goc81, Pas86, Wil81), inhibition of DNA synthesis in testicular cells (100 mg/kg, single oral dose) (Sei77), or sperm abnormalities (55-220 mg/kg, intraperitoneal administration) (Wil81). In rat bone marrow, negative results were obtained in tests for induction of micronuclei (Hos77) and SCE (1-100 mg/kg, oral and intraperitoneal

administration, and 0.2-200 mg/kg, dermal application) (Bra81, Bra86).

- Other tests:
  Resorcinol failed to induce *in vitro* transformation of human diploid fibroblasts and Syrian hamster kidney fibroblasts (Pur78).

Despite the positive results in some *in vitro* genotoxicity tests, the committee concludes that resorcinol is not a genotoxic compound.

Reproduction toxicity

Daily oral (gavage) administration of doses of 125, 250, or 500 mg/kg bw to pregnant Sprague-Dawley rats from gestational days 6 to 15 caused a slight reduction in maternal weight gain at 500 mg/kg bw (dose level not adjusted for pup weights). It was not embryotoxic nor did it have any effect on the numbers of litters produced or did it cause any fetal abnormalities or malformations (DiN85). Similarly, resorcinol was not embryotoxic or teratogenic in pregnant rats and rabbits given daily oral (gavage) doses of 0, 40, 80, or 250 (gestational days 6-15) and of 0, 25, 50, or 100 mg/kg bw (gestational days 6-18), respectively (Bra86, Spe86; only abstract available for evaluation).

Pregnant Sprague-Dawley rats, exposed to single oral doses of 0, 100, 333, 667, or 1000 mg/kg bw on gestational day 11, did not show evidence of maternal toxicity within 72 hours after dosing. No developmental toxicity was observed in the offspring (Kav90).

A series of hair dyes containing 1-2% resorcinol were negative in teratology and reproduction toxicity studies in rats and rabbits (Bra86). Dermal application of 0.5 mL hair dye formulation to mice (2 out of 3 formulations tested contained 1.7% resorcinol), twice a week from 4 weeks prior to mating through the mating and gestation periods, did not result in overt signs of maternal toxicity. There was no evidence of teratogenic effects. Evaluation of the ossification data, however, suggested a retarding effect of the formulations on the ossification process. In addition, slightly lower fetal weights were noted in all formulation-treated groups, although mean crown-rump distances were comparable to controls (Hog77). Because all formulations had similar effects, and one of them did not contain resorcinol, the committee considers the effects observed on ossification and fetal body weights not likely due to resorcinol exposure.

Resorcinol was embryotoxic for 3-day-old chicken embryos with an ED_{50} of 2.4 µmol/egg, whereas the LD_{50} for embryo-mortality in this system was 2.7 µmol/egg (Kor83).

In *in vitro* tests, resorcinol inhibited rat embryo limb cell differentiation (ED_{50}: 56 mg/mL) at concentrations not affecting cell survival. It did not affect rat embryo midbrain cell differentiation *in vitro* (Fli88).

Thus, resorcinol did not induce developmental toxicity, but induced maternal toxicity (slight decrease in body weight gain) in rats at 500 mg/kg bw/day.

Other studies

In isolated rabbit tracheas, ciliary movements on tracheal epithelial cells decreased after 42-45 minutes of exposure to 625 mg/m^3 resorcinol (BUA93).

Resorcinol was found to stimulate glycogen synthesis and inhibit glycolysis in isolated rat hepatocytes (Agi97, Sch95).

In vitro, resorcinol inhibited porcine thyroid peroxidase (50% inhibition at 0.3 nmol/L (33 ng/mL)). In porcine thyroid slices, resorcinol inhibited both thyroidal uptake of ^{125}I and its incorporation into tyrosine to form iodotyrosines, which are the precursors of active thyroid hormones (Coo85).

In a study on the role of GSH depletion in hydroquine-induced development of γ-glutamyltranspeptidase (GGT)-positive enzyme-altered foci in rat liver hydroquinone and other benzene derivatives, among which resorcinol, were studied. GGT-positive cells in enzyme-altered foci are often assumed to represent initiated or pre-malignant cells in the liver. Resorcinol was found not to deplete GSH and clear effects of resorcinol on the development of enzyme-altered foci were not observed (Ste89).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for resorcinol in the Netherlands is 45 mg/m^3 (10 ppm), 8-hour TWA.

Existing occupational exposure limits for resorcinol in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Resorcinol is readily absorbed from the gastrointestinal tract and, in a suitable solvent, is readily absorbed through the (human) skin (estimated flux 0.37 μg/cm^2/h). The compound is metabolised extensively to glucuronide and/or sulphate conjugates, and excreted primarily in the urine. It has little potential for bioaccumulation. Sex differences were not observed.

A survey of 180 workers revealed that none complained of irritation or discomfort at exposure levels of 10 ppm (45 mg/m^3) resorcinol. Prolonged exposure of 52 rubber workers to $\leq$0.3 mg/m^3 resorcinol in air caused no adverse effects. There are virtually no data from which to determine a dose-response relationship for occupational exposure to resorcinol.

Based on acute lethal toxicity data in experimental animals, the committee conciders resorcinol to be of low toxicity following inhalation and dermal exposure and as harmful following oral exposure. Resorcinol is irritating to eyes and skin and may cause sensitisation by skin contact.

In subacute inhalation studies, no toxic effects were noted in rats, guinea pigs, and rabbits exposed to resorcinol at 34 mg/m^3 (8 ppm), 6 hours/day, for 2 weeks, and then maintained for several months with periodic sacrifices.

Rats orally exposed to resorcinol dissolved in water at 0-450 mg/kg bw, over 17 days, displayed tachypnoea and hyperexcitability at dose levels of $\geq$55 mg/kg bw/day. No effects were observed after exposure to 27.5 mg/kg bw/day. In mice, a similar oral exposure to 0-600 mg/kg bw/day resorcinol resulted in clinical signs including prostration and tremors in animals dosed $\geq$150 mg/kg. No toxic effects were noted in mice exposed to 37.5 and 75 mg/kg bw/day.

Subchronic oral (gavage) exposure of rats to 0-520 mg/kg resorcinol, 13 weeks, resulted in increased absolute and relative liver and adrenal weights in rats given resorcinol at $\geq$65 mg/kg bw/day. No other clinical or histological signs or changes in clinical chemistry parameters were seen in those rats that survived to the end of the study. The no-observed adverse effect level (NOAEL) was found to be 32 mg/kg bw/day. In a similar experimental setting, mice were given 0-420 mg/kg bw/day resorcinol or an equivalent amount of deionised water by gavage. Adrenal gland weights were reduced significantly in mice given $\geq$28 mg/kg bw/day, but no other changes were recorded in animals exposed to dose levels of up to 225 mg/kg bw/day.

Exposure of rats to 0.004% resorcinol in drinking water for 12 weeks (calculated intake 5 mg/kg bw/day) resulted in significantly increased mean epithelial cell height and significantly decreased mean follicle diameter upon histometrical evaluation of the thyroid gland. These findings were considered as a precursor phase of goitre. No other effects were studied. In another study, similar exposure (5 mg/kg bw/day) for 30 days had resulted in significant enlargement of the thyroid gland and decreased T_3 and T_4 levels in Wistar rats.

Based on the available genotoxicity data, the committee concludes that resorcinol is not genotoxic.

In 1992, the National Toxicology Program has completed and peer-reviewed a long-term gavage study of resorcinol. The substance was administered in water

by gavage to rats and mice. Clinical signs at doses ≥100 mg/kg bw starting shortly after exposure and lasting 0.5-1 hour, included ataxia, prostration, salivation, and tremors. The NOAEL for these effects was 50 mg/kg bw. At an interim kill after 15 months of exposure, no treatment-related differences in haemotology or clinical chemistry parameters, neoplastic or non-neoplastic lesions were observed. At the end of the study, body weights were lower in most of the highest dose groups. There was neither evidence of carcinogenicity in male or female rats and mice in this study nor in other studies in mice and rabbits following dermal exposure. Tumour-promotion activity was concluded in 1 out of 7 studies; in this study, resorcinol exposure significantly increased the incidence of oesophageal squamous cell carcinomas initiated by methyl-*N*-amylnitrosamine. In experiments in which doses of 225 mg/kg bw were administered by gavage or dermally to various types of genetically altered mice for 24 weeks or 18 months, there were only small, not statistically significant increases in the incidence of lung adenomas in male and female $CB6F_1$-Tg rasH2 mice orally dosed for 18 months.

Based on studies with pregnant rats and rabbits, the committee concludes that resorcinol is not embryotoxic and teratogenic.

The lowest dose level of resorcinol inducing adverse effects was 5 mg/kg bw/day and was observed in the 30-day and 12-week oral (drinking water) studies in rats. At this dose level, changes were noted in thyroid organ weights, and in serum T_3 and T_4 levels (30-day study), whereas histological effects were noted in the thyroid upon histometrical analysis (12-week study). Although thyroid histopathology was evaluated in the latter studies, no effects on the thyroid were found at higher dose levels in subacute, subchronic, and chronic oral studies performed in rats by the NTP (NOAEL 27.5, 32, and 50 mg/kg bw/day, respectively).

The committee considers the NTP studies as well performed and attaches more importance to these studies then to the studies of Seffner et al. (Sef95) and Cooksey et al. (Coo85). The committee questions the relevance of the thyroid effects found by these authors. The chronic NOAEL of 50 mg/kg bw/day observed in the long-term NTP rat study is taken as the starting point for deriving a health-based occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, a factor of 4 for allometric scaling from rats to humans, based on caloric demand, and an overall assessment factor of 9, covering intra- and interspecies variation, are applied, resulting in a no-effect level for humans of 1.4 mg/kg bw. Assuming a 70-kg worker inhales 10 m^3 during an 8-hour working day and a retention of 100%, and applying the preferred-value approach, a health-based occupational exposure limit of 10 mg/m^3 is recommended for

resorcinol. The committee considers this HBROEL of 10 mg/m^3 sufficiently low to protect against irritation by resorcinol. A 'skin notation' is not warranted.

The committee recommends a health-based occupational exposure limit for resorcinol of 10 mg/m^3 (2 ppm), as an 8-hour time-weighted average (TWA).

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Annex

Occupational exposure limits for resorcinol in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	10	45	8 h	administrative		SZW04
Germany						
- AGS	10	45	8 h			TRG04
- DFG MAK-Kommission	-[c]	-[c]			sens	DFG04
Great-Britain						
- HSE	10	46	8 h	OES		HSE02
	20	92	15 min			
Sweden	10	45	8 h		S	Swe00
Denmark	10	45	8 h			Arb02
USA						
- ACGIH	10	-	8 h	TLV	A4[d]	ACG04b
	20	-	15 min	STEL		
- OSHA	-	-				ACG04a
- NIOSH	10	45	10 h	REL		ACG04a
	20	90	15 min			
European Union						
- SCOEL	10	45	ILV[e]			EC04

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Listed among compounds for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values.

[d] Classified in carcinogenicity category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of a lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.

[e] Listed among compounds for which OELs are already included in Commission Directives.