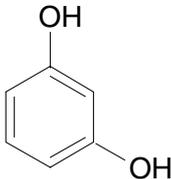


# Resorcinol

<b>MAK value</b>	not yet established, see Section IIb of the <i>List of MAK and BAT Values</i>
<b>Peak limitation</b>	–
<b>Absorption through the skin</b>	–
<b>Sensitization (2002)</b>	<b>Sh</b>
<b>Carcinogenicity</b>	–
<b>Prenatal toxicity</b>	–
<b>Germ cell mutagenicity</b>	–
<b>BAT value</b>	–
<b>Synonyms</b>	<i>m</i> -dihydroxybenzene resorcin
<b>Chemical name (CAS)</b>	1,3-benzenediol
<b>CAS number</b>	108-46-3
<b>Structural formula</b>	
<b>Molecular formula</b>	C <sub>6</sub> H <sub>6</sub> O <sub>2</sub>
<b>Molecular weight</b>	110.11
<b>Melting point</b>	109–111°C
<b>Boiling point</b>	276–280°C
<b>log P<sub>ow</sub>*</b>	0.77–0.93

Resorcinol is used in tanning and photography, in the production of resorcinol-formaldehyde resins for tyre production and colourants, cosmetics (hair tonics and dyes), pharmaceutical skin creams available without a prescription, plastic films and glues. It is also used as a rubber glue and cross-linker for neoprene (ACGIH 1996). Resorcinol used to be used widely in medications for acne and in antibacterial and keratolytic formulations.

---

\* *n*-octanol/water distribution coefficient

The use of Castellani's paint (10% aqueous resorcinol) is obsolete as is that of suppositories containing resorcinol. The topical use of resorcinol, especially for large areas of skin, was criticized in 1994 by the "Aufbereitungskommission B7 of the Bundesgesundheitsamt" (Federal Health Office Commission B7 for pharmaceutical formulations) because of its questionable effectiveness and the possibility of unwanted side-effects (Gloor *et al.* 2000). The *Rote Liste* 2001 listed two formulations containing 2% resorcinol for the treatment of acne (*Rote Liste Service GmbH* 2001). Resorcinol is used in oxidative hair dye formulations as a coupling agent. Information as to whether resorcinol is still used in hair lotions and shampoos is not available. The use of resorcinol in other cosmetics is not mentioned in the German cosmetics regulations. In a review of the use of resorcinol in cosmetics available on the American market in the year 1981, the substance was listed as a component of 482/6344 products, of which 471/826 were hair colouring products ( $20 \times 1-5\%$ , otherwise up to 1%), 4/680 skin cleansers (up to 1%), 1/909 shampoos (0.1-1%), 1/831 make-up products ( $> 1-5\%$ ), 1/148 soaps (0.1-1%), 1/2601 skin fresheners (1-5%) and 3/349 other products ( $2 \times 0.1-1\%$ ,  $1 \times > 1-5\%$ ) (CIR 1986).

## 1 Toxic Effects and Mode of Action

Resorcinol is absorbed rapidly from the gastrointestinal tract of the rat and then rapidly metabolized and excreted (95% within 24 hours). The main urinary metabolite is the monoglucuronide conjugate (70%). The lowest lethal resorcinol concentration ( $LC_{Lo}$ ) for the rat is  $160 \text{ mg/m}^3$ . The oral  $LD_{50}$  values found for rats are in the range between 202 and 980 mg/kg body weight; the dermal  $LD_{50}$  for the rabbit is about 3500 mg/kg body weight. Intravenous injection of resorcinol into the rat causes a reduction in radioiodine uptake by the thyroid and a reduction in the ratio of labelled iodothyronine to iodotyrosine. Administration of resorcinol to rats in the drinking water in doses of 5 mg/kg body weight and day for 12 weeks caused histopathological alterations in the thyroid gland. In contrast, in a 2-year study in which female rats were given resorcinol by gavage and also excess iodine in the diet, the no observed adverse effect level (NOAEL) was 50 mg/kg body weight and day. Resorcinol doses of 100 and 150 mg/kg body weight and day have adverse effects on the CNS. The target organs of repeated oral or subcutaneous resorcinol doses are the CNS, adrenal glands, kidneys, liver and thyroid.

In animal studies, single applications of resorcinol to the intact skin caused irritation; in the eye the substance was highly irritating. Positive results have been obtained with resorcinol in the maximization test with guinea pigs but not after non-occlusive application in the epicutaneous test. The substance also causes sensitization in persons exposed to higher concentrations. Effects in man include CNS effects, mainly in persons who have used creams containing high levels of resorcinol, effects on the erythrocytes (especially methaemoglobinaemia, mainly in babies and infants) and, after prolonged exposure, effects on the thyroid gland (especially chronic myxoedema). In addition, exogenous ochronosis is associated with prolonged exposure to resorcinol. In persons suffering

from resorcinol poisoning the symptoms included anaemia, spleen siderosis and fatty degeneration of the liver and kidneys. Resorcinol did not cause developmental toxicity in rabbits given doses of 100 mg/kg body weight and day, or in rats even at maternally toxic doses of 500 mg/kg body weight and day. Resorcinol has been shown in some *in vitro* tests to cause sister chromatid exchange (SCE) and to be clastogenic. All *in vivo* genotoxicity tests have yielded negative results. In a 2-year gavage study, resorcinol did not cause tumour development in mice or rats. In transgenic Tg.AC mice, epicutaneous application of resorcinol resulted in papilloma formation. Applied to the skin of albino mice after an initiation treatment, resorcinol was shown to be a tumour promoter. In 1 of 9 other studies of its tumour-promoting potential, resorcinol was shown to have promoting activity; administered in the diet it caused a significant increase in the incidence of squamous cell carcinomas in the oesophagus and of papillomas on the tongue.

## 2 Mechanism of Action

*In vitro* and *in vivo* studies have shown that resorcinol can inhibit peroxidases in the thyroid and thus block the synthesis of thyroid hormones and cause goitre (Lynch *et al.* 2001). Resorcinol disrupts the iodination of tyrosine and the oxidation of iodide. In an *in vitro* study with lactoperoxidase (LPO) and thyroid peroxidase (TPO) it was demonstrated that the mechanism of action of these two enzymes was clearly different from that of the classical model peroxidase enzyme, horseradish peroxidase. Unlike horseradish peroxidase and other peroxidases which can hardly be inhibited by resorcinol, LPO and TPO are inhibited irreversibly via a suicide inactivation by this substance. The mechanism assumed to be involved is described below. First the  $\text{Fe}^{3+}$  of the porphyrin residue of the peroxidase is oxidized to  $\text{Fe}^{4+}$  by hydrogen peroxide with the transfer of an oxygen radical. In LPO and TPO, the resulting  $\pi$ -cation radical of the porphyrin can isomerize to a radical cation with the radical in an aromatic side chain of the enzyme. The latter radical can bind, in a pH-dependent reaction, covalently and irreversibly to the resorcinol radical formed during regular oxidation of resorcinol and this reduces the activity of the enzyme markedly. Whereas the inactivation of the enzyme and the binding of resorcinol to the enzyme could be clearly increased by the presence of 0.1 mM iodide, increasing the iodide concentration to 5 mM reduced the resorcinol binding to the enzyme by one quarter but increased the enzyme activity, determined as the rate of iodination of tyrosine, more than proportionally from 6.2 % to 44.7 %. The role played by the iodide ion in the irreversible inactivation of the enzymes is not yet understood (Divi and Doerge 1994).

Enlargement of the thyroid gland was not seen in a 2-year study with F344/N rats given resorcinol doses up to 520 mg/kg body weight and day (NTP 1992). The rats in the NTP study were, however, given iodine in average concentrations of 3.37 mg/kg diet, much more than the average iodine level required by the rat, 0.15 mg/kg diet (Melby and Altmann 1976). In rats given excess iodine, the skin and fur serve as iodine storage organs and can accumulate much more iodine than the thyroid (Kirchgessner *et al.*

1999). Species-specific differences in the synthesis, binding and transport of thyroid hormones make it difficult to extrapolate the data obtained in the rat to man. Human case studies in which effects on the thyroid have been demonstrated involve either persons who had used large quantities of creams containing resorcinol for months or years (resorcinol doses of 34 mg/kg body weight and day or more; Lynch *et al.* 2001, Resorcinol Task Force 2000) or persons with defective renal function. Because of its OH groups, resorcinol is an antioxidant. However, the *meta*-position of the second hydroxy group makes the redox activity of resorcinol lower than that of *ortho*-hydroquinone or *para*-hydroquinone and suggests that the carcinogenic potential of resorcinol must be lower than that of hydroquinone. It has, however, been demonstrated that after sufficiently powerful initiation (Boutwell and Bosch 1959) and in transgenic mice (Eastin *et al.* 1998) with the appropriate disposition, resorcinol can promote tumorigenesis in the skin and the non-keratinized squamous epithelium (Yamaguchi *et al.* 1989).

### 3 Toxicokinetics and Metabolism

Rabbits given oral resorcinol doses of about 100 mg/kg body weight excreted 13.5 % of the administered substance as the monosulfate, 52 % as the glucuronide conjugate and 11.4 % as free resorcinol in the 24-hour urine. Trihydroxybenzenes could not be detected (CIR 1986). Administered to male and female F344 rats, resorcinol was rapidly absorbed from the gastrointestinal tract, metabolized and excreted. Within 24 hours of oral administration of <sup>14</sup>C-labelled resorcinol in a dose of 112 mg/kg body weight, 91 % to 93 % of the dose had been excreted in the urine and 1 % to 2 % in the faeces. The residual radioactivity was evenly distributed in the tissues. 50 % of the resorcinol excreted in the bile was subject to enterohepatic circulation. The main urinary metabolite was the monoglucuronide conjugate (almost 70 % of total urinary radioactivity). The other metabolites detected were a monosulfate, a mixed sulfate-glucuronide and a diglucuronide conjugate. In addition, less than 5 % of the dose was excreted in the urine as free resorcinol. The results obtained after a single resorcinol dose of 225 mg/kg body weight and after daily doses of 225 mg/kg body weight on five consecutive days were essentially the same as those described above (Kim and Matthews 1987). Male Sprague-Dawley rats were given single subcutaneous doses (50 or 100 mg/kg body weight) of <sup>14</sup>C-labelled resorcinol in aqueous solution; the plasma radioactivity decreased rapidly with practically 90 % clearance in the first two hours after the injection. The elimination followed a biphasic course with half-times of 18 to 21 minutes and 9 to 11 hours. Within 24 hours of administration of a resorcinol dose of 10 mg/kg body weight in aqueous solution, 94 % of the dose was excreted with the urine and less than 0.5 % with the faeces, mainly in the form of the glucuronide (84 %). The radioactivity was rapidly distributed, especially in the muscles, kidneys and liver, but was shown not to accumulate by repeated administration during a period of 30 days. The toxicokinetics were not different when a resorcinol dose of 50 mg/kg body weight was injected subcutaneously twice daily for 30 days (Merker *et al.* 1982).

After epicutaneous application of 20 ml of a 2 % aqueous-alcoholic solution of resorcinol to 2600 cm<sup>2</sup> skin area on three test persons (daily dose of resorcinol 12 mg/kg body weight, application twice daily, 6 days/week for 4 weeks, 150 µg/cm<sup>2</sup>), 0.5 % to 2.9 % of the applied dose was detected in the 24-hour urine as glucuronides or sulfates. The flux was calculated to be 0.37 µg/cm<sup>2</sup> and hour (Yeung *et al.* 1983). The urine of a patient with ulcerated legs which had been treated for years with a cream containing 12.5 % resorcinol (1.5 pound cream every 10 days, about 68 g/day), was found to contain 2.1 % of a mixture of resorcinol glucuronides and resorcinol monosulfate (no other data; Thomas and Gisburn 1961). *In vitro* tests with human “full thickness” skin revealed a flux of 0.86 µg/cm<sup>2</sup> and hour after application of 390 µg resorcinol per cm<sup>2</sup> skin (Yeung *et al.* 1983) and of 0.02 µg/cm<sup>2</sup> and hour after application of a 1.2 % to 2 % resorcinol solution (Lundberg 1992).

*In vitro* studies with human skin and resorcinol in aqueous solution yielded an equilibrium permeability coefficient of 0.00024 cm/h (Roberts *et al.* 1977).

## 4 Effects in Man

Resorcinol has been used for medicinal purposes since the 19th century. At first it was given orally to treat digestive disorders in children until, by the beginning of the 20th century, numerous reports of poisonings had appeared. However, because of its antiseptic activity, the substance continued to be used with considerable success for the local treatment of various skin disorders (Graham and Tisdall 1922) and is still used today in the treatment of acne (Rote Liste Service GmbH 2001). But the treatment resulted in resorcinol poisoning, especially of babies and occasionally also of young persons and adults, and was sometimes fatal. Nonetheless, in assessing these reports it must be remembered that resorcinol was used widely as an antiseptic until the 1950s and that poisoning was the exception. For the two acne lotions containing 2 % resorcinol which are currently available in Germany, the use on babies and infants, on acutely inflamed skin and on persons with renal insufficiency is contraindicated. Likewise, users are warned not to use the lotion on large areas of skin without medical supervision (Rote Liste Service GmbH 2001).

There are no data available from studies of reproductive and developmental toxicity, genotoxicity or carcinogenicity of resorcinol in man.

### 4.1 Single exposures

Cases of resorcinol poisoning from the first half of the 20th century have been reviewed by Cunningham (1956) and by Graham and Tisdall (1922). The “probably lethal” oral dose for an adult has been given as 2000 mg (no other data; Deichmann and Gerarde 1969) but a 2.5-month-old female baby survived, with symptoms of haemoglobinaemia,

an accidental overdose of an oral diarrhoea medicine containing 1500 mg resorcinol (Cunningham 1956).

A 29-year-old man with psoriasis was treated once on the diseased skin with 100 g of a cream containing 50 % resorcinol; shortly after the treatment he complained of a burning sensation on the treated skin, began to perspire heavily and, 45 minutes after the treatment, shortly after the cream had been removed, he lost consciousness for more than an hour. Dilated pupils, a weak and very rapid pulse and spastic convulsions were recorded. 3.5 hours after the treatment, the man excreted greenish urine in which phenols were detected. The patient recovered within 3 to 4 days (Graham and Tisdall 1922). The poisoning of a 19-year old man treated for the first time on eczematous skin with 220 g of an ointment containing 9 % resorcinol produced similar symptoms (no burning sensation on the skin but dizziness shortly after the treatment and then prolonged unconsciousness, contracted pupils). In this case too, the cream was removed shortly after its application and the patient recovered within a few days (Graham and Tisdall 1922).

One and a half hours after treatment of the almost intact skin of the calf with a paste containing 25 % resorcinol, a 16-year-old youth was found unconscious and cyanotic; shortly afterwards sweating and slight twitchings of the whole body were seen. Dilation of the pupils was followed by contraction. 10 hours after the ointment had been applied, the youth died without having regained consciousness (Graham and Tisdall 1922).

A 41-day-old male baby was treated for eczema and soreness on his bottom, legs and right hand by application of a zinc paste containing 2 % resorcinol. The baby developed cyanosis and methaemoglobinaemia one day after the first use of the ointment and died after 5 days although the residual ointment had been removed on appearance of the symptoms. The publication does not make it clear whether the ointment was re-applied; ingestion of the ointment after licking of the hand is conceivable. Autopsy revealed very severe generalized anaemia, jaundice, severe fatty degeneration and anaemia of the liver and kidneys with marked softening of the tissues, slight fatty degeneration of the heart muscle, slight enlargement and brown discoloration of the spleen, peripheral emphysema in the lung and severe pulmonary oedema in the other lung regions (Becker 1933).

Because the studies cited above are old, it can no longer be established with any certainty whether the effects were actually caused by resorcinol or whether they could have been caused by other components possibly contained in the medications.

## 4.2 Repeated exposures

### 4.2.1 Inhalation

Of 180 persons who worked with resorcinol, none complained of irritation or feeling unwell after exposure to a concentration of 10 ml/m<sup>3</sup> (Flickinger 1976). There are, however, no detailed exposure data. No adverse effects were seen in 52 workers in the rubber tyre industry who were exposed to resorcinol concentrations up to 0.3 mg/m<sup>3</sup> (Gamble *et al.* 1976).

Time-weighted average (8-hour) determinations of resorcinol concentrations, obtained after both static and personal sampling, are available from a firm producing resorcinol by sulfonation of benzene and also products such as *beta*-resorcylic acid and resorcinol-formaldehyde resins. For 20 samples, values between 0.6 and 66 mg/m<sup>3</sup> were obtained. The distribution of exposure concentrations was as follows: grinders, personal sampling: 2 to 45 mg/m<sup>3</sup>, static sampling: 2 to 66 mg/m<sup>3</sup>; resorcinol flaker operators, personal sampling: 0.6 to 2 mg/m<sup>3</sup>, static sampling 1 to 53 mg/m<sup>3</sup>; pharmaceutical-grade resorcinol operators, personal sampling: 0.7 to 2 mg/m<sup>3</sup> (in each case 4 samples). Three occupational medical cross-sectional studies carried out in this firm in the years 1978, 1980 and 1984 in which 281 of 329, 247 of 387 and 192 of 312 workers were examined yielded no evidence of adverse effects on thyroid function, although the authors of the second study suspected that resorcinol was the cause in 2 of 5 cases of hypothyroidism (total thyroxine (T<sub>4</sub>) and thyreotropin (TSH) levels were determined in 153 of the 247 workers). The values were, however, not above the mean value for the general population. The meaningfulness of these studies is limited because only some of the workforce took part, the number of persons studied was too small, there were no control groups or concurrent or historical individual control data, and no subdivision of the individuals into exposure categories (Resorcinol Task Force 2000). Nor is the simple determination of the TSH level very useful; a thyreotropin releasing hormone stimulation test would have been more informative.

In a textile factory in which resorcinol and thiourea were used and which employed 539 persons, thyroid gland function tests were carried out in the workforce because of the appearance of 4 clinical cases of hypothyroidism in 6 years. About 44 % of the workforce took part in the study, that is, 189 men and 48 women, but only some of these (115) were actually involved in the production process. The concentration determination in the production rooms revealed resorcinol concentrations below 20 µg/m<sup>3</sup> and thiourea concentrations of 5 µg/m<sup>3</sup>. The thyroid function test included TSH determination and assay of auto-antibodies against thyroglobin and thyroid microsomes; the participants also filled in a questionnaire. The study revealed 15 new cases of thyroid disease. These included one case of thyroid hyperactivity and 14 of hypothyroidism. Closer analysis revealed that of these 14 persons, 8 had normal TSH values, no symptoms, but increased levels of circulating anti-thyroid antibodies. One person suffered from an inherited pituitary-mediated hypoactive thyroid whereas another person had previously undergone partial thyroidectomy. In 4 persons (2 men, 2 women) the TSH levels were slightly increased; in 3 of these persons slight symptoms of hypothyroidism were seen. Because the publication included no information as to the age distribution of the persons nor data for individual resorcinol exposure levels, the results cannot be interpreted and do not provide evidence of an association between exposure to resorcinol and the development of hypothyroidism (Resorcinol Task Force 2000, Roberts *et al.* 1990). Another study, a case-control study of munitions factory workers which attempted to identify the potential causes of anomalous haematological parameters by retrospective questionnaires, also permits no reliable conclusions. In this study, exposure to low levels of resorcinol was recorded for 4 of 29 male workers with blood count changes (in comparison with 15 healthy male persons who worked with resorcinol among 282 control persons). An odds ratio of 2.9 (95 % confidence interval of 0.9–9.2) was calculated from these data. This

study may be criticized for the fact that the number of cases is very small, the persons were exposed to other substances as well as resorcinol (only 4 of the 29 affected persons had no contact with trinitrotoluene which has long been known to have effects on the blood count) and the resorcinol exposure levels were not considered to be high for any of the workers (West and Stafford 1997).

#### **4.2.2 Ingestion**

An increased incidence of goitre in a region of western Columbia was ascribed to the presence in the drinking water of humic substances including resorcinol (Gaitan 1983, 1990). However, these studies do not demonstrate an association between exposure to resorcinol and goitre.

#### **4.2.3 Dermal exposure**

##### **Laboratory studies**

The dermal application of resorcinol in doses of 12 mg/kg body weight and day, twice daily, 6 days/week for 4 weeks (as 2 % resorcinol in aqueous-alcoholic solution, no other details) had no effects on the thyroid function of three young healthy adults (Yeung *et al.* 1983).

##### **Case reports**

Effects of resorcinol on the human central nervous system have been seen mostly in persons who had used ointments containing high levels of resorcinol and took the form of dizziness, trembling (Bontemps *et al.* 1995, Wüthrich *et al.* 1970), convulsions, unconsciousness (Graham and Tisdall 1922, Wüthrich *et al.* 1970), memory problems (Bontemps *et al.* 1995, Bull and Fraser 1950) or psychotic character changes (Katin *et al.* 1977). Twenty minutes after the treatment of acne on a large area of skin on her back with an ointment containing 50 % resorcinol, a female patient reacted with confusion, postcritical amnesia, disorientation and tremor. The symptoms persisted for 30 minutes and could be induced again by another application of the cream (Bontemps *et al.* 1995).

Goitrogenic action of resorcinol has been described in persons who had been exposed to the substance for years (Berthezene *et al.* 1973, Bull and Fraser 1950, Katin *et al.* 1977, Thomas and Gisburn 1961). In persons whose ulcerated legs were treated for long periods with pastes containing 4 % to 12.5 % resorcinol, the development of chronic myxoedema has been documented (Berthezene *et al.* 1973, Bull and Fraser 1950, Thomas and Gisburn 1961). All the patients who developed hypothyroidism during treatment with resorcinol had applied the substance in large quantities (estimated resorcinol doses between 34 and 122 mg/kg body weight and day) for long periods (months to years) onto open wounds in the skin. It may be assumed that when resorcinol is applied in this way, more is absorbed than through intact skin (Resorcinol Task Force 2000).

An exceptional case is that of a 70-year-old diabetic requiring dialysis who suffered from hypothyroidism, organic psychosis, weakness, lethargy and hoarseness. To treat the pruritis which is common among dialysis patients, each day in the previous three months the man had used three 2.5 g tubes of a preparation containing 2.5 % resorcinol and 3 % benzocaine. Assuming a body weight of 75 kg, this is equivalent to a resorcinol dose of 2 mg/kg body weight and day. In the man's blood, increased TSH and reduced T<sub>4</sub> values were found. After stopping the resorcinol applications and treatment with T<sub>4</sub>, the hoarseness and weakness regressed as did the psychotic symptoms. After three months, the treatment with T<sub>4</sub> was discontinued and the man kept under clinical observation; at the examinations after 2 weeks and 2 months the thyroid hormone values were in the normal range. In contrast to all other described cases of hypothyroidism resulting from resorcinol treatment, in this case the substance was applied to intact skin; it may, however, be assumed that the elimination of resorcinol from the body was reduced by the renal insufficiency (Katin *et al.* 1977).

Exogenous ochronosis, the deposition in tissues of polymerization products of homogentisic acid (described e.g. after long-term exposure to phenolics (Pschyrembel 1994)), has also been reported to result from resorcinol exposure (1.5 pounds cream every 10 days, about 8.5 g resorcinol/day) (Thomas and Gisburn 1961).

Red blood cell changes such as methaemoglobinaemia, haemolytic anaemia and haemoglobinuria and cyanosis resulting from the methaemoglobinaemia have often been diagnosed, especially in babies, infants and young people treated dermally or gingivally with formulations containing 2 % to 40 % resorcinol (Blondet *et al.* 1985, Cunningham 1956, Graham and Tisdall 1922, Tush and Kuhn 1996, Wüthrich *et al.* 1970). In some of these cases (Blondet *et al.* 1985, Tush and Kuhn 1996), however, the formulations used also contained benzocaine, an aromatic amine which can contribute to methaemoglobinaemia development. Numerous cases of resorcinol poisoning in babies with death from methaemoglobinaemia after single or repeated application of creams containing resorcinol (2–25 %) have been described (Becker 1933, Cunningham 1956, Graham and Tisdall 1922, Haenelt 1925).

### 4.3 Local effects on skin and mucous membranes

The occurrence of dermatitis among 42 persons who worked in a tyre factory was directly correlated with work in processes using resorcinol (Abbate *et al.* 1989).

In a firm producing and processing resorcinol, 13 of the 247 workers who were examined had skin rashes which were put down to the handling of resorcinol (no other details; Resorcinol Task Force 2000). In a later cross-sectional study, no cases of contact dermatitis was found among 192 workers (Resorcinol Task Force 2000).

Topical application of formulations containing 3 % to 25 % resorcinol can cause local hyperaemia, itching, dermatitis, oedema or destruction and loss of the upper layers of skin, in severe cases even enlargement of local lymph nodes (Deichmann and Keplinger 1981).

#### 4.4 Allergenic effects

In a firm producing and processing resorcinol, one of the 281 workers who were examined was said to avoid handling resorcinol because of “allergic symptoms” (no other details; Resorcinol Task Force 2000).

In patch tests with large collectives of persons, positive results were generally obtained with less than 2% of the patients, but in occasional studies in about 2% (Rudzki and Kleniewska 1970, Schubert *et al.* 1982; see Table 1). In earlier studies the percentage of positive results was much higher, almost 8%, but these studies cannot be used for an assessment of the sensitizing activity of resorcinol because the methods used are no longer accepted and the concentration of test substance used, 5% to 10%, is too high. In case reports, sensitization has been described to result from the therapeutic use of Castellani's paint (Cronin 1973, Dave 1973, Erdmann *et al.* 1997, Fisher 1982, Köhn 1993), its use to mark the irradiated area in radiotherapy (Marks and West 1978, Pecegueiro 1992) or the area for the patch test (Barbaud *et al.* 1995, Langeland and Braathen 1987), the use of preparations for the treatment of warts (Barbaud *et al.* 2001) or acne (Nakagawa *et al.* 1992, Serrano *et al.* 1992) and of other topically applied preparations (Massone *et al.* 1993, Waddell and Finn 1981). Although the use of resorcinol-containing hair dyes can cause occasional sensitization (Vilaplana *et al.* 1991), testing of hairdressers and their customers did not reveal a significantly higher incidence of positive results in the patch test with resorcinol (Frosch *et al.* 1993, Guerra *et al.* 1992a, 1992b).

Several of the patients who developed clear vesiculobullous skin reactions 1 to 3 days after the use of a preparation containing 8 g salicylic acid, 6 g resorcinol and 15 g petrolatum (about 20% resorcinol) to treat *verruca plantaris* also produced marked to severe reactions to 2% resorcinol in petrolatum in the patch test, and less pronounced reactions to resorcinol monobenzoate, catechol, pyrogallol, and hydroquinone, but no reaction to salicylic acid. Of these 18 patients, 11 developed generalized reactions such as generalized urticaria (4 cases), dyshidrosis (1 case), or papulovesicular lesions combined with dyshidrosis (6 cases). The authors concluded from their studies that high concentrations of resorcinol should not be used in formulations for topical use because of the risk of sensitization (Barbaud *et al.* 1996, 2001).

On the other hand in a maximization test, after induction with 15% resorcinol and provocation with 5% resorcinol in petrolatum sensitization was not detected in any of the 22 test persons (Kligman 1966).

Of 600 workers who were repeatedly exposed in the rubber tyre industry, 210 developed inflammatory disorders of the upper and lower airways and conjunctiva after the introduction of a new resorcinol-containing resin. The authors suggested that the cause of the airway disorders could be delayed hypersensitivity reactions to volatile components or condensation products in the resin. The chemical responsible for the reactions was, however, not identified (doPico *et al.* 1975); therefore this study cannot be used in the present assessment.

**Table 1.** Allergic reactions in the patch test with resorcinol

Persons tested	Concentration (vehicle)	Result	Contact / comments	References
690 patients with reactions to topically applied medications	10 % (water)	21 × 1+, 21 × 2+, 13 × 3+ or 4 +	high test concentration, reaction could have been irritation; the scoring system used is no longer accepted	Baer <i>et al.</i> 1955
340 patients	5 % (petrolatum or water)	positive with 7.9 % (no other data)	vehicle described inconsistently	Baer <i>et al.</i> 1973
1001 patients	1 % (petrolatum)	18/1001 positive (no other data)	test period 1994–1999, between 10/1997 and 5/1999 positive results obtained for 5/983 consecutively tested patients; in all for 1992–1999 24 observed cases. Causes: resorcinol-containing preparation for treatment of warts (18 cases), pen for marking the test area (2 cases), occupational contact with resorcinol-containing resins (1 case)	Barbaud <i>et al.</i> 1995, 1996, 2001
5202 patients	n.s. (probably 2 % in petrolatum)	11/5202 positive (no other data)	n.s. whether tests with resorcinol were carried out on all patients; retrospective data analysis	Broeckx <i>et al.</i> 1987
834 patients	2 % (n.s.)	4/834 positive (no other data)	test period 1977/1978	Dröblier 1981
340 patients	2 % (n.s.)	3/340 positive (no other data)	tests with components of an acrylic resin series	Enders 1986
218 patients	2 % (n.s.)	4/218 positive (no other data)	tests with components of a wood industry series test period 1/1977–12/1983	
74 patients with stasis eczema or <i>ulcus cruris</i>	2 % (petrolatum)	2/74 positive (no other data)		Fräki <i>et al.</i> 1979
10892 patients	1 % (petrolatum)	50 × 1+, 17 × 2+, 7 × 3+	test period 1992–2000; only results of the 72-h readings evaluated; also 7 × irritative and 28 × questionable reactions	IVDK 2001
1385 patients	0.5 % (petrolatum)	6/1385 positive (no other data)	test period 1972–1976	Jarisch and Sandor 1978
290 patients	2 % (petrolatum)	2/290 positive (no other data)	test period 1967–1970	Meneghini <i>et al.</i> 1971
888 patients	3 % (water)	27/888 positive (no other data)	test period 1979–1984	Novák and Kvíčalová 1985

**Table 1.** continued

Persons tested	Concentration (vehicle)	Result	Contact / comments	References
877 patients	1 % (petrolatum)	positive with 2.1 %	test period 9/1967–1/1970	Rudzki and Kleniewska 1970
693 patients	2 % (petrolatum)	2/693 positive (no other data)	test period 1987–1989	Scheuer <i>et al.</i> 1992
1890 patients	n.s.	42/1890 positive (no other data)	results of a multicentric study in several centres in each of 4 countries (Bulgaria, Hungary, Slovakia, GDR)	Schubert <i>et al.</i> 1982
839 patients with suspected intolerance of components of plastics and glues	1 % (petrolatum)	4/839 positive (no other data)	2 positive results considered relevant (topical medications)	Tarvainen 1995
349 patients	2 % (n.s.)	7/349 positive (no other data)	tests with components of a hairdresser's series; test period 1/1977–12/1983	Enders 1986
178 patients	1 % (petrolatum)	1/178 positive (no other data)	tests with components of a hairdresser's series; multicentric study in 11 German centres; test period 1988/1989	Frosch 1990
354 hairdres- sers, 104 hair- dressers' cus- tomers	2 % (petrolatum)	2/354 positive (no other data) 1/104 positive (no other data)	test results from a multicentric study in 6 clinics, 3 other clinics had not tested with resorcinol; test period mostly 1988–1991	Frosch <i>et al.</i> 1993
261 hairdres- sers' customers with dermatitis	2 % (petrolatum)	1/261 positive (no other data)		Guerra <i>et al.</i> 1992a
302 hairdressers with contact dermatitis	2 % (petrolatum)	4/302 positive (no other data)	test results from a multicentric study in 9 clinics	Guerra <i>et al.</i> 1992b
53 hairdressers	2 % (petrolatum)	0/53 positive		Holness and Nethercott 1990
106 hairdressers with contact dermatitis	2 % (petrolatum)	5/106 positive (no other data)	test period 1985–1994	Katsarou <i>et al.</i> 1995
191 patients with suspected intolerance of components of hair cosmetics	1 % (petrolatum)	1/191 positive (no other data)	test results from a multicentric study in 8 clinics; test period 12–14 months in the years 1990 and 1991	Peters <i>et al.</i> 1994

Table 1. continued

Persons tested	Concentration (vehicle)	Result	Contact / comments	References
1 hairdresser	2 % (petrolatum)	2+ (reading after 2 days), 4+ (after 4 days)	hair dyes / no reaction to <i>p</i> -phenylenediamine or to numerous other hair dye components	Vilaplana <i>et al.</i> 1991
855 patients	2 % (n.s.)	20/855 positive (no other data)	tests with components of an antimycotica series	Enders 1986
446 patients	2 % (n.s.)	13/446 positive (no other data)	tests with components of an anal series; test period 1/1977–12/1983	
8 patients	2 % (alcohol)	1 × 1+ 4 × 2+ 1 × 3+ 2 × 4+	resorcinol-containing preparations (in 2 cases only anamnestic evidence) / in 7 patients also reactions to resorcinol monoacetate; this scoring system is no longer accepted	Keil 1962
1 female patient with erythematous scaling dermatitis of the eye lids and in the periorbital region	1 % (petrolatum)	2+ (after 2 and 4 days)	keratolytic preparation against blepharitis / also positive results with the preparation	Massone <i>et al.</i> 1993
1 patient with contact dermatitis on the face	0.1 %, 1 % or 5 % (water)	2+ in all tests (no other data)	dermatitis developed after 3 years' use of a preparation containing resorcinol to treat acne / also positive results with 1 % resorcinol monobenzoate in petrolatum	Nakagawa <i>et al.</i> 1992
3 women with contact dermatitis	2 % (petrolatum)	3 × 2+ (after 2 days and 3 days)	preparation containing resorcinol for treating acne / for all women also positive results with their preparation	Serrano <i>et al.</i> 1992
1 female patient with erythematous-vesicular skin reactions	2 % (petrolatum)	strongly positive (no other data)	resorcinol-containing preparation for treating psoriasis/ resorcinol tested in non-occlusive patch test	Waddell and Finn 1981
1 patient with dermatitis on the feet	0.5 % (petrolatum)	2+ (no other data)	Castellani's paint to treat maceration on the toes / 6 years later again a positive test result	Cronin 1973
3 patients	2 % (petrolatum)	positive (no other data)	Castellani's paint, 2 × use on the feet; 1 × use to treat <i>ulcus cruris</i>	Cronin 1980
1 patient with tinea	5 % (petrolatum)	2+ (after 48 h)	use of Castellani's paint 3 × daily, for 10 days / also positive result with Castellani's paint	Dave 1973
1 patient with posttraumatic <i>ulcus cruris</i>	n.s. (probably 1 % in petrolatum)	3+ (no other data)	Castellani's paint for therapy / also positive results with Castellani's paint	Erdmann <i>et al.</i> 1997

**Table 1.** continued

Persons tested	Concentration (vehicle)	Result	Contact / comments	References
1 patient with chronic inguinal dermatitis	2 % (petrolatum)	highly positive (no other data)	Castellani's paint for therapy	Fisher 1982
1 female patient with chronic recurring hand and foot eczema	0.4 % to 1 % (petrolatum)	highly positive (after 24, 48 and 72 h)	Castellani's paint for therapy and to mark the test area / crescendo reaction	Köhn 1993
2 patients	8 % (water)	both positive (no other data)	Castellani's paint to mark the test area / also positive results with Castellani's paint and in 1 case with 1 % resorcinol in petrolatum	Langeland and Braathen 1987
1 patient	5 % (petrolatum)	3+ (after 48 h)	Castellani's paint to mark the area irradiated for radiotherapy / also positive results with Castellani's paint	Marks and West 1978
1 female patient	5 % (petrolatum)	2+ (no other data)	Castellani's paint to mark the area irradiated for radiotherapy / also positive results with Castellani's paint after 2 and 4 days and positive results with 1 % phenol in water	Pecegueiro 1992

## 5 Animal Experiments and *in vitro* Studies

### 5.1 Acute toxicity

Symptoms seen after single exposures of experimental animals were initial CNS stimulation followed by CNS depression, glomerular and tubular degeneration in the kidneys, central hepatic necrosis, myocardial depression, pruritis and reddening of the skin (ACGIH 1996, Flickinger 1976).

#### 5.1.1 Inhalation

Groups of 6 female Wistar rats were exposed to an aerosol of resorcinol in water in concentrations up to 7800 mg/m<sup>3</sup> for one hour and up to 2800 mg/m<sup>3</sup> for 8 hours. In the gross pathological examination carried out 14 days after the exposure, neither deaths nor

exposure-related lesions were detected (Flickinger 1976). In contrast, the lowest lethal resorcinol concentration ( $LC_{Lo}$ ) for the male rat exposed for one hour was  $160 \text{ mg/m}^3$  (BioFax 1970).

### 5.1.2 Ingestion

For the rat, oral  $LD_{50}$  values between 202 and 980 mg/kg body weight have been reported for resorcinol (BioFax 1970, BUA 1993, Flickinger 1976, Lloyd *et al.* 1977, Woodard 1951). The oral  $LD_{50}$  for the mouse was 500 mg/kg body weight (Woodard 1951), the approximate lethal oral resorcinol dose for the guinea pig 370 mg/kg body weight and for the rabbit 750 mg/kg body weight when the substance was administered in aqueous solution (Deichmann and Keplinger 1981).

### 5.1.3 Dermal absorption

The dermal  $LD_{50}$  values reported for resorcinol administered to rabbits are 3360 mg/kg body weight (Flickinger 1976) and 3830 mg/kg body weight (BioFax 1970).

### 5.1.4 Intravenous, intraperitoneal and subcutaneous injection

Intravenous injection of resorcinol doses of 700 to 1000 mg/kg body weight was lethal for dogs (Abderhalden 1935); cats died after subcutaneous injection of as little as 1000 mg/animal (Abderhalden 1935). After subcutaneous injection of resorcinol, the  $LD_{50}$  for the rat was 450 mg/kg body weight and for the mouse 213 mg/kg body weight (ECB 2000). The subcutaneous  $LD_{Lo}$  for the guinea pig was found to be 400 mg/kg body weight (Binet 1895).

The intraperitoneal  $LD_{50}$  for the mouse was 215 mg/kg body weight (ECB 2000). The intraperitoneal dose of resorcinol which induced myoclonic convulsions in 50 % of urethan-anaesthetized male Sheffield mice was 0.92 mmol/kg body weight (101 mg/kg body weight; Angel and Rogers 1972).

Subcutaneous injection of resorcinol in aqueous solution in doses of 55, 88, 140, 220 or 350 mg/kg body weight into groups of 5 male CD(SD) rats caused, at doses of 140 mg/kg or more, slight tremor and tonic-clonic convulsions progressing from moderate to marked within 10 minutes after dosing. Within 1 to 1.5 hours after the treatment, the symptoms had disappeared. No marked signs of toxicity were seen after resorcinol doses up to 88 mg/kg body weight (Merker *et al.* 1982). Subcutaneous injection of resorcinol in aqueous solution in doses of 70 or 180 mg/kg body weight to groups of 4 rats reduced after 2 hours the iodine uptake in the thyroid by 76 % to 86 % (Arnott and Doniach 1952). Subcutaneous resorcinol doses of 55 mg/kg body weight administered to 5 rats did not have any such effects within 3 to 5 hours of dosing (Doniach and Logothetopoulos 1953). Intravenous injection of resorcinol doses of 24.5 mg/animal (vehicle not specified) into rats (number not specified) caused a reduction in radio-iodine

uptake by the thyroid and in the ratio of labelled iodothyronine to iodotyrosine (Berthezene *et al.* 1979).

One hour *post applicationem*, the uptake of iodine by the thyroid gland was reduced to 11 % to 20 % of the normal values in single rats given a dose of resorcinol in aqueous solution  $\geq 5$  mg/kg body weight, once or twice. The antithyroid effect could not be increased by increasing the dose (up to 300 mg/kg body weight) and was less pronounced after administration of 2 % resorcinol in the drinking water. Doses of 250 mg/kg body weight caused severe tremor during the first half hour *post applicationem* (Doniach and Fraser 1950).

## 5.2 Subacute, subchronic and chronic toxicity

### 5.2.1 Inhalation

Rats, guinea pigs and rabbits were exposed to resorcinol in a concentration of 34 mg/m<sup>3</sup>, 6 hours daily for 2 weeks. After a recovery period of up to several months, no toxic effects (not specified) were observed (Flickinger 1976). No data were given for numbers of animals or parameters examined. The animals were apparently not examined immediately after the exposure. The results can therefore not be used in the present assessment.

### 5.2.2 Ingestion

In a two-week study with rats (number not specified) the thyroid gland weights increased in animals given 5 % resorcinol in the diet whereas the serum T<sub>4</sub> levels and the half-life of T<sub>4</sub> decreased (estimated dose 3000 mg/kg body weight and day, assuming 250 g body weight) (Berthezene *et al.* 1979). Groups of 5 F344/N rats per sex and dose were given resorcinol dissolved in water by gavage of doses of 27.5, 55, 110, 225 or 450 mg/kg body weight, daily on 5 days per week for 17 days. In animals given resorcinol doses of 55 mg/kg body weight and day or more, tachypnoea and hyperexcitability were seen during the 30 minutes after dosing and regressed during the subsequent two hours (NTP 1992). The no observed effect level (NOEL) was 27.5 mg/kg body weight. Administration of resorcinol in aqueous solution by gavage of doses of 37.5, 75, 150, 300 or 600 mg/kg body weight and day on 5 days weekly for 17 days to groups of 5 B6C3F<sub>1</sub> mice of each sex resulted in the deaths of 4 male and 5 female animals from the highest dose group and of one male animal from the 300 mg/kg group. In animals given doses of 150 mg/kg body weight or more, clinical symptoms such as prostration and tremor developed within 30 minutes and persisted for 1 to 2 hours (NTP 1992). The NOEL was 75 mg/kg body weight. Effects on the thyroid were not investigated in the 17-day NTP studies. Administration of resorcinol in the drinking water to 5 Wistar rats (9  $\mu$ mol per animal, about 5–10 mg/kg body weight) for a period of 30 days resulted in significant enlargement of the thyroid gland and reduction in the triiodothyronine (T<sub>3</sub>) and T<sub>4</sub> values. The animals were given a diet with low levels of iodine and protein (no further

details) (Cooksey *et al.* 1985). Feeding of resorcinol doses of up to 260 mg/kg body weight and day for 4 weeks did not cause mortality, clinical symptoms, histopathological changes or effects on the body weights of the rats (groups of 10). The relative adrenal weights decreased in all exposed animals (CIR 1986). Groups of 5 male F344 rats were given a diet containing 0.8 % resorcinol (480 mg/kg body weight and day) for a period of 8 weeks; no effects on body weight gains, food or water consumption or on cell proliferation in the pyloric gland or the forestomach epithelium were detected (Shibata *et al.* 1990).

Administration of 0.004 % resorcinol in the drinking water to groups of 12 male and female rats ( $F_1$  of 1.0 BDIX  $\times$  0.1 WELS/Fohm) for a period of 12 weeks (equivalent to resorcinol doses of about 5 mg/kg body weight and day, assuming 35 ml/day and 0.275 kg body weight) resulted in a significant increase in the average follicular epithelial cell height and a significant decrease in the average follicle diameter in the thyroid gland. The authors considered these changes to be preliminary stages in goitre development. Other effects were not investigated. The iodine content was about 0.9 mg/kg diet. In these experiments, resorcinol was used as a control substance in a study of the effects of humic acids on the thyroid gland (Seffner *et al.* 1995). Groups of 10 male and 10 female F344/N rats per dose were given resorcinol in aqueous solution by gavage of doses of 32, 65, 130, 260 or 520 mg/kg body weight and day, daily on 5 days per week. In the highest dose group all the female rats and 8 of 10 male rats died. The absolute and relative weights of the adrenal glands increased in all male animals of all dose groups but there was no clear dose-response relationship. Increased absolute and relative liver weights were found in female animals given resorcinol doses of 65 mg/kg body weight and day or more and in males given 130 mg/kg body weight and day or more. Again, there were no clear dose-response relationships. In the rats which survived until the end of the study, no clinical symptoms, histopathological changes, or changes in clinico-chemical parameters were seen. The thyroid gland was subjected to histopathological examination but was not weighed. Blood  $T_3$  and  $T_4$  levels were determined and were not found to be significantly altered (NTP 1992). The iodine concentration in the diet was 3.37 mg/kg diet instead of the 0.15 mg/kg diet which is normally considered sufficient (see Section 2). A NOEL cannot be derived. Groups of 10 male and 10 female B6C3F<sub>1</sub> mice per dose were given resorcinol in aqueous solution by gavage of doses of 28, 56, 112, 225 or 420 mg/kg body weight, daily on 5 days per week. In the highest dose group, 7 of 10 mice of each sex developed dyspnoea, prostration and tremor and then died. The absolute and relative weights of the adrenal glands were significantly reduced in all dose groups but no dose-response relationship was apparent (NTP 1992). A NOEL cannot be derived. The thyroid glands were not weighed but were subjected to histopathological examination; no significant alterations were found in the animals treated with resorcinol. The  $T_3$  and  $T_4$  levels were not determined.

15 female Syrian golden hamsters were given a diet containing 1.5 % resorcinol for a period of 16 weeks (estimated dose 2250 mg/kg body weight and day, assuming 100 g body weight and consumption of 15 g diet per day). Body weights were increased, relative pancreas weights unchanged and relative liver weights reduced (Maruyama *et al.* 1991).

In a 2-year study, groups of 60 animals were given resorcinol in aqueous solution by gavage, male F344/N rats doses of 112 or 225 mg/kg body weight and day, female F344/N rats 50, 100 or 150 mg/kg body weight and day, and B6C3F<sub>1</sub> mice of both sexes 112 or 225 mg/kg body weight and day. Shortly after administration of resorcinol doses of 100 mg/kg body weight or more, ataxia, prostration, salivation and tremor were observed. After exposure for 15 months, 10 animals per group were examined; no treatment-related differences in haematological or clinicochemical parameters were found. At the end of the study the body weights of the animals in all of the high dose groups except for the male mice were about 10 % to 15 % lower and survival of the high dose group rats was reduced. No effects were seen in the histopathological examination (NTP 1992). For female rats the no observed adverse effect level (NOAEL) was 50 mg/kg body weight and day. For male rats and for mice no NOAEL can be derived because of the clinical symptoms. The thyroid gland was not weighed but was subjected to histopathological examination. The T<sub>3</sub> and T<sub>4</sub> levels were not determined.

### 5.2.3 Dermal absorption

No changes in thyroid gland weights were seen in 6 rats treated epidermally with a ointment containing 12.5 % resorcinol twice daily for a quarter of an hour during three weeks (no other details; Doniach and Logothetopoulos 1953). However, when Wistar rats were treated twice daily for 28 days by rubbing 6 g of an ointment containing 12.5 % resorcinol into the shaved (n = 6) or shaved and scarified skin (n = 4 with and without resorcinol; resorcinol dose about 8300 mg/kg body weight and day assuming an average body weight of about 180 g), the thyroid gland weights were increased to two and a half to four times the control values and there were histological alterations indicative of a goitrogenic effect (Samuel 1955).

### 5.2.4 Subcutaneous injection

Twice daily subcutaneous injection of resorcinol in oil in doses of 1.4 mmol/kg body weight and day (154 mg/kg body weight and day) into one rat for each of 10, 31, 47 and 69 days produced thyroid hyperplasia with goitre-like histology in the animals treated for 47 and 69 days. Control animals were examined after 47 (n = 1) and 69 (n = 2) days. The thyroid glands of animals treated for up to 31 days appeared normal in the gross pathological examination and were not examined in more detail (Doniach and Logothetopoulos 1953). In a repeat of this study, no significant changes were found in the thyroid glands of two rats treated for 28 and 38 days, respectively. In animals given the higher resorcinol dose of 1.8 mmol/kg body weight (198 mg/kg body weight; n = 3) the thyroid glands were enlarged (up to twice the weight) and histological changes were seen in the thyroid and the anterior lobe of the pituitary gland (Samuel 1955). Daily subcutaneous doses of 100 mg/kg body weight (2 injections of 50 mg/kg body weight, 6 hours apart, resorcinol in aqueous solution) administered for periods of 14 or 30 days to male Sprague-Dawley rats (number not specified) did not result in clinical symptoms or

changes in body weight gains or organ weights (the thyroid glands were not weighed), thyroid function (serum T<sub>3</sub> and T<sub>4</sub>), blood parameters (erythrocyte count, haemoglobin, haematocrit), clinicochemical parameters or histopathology of thyroid, spinal cord or brain (Merker *et al.* 1982).

## 5.3 Local effects on skin and mucous membranes

### 5.3.1 Skin

Applied epidermally in high doses (1000–7950 mg/kg body weight, 2500–19300 mg total dose for a maximum of 24 hours; amount per cm<sup>2</sup> not specified) in an acute toxicity test, resorcinol caused irritation in rabbits given doses of 1000 mg/kg body weight or more and necrosis at 2000 mg/kg body weight or more (Flickinger 1976). In rabbits treated locally with a preparation containing 2.5 % resorcinol (dose not specified), no reactions were seen during the 72-hour observation period (Lloyd *et al.* 1977). Aqueous solutions containing 0.1 % to 10 % resorcinol were not irritating in a screening test with guinea pigs (CIR 1986). Epidermal application of 500 mg resorcinol mixed to a paste with physiological saline to the intact skin of rabbits for 24 hours caused either no irritation or slight to moderate irritation. When the substance was applied to scarified skin, the reactions varied widely, including necrosis (the primary irritation index calculated for both application methods together was 4.4) (Flickinger 1976). Local application of 1 % or 3 % resorcinol in petrolatum to the ears and flanks of 10 male Pirbright guinea pigs, daily for up to 14 days (the animals were killed 24 hours after application on days 2, 4, 7, 11 and 14) resulted in concentration-dependent acanthosis, hypergranulosis, hyperkeratosis and in the epidermis of the ears also “papillomatosis” (multiple skin papillomas resulting from proliferation of the papillary layer, defined here as extension of the depth of the dermo-epidermal contact zone relative to the epidermis). Keratinocyte proliferation was induced in the treated skin areas (Windhager and Plewig 1977).

### 5.3.2 Eyes

Instillation of 0.1 g resorcinol into the rabbit eye caused discomfort, conjunctivitis and irreversible corneal ulceration (BUA 1993, Flickinger 1976). Application of a preparation containing 2.5 % (w/v) resorcinol to the rabbit eye resulted in transient mild conjunctivitis which did not persist for longer than 24 hours (Lloyd *et al.* 1977).

## 5.4 Allergenic effects

Resorcinol (99.9 %) was shown to be sensitizing in a guinea pig maximization test. Induction was carried out by pairwise intradermal injections of 0.1 ml of a 2 % solution of resorcinol in physiological saline and in 50 % Freund's complete adjuvant (FCA) and

pairwise injections of 0.1 ml 50 % FCA. The injection sites were not covered. Epicutaneous induction was carried out on day 8 by application of 0.5 ml of a 25 % solution of resorcinol in physiological saline occlusively for 48 hours in the area of the intradermal injections. Pretreatment with sodium dodecyl sulfate was not carried out. The provocation of the 10 treated animals and the 5 control animals treated only with FCA was carried out twice in the same way, occlusively for 24 hours on the depilated left flank, on days 22 and 29 and the provocation of the 5 animals of another control group treated with FCA on days 14 to 17. At the first provocation, reactions were seen in 3/10 treated animals, at the second in 7/10. No reactions were seen in the two control groups (Hoechst 1989). A patch test with 3 % resorcinol and without occlusion yielded, however, negative results (BUA 1993, CIR 1986). Negative results were also obtained in the local lymph node assay with CBA/Ca mice treated with 5 %, 10 % or 25 % resorcinol in dimethyl formamide (Basketter *et al.* 1994).

The results of a study in which spleen cells from CBA/J mice were incubated for 18 hours with the "highest non-cytotoxic concentration" of resorcinol (3 mg/ml) and then injected intraperitoneally into CBA/J mice in a dose of  $10^7$  cells three times at 7-day intervals cannot be assessed conclusively. The animals were subjected 10 days later to a provocation treatment by non-occlusive application to the ear of 1 % resorcinol in hydroxyethyl cellulose. The ear thickness was increased after 24 and 48 hours and less so after 72 hours. The reaction seen with resorcinol was like that with *p*-toluenediamine (Kalish and Wood 1995).

Resorcinol (0.3 ml of a 10 % aqueous solution) was applied to guinea pigs 6 times for induction, occlusively for 2 hours on alternate days, and then provocation treatment was carried out, also occlusively for 2 hours, with 0.3 ml of a 10 % or 2 % aqueous solution. The substance was not sensitizing or photosensitizing (10 J/cm<sup>2</sup>, UV 320–400 nm) for guinea pigs treated with 2 % resorcinol for provocation. Positive results were obtained with 2 of 20 animals for which the provocation treatment was carried out with 10 % resorcinol. UV irradiation did not intensify the skin reactions. One further animal produced a reaction after treatment with 10 % resorcinol and UV irradiation (CIR 1986).

## 5.5 Reproductive and developmental toxicity

### 5.5.1 Fertility

Treatment of mice once with resorcinol did not result in inhibition of testicular DNA synthesis (resorcinol dose 100 mg/kg body weight, oral; Seiler 1977) or in sperm head anomalies (55–220 mg/kg body weight, intraperitoneal; Wild *et al.* 1981).

### 5.5.2 Developmental toxicity

Groups of 15 Sprague-Dawley rats were given resorcinol by gavage of doses of 333, 667 or 1000 mg/kg body weight on day 11 of gestation; no signs of maternal toxicity apart

from slight weight losses were seen within the 72 hours after dosing. No developmental toxicity (viability, litter weights, perinatal losses) was observed in the litters. This study was carried out without a positive control, only macroscopic malformations were recorded for the progeny, and autopsy was carried out only on diseased or dead pups (Kavlock 1990).

Daily administration of resorcinol in doses of 125, 250 or 500 mg/kg body weight by gavage to groups of 13 pregnant Sprague-Dawley rats on days 6 to 15 of gestation caused slight but not significant reductions in maternal weight gains in the 500 mg/kg dose group. Resorcinol had neither embryotoxic effects nor effects on litter size, nor did it cause foetal anomalies or malformations (DiNardo *et al.* 1985). Similarly, resorcinol was not embryotoxic or teratogenic for groups of 23 Sprague-Dawley rats given the substance in aqueous solution by gavage of daily doses of 40, 80 or 250 mg/kg body weight on days 6 to 15 of gestation (Wella 1982a).

Also with groups of 18 to 26 rabbits given resorcinol in aqueous solution by gavage of daily doses of 25, 50 or 100 mg/kg body weight on days 6 to 18 of gestation, no embryotoxic or teratogenic effects were observed. A slight but not significant reduction in maternal body weight gains was seen in the dams of the 100 mg/kg dose group during the administration period (Wella 1982b).

## 5.6 Genotoxicity

### 5.6.1 *In vitro*

The results of *in vitro* genotoxicity studies with resorcinol are summarized in Table 2.

Resorcinol (in concentrations up to 5.5 mg/plate) did not induce gene mutations, neither with nor without the addition of S9 for metabolic activation, in various strains of *Salmonella typhimurium* or *Escherichia coli* (Bracher *et al.* 1981, BUA 1993, Crebelli *et al.* 1981, 1985, Florin *et al.* 1980, Haworth *et al.* 1983, NTP 1992, Probst *et al.* 1981, Shahin *et al.* 1980). In only one test with *S. typhimurium* TA1535 and TA100 without S9 and with an unusual medium was a positive result obtained (Gocke *et al.* 1981). Resorcinol did not induce an SOS response in *S. typhimurium* TA1535/pSK1002, either with or without S9 (Nakamura *et al.* 1987).

In *in vitro* studies without metabolic activation, resorcinol did not cause SCE in cultures of V79 cells (Wild *et al.* 1981), in CHO cells (a cell line from Chinese hamster ovary) (Darroudi and Natarajan 1983) or in human peripheral blood lymphocytes (Darroudi and Natarajan 1983, Jansson *et al.* 1986). Positive results were obtained in one study with CHO cells (NTP 1992). A test for unscheduled DNA synthesis (UDS) in primary rat hepatocytes yielded negative results with resorcinol (Probst *et al.* 1981). Without metabolic activation, resorcinol induced a significant increase in the number of trifluorothymidine-resistant colonies of L5178Y mouse lymphoma cells (McGregor *et al.* 1988). With and without S9, resorcinol caused chromosomal aberrations in Chinese hamster lung fibroblasts (Sakano *et al.* 1985). From studies with CHO cells, both positive (NTP 1992, Stich *et al.* 1981) and negative (Darroudi and Natarajan 1983) results

have been published. Chromosomal aberrations were not found in tests with human diploid fibroblasts (Darroudi and Natarajan 1983), but were found with cultured human amniotic cells and peripheral blood lymphocytes (Darroudi and Natarajan 1983, Schulz *et al.* 1982).

Resorcinol did not induce DNA strand breaks either in cultured mammalian cells or in isolated DNA (Kawanishi *et al.* 1989, Miura *et al.* 2000, Walles 1992, Yamada *et al.* 1985).

**Table 2.** *In vitro* genotoxicity studies with resorcinol

Test system	Concentration	Results		References
		-S9	+S9	
<b>Mutations</b>				
<i>Salmonella typhimurium</i> TA98, TA100, TA1000, TA1535, TA1537, TA1538, G46, C3076, D3052	0–5500 µg/plate	–	–	Bracher <i>et al.</i> 1981, BUA 1993, Crebelli <i>et al.</i> 1981, 1985, Florin <i>et al.</i> 1980, Haworth <i>et al.</i> 1983, NTP 1992, Probst <i>et al.</i> 1981, Shahin <i>et al.</i> 1980
<i>Salmonella typhimurium</i> TA100 TA1535	20–60 µmol/plate (2200–6600 µg/plate)	+ <sup>a</sup> –	– + <sup>a</sup>	Gocke <i>et al.</i> 1981
<i>Escherichia coli</i> WP2, WP2 uvrA <sup>-</sup>	n.s.	–	–	Probst <i>et al.</i> 1981
L5178Y cells, TK <sup>+/-</sup> (mouse lymphoma test)	125–5000 µg/ml toxic at 1250 µg/ml or more lethal at 5000 µg/ml or more	+ <sup>b</sup>	n.d.	McGregor <i>et al.</i> 1988
<b>Chromosomal aberrations</b>				
CHL cells (Chinese hamster lung)	no data	+	+	Sakano <i>et al.</i> 1985
CHO cells (cell line from Chinese hamster ovary)	0.004–0.16 % (40–1600 µg/ml)	–	–	Darroudi and Natarajan 1983
CHO cells	750–5000 µg/ml -S9: toxic at 2000 µg/ml or more	?	+	NTP 1992
CHO cells	1600 µg/ml	+	+	Stich <i>et al.</i> 1981
diploid human fibroblasts (VH)	0.0012–0.005 % (12–50 µg/ml)	–	n.d.	Darroudi and Natarajan 1983
human amnion cells	40 µg/ml	+	n.d.	Schulz <i>et al.</i> 1982
human blood lymphocytes	0.002–0.01 % (20–100 µg/ml)	+	n.d.	Darroudi and Natarajan 1983
human blood lymphocytes	80–320 µg/ml	+	n.d.	Schulz <i>et al.</i> 1982

Table 2. continued

Test system	Concentration	Results		References
		-S9	+S9	
<b>Sister chromatid exchange</b>				
CHO cells	0.005–0.16 % (50–1600 µg/ml)	–	–	Darroudi and Natarajan 1983
CHO cells	50–5000 µg/ml –S9: toxic at 1670 µg/ml or more	+	+	NTP 1992
V79 Chinese hamster cells	5–20 µM (0.55–2.2 µg/ml)	–	n.d.	Wild <i>et al.</i> 1981
human blood lymphocytes	0.002–0.01 % (20–100 µg/ml)	–	n.d.	Darroudi und Natarajan 1983
human blood lymphocytes	0–0.25 mM (0–27 µg/ml)	–	n.d.	Jansson <i>et al.</i> 1986
<b>UDS</b>				
rat hepatocytes	1000 nmol/ml (110 µg/ml)	–	n.d.	Probst <i>et al.</i> 1981
<b>DNA damage</b>				
<i>Salmonella typhimurium</i> TA1535/pSK1002 UMU test	0–3333 µg/ml	–	–	Nakamura <i>et al.</i> 1987
<b>DNA strand breaks</b>				
λ-DNA	250 µM (27 µg/ml)	–	n.d.	Yamada <i>et al.</i> 1985
human DNA	2.5–5 mM (275–550 µg/ml)	–	n.d.	Kawanishi <i>et al.</i> 1989
plasmid DNA	40 µM (440 µg/ml)	–	n.d.	Miura <i>et al.</i> 2000
rat foetal lung cells HeLa cells	250 µM (27 µg/ml)	–	n.d.	Yamada <i>et al.</i> 1985
rat hepatocytes	10–20 mM (1100–2200 µg/ml)	+	n.d.	Walles 1992

n.d. not determined

? unclear results

n.s. not specified

UDS unscheduled DNA synthesis

<sup>a</sup> positive results in only one of two media<sup>b</sup> large and small colonies were not distinguished in the reporting

### 5.6.2 *In vivo*

In male *Drosophila melanogaster* given resorcinol in a concentration of 11000 mg/l diet, sex-linked recessive lethal (SLRL) mutations were not induced in the germ cells; on the other hand, after injection of a resorcinol solution in a concentration of 11940 mg/l, questionably positive results were obtained (NTP 1992). No SLRL mutations were found in the Basc test with *Drosophila melanogaster* fed with 55 mM resorcinol in sucrose (Gocke *et al.* 1981).

Neither in mice nor rats did resorcinol induce micronucleus formation in the bone marrow cells. Groups of 2 male and 2 female NMRI mice per dose (resorcinol dose 0.5–2 mmol/kg body weight; 55, 110, 220 mg/kg body weight) were given two intraperitoneal injections 24 hours apart; the micronuclei were counted 30 hours after the first injection (Gocke *et al.* 1981). Groups of 4 male mice were given single intraperitoneal injections of resorcinol in doses of 37.5, 75, 150 or 300 mg/kg body weight and were examined after 24 and 48 hours (Darroudi and Natarajan 1983). In another micronucleus test, the bone marrow of groups of 5 mice per examination time (24, 48, 72 and 96 hours) was examined after a single intraperitoneal resorcinol dose of 75 mg/kg body weight (Paschin *et al.* 1986). Resorcinol was administered to groups of 5 male and 5 female Sprague-Dawley (CFY) rats by gavage of two doses of 250 mg/kg body weight, 24 hours apart. The animals were examined 6 hours after the second injection (Hossack and Richardson 1977).

SCE tests (oral 0.8–100 mg/kg body weight, i.p. 1–100 mg/kg body weight and epicutaneous 0.2–300 mg/kg body weight) also yielded negative results with Sprague-Dawley rats (number not specified) (Bracher *et al.* 1981).

## 5.7 Carcinogenicity

### 5.7.1 Short-term tests

#### *In vitro*

In human colon cancer DLD-1 cells which had been transfected with a  $\beta$ -galactosidase reporter gene system, resorcinol and structurally related compounds were shown to inhibit the cyclooxygenase-2 promoter activity with and without stimulation of transforming growth factor  $\alpha$  (TGF $\alpha$ ). Inhibition of cyclooxygenase-2 activity results in prevention of colon carcinogenesis (Mutoh *et al.* 2000).

Resorcinol does not induce transformation in human diploid fibroblasts or in kidney fibroblasts from Syrian golden hamsters *in vitro* (no other data; Purchase *et al.* 1978).

#### *In vivo*

#### Cell proliferation studies

15 male Syrian golden hamsters were given a diet containing 0.25 % resorcinol for a period of 20 weeks (estimated dose 375 mg/kg body weight and day, assuming 100 g

body weight and consumption of 15 g diet per day); neither an increase in the rate of cell division in the epithelia of the forestomach or urinary bladder nor treatment-related histopathological alterations were found. The thyroid gland was not examined (Hirose *et al.* 1986).

Resorcinol caused neither proliferation nor preneoplastic alterations in the stomach mucosa of 5 male F344 rats given 0.8 % resorcinol in the diet (480 mg/kg body weight and day) for a period of 8 weeks (Shibata *et al.* 1990).

### Initiation-promotion studies

Because of its antioxidative properties, resorcinol has been tested for anticarcinogenic activity in several initiation-promotion studies. Groups of female Syrian golden hamsters were given two subcutaneous injections of either physiological saline (n = 15) or *N*-nitrosobis(2-oxopropyl)amine (70 mg/kg body weight, n = 20) 14 days apart, and then from week 4 of the study 1.5 % resorcinol in the diet for 16 weeks (estimated resorcinol dose 2250 mg/kg body weight and day). 20 animals were given only the initiation treatment. In week 20, the incidence of atypical hyperplasia in the pancreas ducts in animals fed with resorcinol after the initiation treatment was significantly lower than that in the animals given only the initiation treatment (10/16 compared with 17/18). The incidence of pancreas carcinomas in the resorcinol group (10/16) was not significantly smaller than that in the "initiation only" group (14/18). Resorcinol had no effect on the incidence of (pre)neoplastic lesions in the gall bladder or liver (nodules, adenomas, carcinomas). In the forestomachs and glandular stomachs of animals given resorcinol (not clear whether with or without initiation), however, there was an increased incidence of epithelial hyperplasia (no data) but no neoplasms (Maruyama *et al.* 1991).

15 male F344 rats were given 0.05 % *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine in the drinking water for two weeks as initiation treatment. Then the rats were given 0.2 % resorcinol in the diet (120 mg/kg body weight and day) for another 22 weeks. No increase in the incidence of hyperplasia or papillomatous alterations in the urinary bladder was found (Miyata *et al.* 1985). The same results were obtained with 20 F344 rats given 0.05 % *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine in the drinking water for four weeks for initiation and then 0.8 % resorcinol in the diet (480 mg/kg body weight and day) for 32 weeks for promotion (Kurata *et al.* 1990). The tumour-promoting activity of resorcinol for the liver was studied in 14 male F344 rats given a single intraperitoneal injection of diethylnitrosamine for initiation. Two weeks after the initiation treatment, the animals were given a diet containing resorcinol in a concentration of 20000 mg/kg diet (estimated dose 1200 mg/kg body weight and day, assuming 250 g body weight and food consumption of 60 g/kg body weight per day) for a period of 6 weeks. Three weeks after the initiation treatment, two thirds of the liver was removed. Resorcinol did not cause an increase in the incidence of foci with increased expression of glutathione-*S*-transferase (placental form). This was considered to be evidence for the absence of tumour-promoting activity in the liver (Hasegawa and Ito 1992).

In 20 male F344 rats given 0.1 % *N*-bis(2-hydroxypropyl)nitrosamine in the drinking water for two weeks for initiation, administration of 0.8 % resorcinol in the diet (480 mg/kg body weight and day) for 30 weeks reduced slightly the incidence of lung

tumours. Both the numbers and sizes of lung lesions were reduced. Resorcinol had no effects on the incidence of neoplastic changes in the urinary bladder or kidneys; in the thyroid gland an increase in the incidence of adenomas (6/20 with and 1/20 without resorcinol) and carcinomas (5/20 with and 4/20 without resorcinol) was found. Administration of resorcinol without previous initiation treatment caused no changes in the thyroid (Hasegawa *et al.* 1990).

20 male Wistar/Crj rats (6 weeks old) were given 0.1 % *N*-ethyl-*N*-hydroxyethyl-nitrosamine in the drinking water for 3 weeks for initiation and, starting one week later, 0.8 % resorcinol in the diet (480 mg/kg body weight and day) for 36 weeks for promotion. In the animals given resorcinol, the number of hepatocellular adenomas and carcinomas per rat was significantly reduced. In the kidney, however, the incidence and multiplicity of atypical tubules, microadenomas and kidney cell tumours were unchanged; other organs were not studied (Okazaki *et al.* 1993).

A single dose of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (150 mg/kg body weight) was administered to each of 16 F344 rats by gavage. Starting one week later, the rats were given 0.8 % resorcinol in the diet (480 mg/kg body weight and day) for 51 weeks. Resorcinol had no tumour-promoting activity in the forestomach or glandular stomach. The incidence of forestomach hyperplasia was not increased by the administration of resorcinol alone (Hirose *et al.* 1989).

In contrast, in a group of 12 male F344 rats which had been given 3-methyl-*N*-amyl-nitrosamine (25 mg/kg body weight, 3 intraperitoneal doses at one week intervals) for initiation and, after a one-week pause, 0.8 % resorcinol in the diet (480 mg/kg body weight and day) for 49 weeks, significant increases in the incidences of squamous cell carcinomas in the oesophagus (7/12) and papillomas of the tongue (6/12) were found. The respective incidences in animals which had received only the nitrosamine were 0/11 and 1/11 (Yamaguchi *et al.* 1989). Groups of 50 female ICR/Ha-Swiss mice (6 to 8 weeks old) were exposed simultaneously to benzo[*a*]pyrene (5 mg/day) and resorcinol (10 mg/day) by epicutaneous application daily for 368 days. The incidence of skin tumours produced by benzo[*a*]pyrene was inhibited by more than 50 %. A second group of animals was treated epicutaneously, once with 150 mg benzo[*a*]pyrene and then, starting 14 days later, with resorcinol in doses of 10 mg/day on three days weekly during a period of 449 days. No skin tumours developed (Van Duuren and Goldschmidt 1976). Mice were treated with 0.3 % 9,10-dimethyl-1,2-benzanthracene for initiation and then with a 20 % solution of resorcinol in acetone for 12 weeks for promotion. Papillomas developed in 17 % of the animals but in 0 % of the control animals given only the initiation treatment (Boutwell and Bosch 1959).

### **Short-term tests with transgenic animals**

In groups of 15 heterozygote p53-deficient mice of each sex, no increases in tumour incidence were detected after intubation of resorcinol doses of 225 mg/kg body weight and day, 5 days weekly for 24 weeks (Eastin *et al.* 1998).

Resorcinol in acetone was applied epidermally, probably without occlusion, to groups of 15 hemizygote Tg.AC mice (carriers of an activated H-ras oncogene) of each sex in doses of 225 mg/kg body weight, 5 days weekly for 24 weeks. There was a significant

increase in the incidence of squamous cell papillomas (♂: 10/15 versus 3/30, ♀: 12/15 versus 1/30). In addition, skin hyperplasia was seen in mice of both sexes and inflammation and sebaceous gland hyperplasia in the male animals. The authors were uncertain whether these changes were a reaction to the papillomas or were involved causally in their development. With rotenone, which was tested in parallel, inflammatory skin changes were also found but no neoplasms (Eastin *et al.* 1998). This test model has, however, not yet been validated.

### 5.7.2 Long-term studies

8-week-old CB6F<sub>1</sub>-Tg rasH2 transgenic mice (which carry 5 to 6 copies of the intact human c-Ha-ras gene with its own promoter and enhancer) and also genetically not modified animals of both sexes were given resorcinol by gavage (225 mg/kg body weight and day) on 5 days weekly for 18 months in two laboratories under identical test conditions for evaluation of the test. When the results are taken together, a slight but not significant increase in the incidence of lung tumours is seen in the transgenic and not transgenic animals treated with resorcinol (adenomas: ♂, transgenic 4/50 versus 1/24; ♀, transgenic 4/55 versus 0/25; ♂, not transgenic 3/51 versus 0/24; ♀, not transgenic 1/56 versus 1/25; carcinomas: ♂, transgenic 0/50 versus 1/24; ♀, transgenic 2/55 versus 0/25; ♂, not transgenic 0/51 versus 0/24; ♀, not transgenic 0/56 versus 0/25) (Maronpot *et al.* 2000).

In a 2-year study, groups of 60 animals were given resorcinol by gavage, male F344/N rats doses of 112 or 225 mg/kg body weight and day, female F344/N rats 50, 100 or 150 mg/kg body weight and day, and B6C3F<sub>1</sub> mice of both sexes 112 or 225 mg/kg body weight and day. At the interim killing of 10 animals per group after exposure for 15 months, no differences in the incidences of neoplasms were found. At the end of the study, increased tumour incidences were also not found (NTP 1992).

Groups of 50 female Swiss mice were treated epidermally with 0.02 ml of 5 %, 25 % or 50 % solutions of resorcinol in acetone, twice weekly for 100 weeks. No significant increases in the incidences of skin tumours or other tumours were observed (Stenbäck and Shubik 1974). Treatment of the inner side of the ear of each of 5 rabbits, twice weekly for 180 weeks, with 0.02 ml of 5 %, 10 % or 50 % resorcinol solutions caused neither local nor systemic tumours or systemic toxicity (Stenbäck 1977).

## 5.8 Other effects

Studies with isolated hepatocytes from male Wistar rats demonstrate that resorcinol stimulates glycogen synthesis and inhibits glycolysis (Agius 1997).

## 6 Manifesto (MAK value/classification)

Although resorcinol can without doubt have goitrogenic effects in man, in all the cases which have been described very high doses were applied for months or years to damaged skin or the persons suffered from renal insufficiency. Application of resorcinol doses of 12 mg/kg body weight and day for several weeks to the skin of young test persons had no effect on the thyroid gland. Results of studies of exposed persons which would be suitable for the derivation of a MAK value are not available. Appropriate animal studies with repeated inhalation exposure are also not available. Because resorcinol causes marked local irritation, inhalation studies are necessary before a threshold value for this substance at the workplace can be established. In a 2-year study in which oral doses up to 225 mg/kg body weight and day were administered to rats and mice, resorcinol was not carcinogenic. On the other hand, resorcinol induced a slight but not significant increase in the incidence of lung tumours in transgenic CB6F<sub>1</sub>-Tg rasH2 mice (with human c-Ha-ras genes) and a significant increase in the incidence of squamous cell papillomas on the dorsal skin of hemizygote Tg.AC mice (with activated Hras oncogenes). The models with transgenic animals have, however, not yet been validated.

Tumour initiation-promotion studies have yielded contradictory results for tumour-promoting activity of resorcinol. In Syrian golden hamsters, no tumour-promoting activity was found in the pancreas, liver, bile duct or urinary bladder. In one of two studies, the incidence of epithelial hyperplasia in the forestomach and glandular stomach was increased. In rats, tumour-promoting effects were not found in the liver, lungs, urinary bladder, kidneys or stomach. In the thyroid gland of the rat there was a not significant increase in the incidence of adenomas and carcinomas after initiation treatment. In one rat study, the incidences of squamous cell carcinomas in the oesophagus and of papillomas on the tongue were markedly increased. In one of two studies with mice, weak tumour-promoting activity was seen.

In view of the negative results of the carcinogenicity study, the fact that the test systems with transgenic animals are still not validated, and the contradictory results of the initiation-promotion studies, the data base must be considered inadequate for the classification of resorcinol in one of the categories for carcinogens.

Because a MAK value can also not be established, resorcinol is included in Section IIb of the *List of MAK and BAT Values*.

The results of sensitization studies with experimental animals are not consistent; a positive result in a maximization test suggests that resorcinol could have sensitizing effects but cannot be evaluated conclusively because the concentration used for provocation was high. Contact sensitization in man by resorcinol has been demonstrated in several cases. Apparently sensitization develops especially after prolonged use on damaged skin; thus the sensitizing potency of resorcinol is considered to be low. Higher concentrations or direct contact with the substance can, however, cause sensitization even if the skin barrier is intact. Resorcinol is therefore designated with an "Sh". There are no useful data for sensitizing effects on the respiratory passages.

When resorcinol was applied several times to 2600 cm<sup>2</sup> of the skin of test persons in doses of 12 mg/kg body weight (as a 2 % solution) the absorbed amount was found to be

at most 3 % of the dose; the flux calculated from these data was 0.37  $\mu\text{g}/\text{cm}^2$  and hour. Under standard conditions (1 hour, 2000  $\text{cm}^2$ ) these human data reveal a very small potentially absorbed dose of 0.74 mg. Therefore the amount of resorcinol which could be absorbed through the skin of persons at the workplace does not seem to be large enough to justify designation with an "H". The substance cannot be classified as a germ cell mutagen on the basis of the data available.

## 7 References

- Abbate C, Polito I, Puglisi A, Brecciaroli R, Tanzariello A, Germano D (1989) Dermatitis from resorcinol in tyre makers. *Br J Ind Med* 46: 212–214
- Abderhalden E (1935) *Handbuch der biologischen Arbeitsmethoden, Band 7B* (Biological Methods, Volume 7B) (German), Urban & Schwarzenberg, Berlin, 1390
- ACGIH (American Conference of Governmental Industrial Hygienists) (1996) Resorcinol. in: *Documentation of the TLVs and BEIs*, ACGIH, Cincinnati, OH, USA
- Agius L (1997) Involvement of glucokinase translocation in the mechanism by which resorcinol inhibits glycolysis in hepatocytes. *Biochem J* 325: 667–673
- Angel A, Rogers KJ (1972) An analysis of the convulsant activity of substituted benzenes in the mouse. *Toxicol Appl Pharmacol* 21: 214–229
- Arnott DG, Doniach I (1952) The effect of compounds allied to resorcinol upon the uptake of radioactive iodine ( $^{131}\text{I}$ ) by the thyroid of the rat. *Biochem J* 50: 473–479
- Baer RL, Serri F, Weissenbach-Vial C (1955) Studies on allergic sensitization to certain topical therapeutic agents. *Arch Dermatol* 71: 19–23
- Baer RL, Ramsey DL, Biondi E (1973) The most common contact allergens 1968–1970. *Arch Dermatol* 108: 74–78
- Barbaud A, Bertrand O, Reichert S, Modiano P, Weber M, Schmutz JL (1995) Allergies de contact à la résorcine d'un crayon marqueur pour tests épicutanés (Contact allergy to resorcinol in a marking pen for patch tests) (French). *Ann Dermatol Venereol* 122, Suppl: S103–104
- Barbaud A, Modiano P, Cocciale M, Reichert S, Schmutz J-L (1996) The topical application of resorcinol can provoke a systemic allergic reaction. *Br J Dermatol* 135: 1014–1015
- Barbaud A, Reichert-Penetrat S, Trechot P, Granel F, Schmutz J-L (2001) Sensibilisation à la résorcine due à une préparation magistrale verrucide. Manifestations cliniques systémiques et prévalence inhabituelles (Sensitization to resorcinol in a prescription verrucide preparation: unusual systemic clinical features and prevalence) (French). *Ann Dermatol Venereol* 128: 615–618
- Basketter DA, Scholes EW, Kimber I (1994) The performance of the local lymph node assay with chemicals identified as contact allergens in the human maximization test. *Food Chem Toxicol* 32: 543–547
- Becker J (1933) Resorzin-Salbe verursacht tödliche Vergiftung bei einem Säugling (Ointment containing resorcinol caused lethal poisoning of a baby) (German). *Samml Vergiftungsfaellen* 4: 7–8
- Berthezene F, Fournier M, Bernier E, Mornex R (1973) L'hypothyroïdie induite par la résorcine (Hypothyroidism induced by resorcinol) (French). *Lyon Med* 230: 319–323
- Berthezene F, Perrot L, Munari Y, Ponsin G (1979) Effets multiples du resorcinol sur la fonction thyroïdienne (Multiple effects of resorcinol on thyroid function) (French). *Ann Endocrinol (Paris)* 40: 67–68
- Binet P (1895) Toxicologie comparée des phénols (Comparative toxicology of phenols) (French). *Rev Med Suisse Romande* 15: 561–596

- BioFax (1970) *Datasheet No. 11-4/70, Resorcin*, Industrial Bio-Test Laboratories, Northbrook, IL, USA
- Blondet P, Le Roux P, Schandelong A, Legueult LC, Laine G (1985) Méthémoglobinémie et anémie hémolytique aiguë toxique par lotion gingivale à base de benzocaïne et résorcine. (Methemoglobinemia and acute toxic hemolytic anemia caused by gingival lotion containing benzocaine and resorcinol) (French). *Presse Med* 14: 1757
- Bontemps H, Mallaret M, Besson G, Bochaton H, Carpentier F (1995) Confusion after topical use of resorcinol. *Arch Dermatol* 131: 112
- Boutwell RK, Bosch DK (1959) The tumor-promoting action of phenol and related compounds for mouse skin. *Cancer Res* 19: 413–427
- Bracher M, Swistak J, Noser F (1981) Studies on the potential *in vivo* induction of sister-chromatid exchanges in rat bone marrow by resorcinol. *Mutat Res* 91: 363–369
- Broeckx W, Blondeel A, Dooms-Goossens A, Achten G (1987) Cosmetic intolerance. *Contact Dermatitis* 16: 189–194
- BUA (Beratergremium für umweltrelevante Altstoffe der Gesellschaft Deutscher Chemiker) (1993) *Resorcin, BUA-Stoffbericht 99*, Hirzel Wissenschaftliche Verlagsgesellschaft, Stuttgart, also available in English translation
- Bull GM, Fraser R (1950) Myxoedema from resorcinol ointment applied to leg ulcers. *Lancet* 1: 851–855
- CIR (Cosmetic Ingredient Review) (1986) Final report on the safety assessment of 2-methylresorcinol and resorcinol. *J Am Coll Toxicol* 5: 167–203
- Cooksey RC, Gaitan E, Lindsay RH, Hill JB, Kelly K (1985) Humic substances, a possible source of environmental goitrogens. *Org Geochem* 8: 77–80
- Crebelli R, Conti L, Carere A, Zito R (1981) Mutagenicity of commercial *p*-phenylenediamine and of an oxidation mixture of *p*-phenylenediamine and resorcinol in *Salmonella typhimurium* TA98. *Food Cosmet Toxicol* 19: 79–84
- Crebelli R, Paoletti A, Falcone E, Aquilina G, Fabri G, Carere A (1985) Mutagenicity studies in a tyre plant: *in vitro* activity of workers' urinary concentrates and raw materials. *Br J Ind Med* 42: 481–487
- Cronin E (1973) Resorcin in Castellani's paint. *Contact Dermatitis Newslett* 14: 401
- Cronin E (1980) *Contact Dermatitis*, Churchill Livingstone, Edinburgh, 264–265
- Cunningham AA (1956) Resorcin poisoning. *Arch Dis Child* 31: 173–176
- Darroudi F, Natarajan AT (1983) Cytogenetic analysis of human peripheral blood lymphocytes (*in vitro*) treated with resorcinol. *Mutat Res* 124: 179–189
- Dave VK (1973) Contact dermatitis due to resorcin in Castellani's paint. *Contact Dermatitis Newslett* 13: 384
- Deichmann WB, Gerarde HW (1969) *Toxicology of Drugs and Chemicals*, Academic Press, New York, 519
- Deichmann WB, Keplinger ML (1981) Phenols and phenolic compounds. in: Clayton GD, Clayton FE (Eds) *Patty's Industrial Hygiene and Toxicology, Vol. 2A*, John Wiley & Sons, New York, 2567–2627
- DiNardo JC, Picciano JC, Schnetzinger RW, Morris WE, Wolf BA (1985) Teratological assessment of five oxidative hair dyes in the rat. *Toxicol Appl Pharmacol* 78: 163–166
- Divi RL, Doerge DR (1994) Mechanism-based inactivation of lactoperoxidase and thyroid peroxidase by resorcinol derivatives. *Biochemistry* 33: 9668–9674
- Doniach I, Fraser R (1950) Effect of resorcinol on the thyroid uptake of I<sup>131</sup> in rats. *Lancet* 1: 855–856
- Doniach I, Logothetopoulos J (1953) The goitrogenic action of resorcinol in rats. *Br J Exp Pathol* 34: 146–151
- Dröbler H (1981) *Häufigkeit und Verteilungsmuster der Kontaktallergene untersucht am Patientengut der Universitätshautklinik Düsseldorf in den Jahren 1977 und 1978* (Incidence and distribution of contact allergens studied in the collective of patients of the dermatological clinic of the university of Düsseldorf in the years 1977 and 1978) (German), Doctoral thesis, Medizinische Fakultät der Universität Düsseldorf, 60–62

- Eastin WC, Haseman JK, Mahler JF, Bucher JR (1998) The National Toxicology Program evaluation of genetically altered mice as predictive models for identifying carcinogens. *Toxicol Pathol* 26: 461–473
- ECB (European Chemicals Bureau) (2000) Resorcinol, *IUCLID dataset*, ECB, Ispra, Italy
- Enders F (1986) *Häufigkeiten positiver Epikutantestreaktionen an 12993 Patienten der Dermatologischen Klinik und Poliklinik der Universität München von 1977–1983* (Incidence of positive patch test results among 12993 patients of the dermatological clinic of the University of Munich in 1977 to 1983) (German), Doctoral thesis, Ludwig-Maximilians-Universität, München, 138, 139, 146, 148
- Erdmann S, Dickel H, Merk H-F (1997) Allergische Kontaktdermatitis durch Resorcin nach Anwendung von Solutio Castellani (Allergic contact dermatitis caused by resorcinol after use of Castellani's lotion) (German). *Z Hautkr* 72: 926–927
- Fisher AA (1982) Resorcinol – a rare sensitizer. *Cutis* 29: 331–332, 338
- Flickinger CW (1976) The benzenediols: catechol, resorcinol and hydroquinone – a review of the industrial toxicology and current industrial exposure limits. *Am Ind Hyg Assoc J* 37: 596–606
- Florin I, Rutberg L, Curvall M, Enzell CR (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. *Toxicology* 18: 219–232
- Fräki JE, Peltonen L, Hopsu-Havu VK (1979) Allergy to various components of topical preparations in stasis dermatitis and leg ulcer. *Contact Dermatitis* 5: 97–100
- Frosch PJ (1990) Aktuelle Kontaktallergene (Currently relevant contact allergens) (German). *Hautarzt* 41, Suppl 10: 129–133
- Frosch PJ, Burrows D, Camarasa JG, Dooms-Goossens A, Ducombs G, Lahti A, Menné T, Rycroft RJG, Shaw S, White IR, Wilkinson JD (1993) Allergic reactions to a hairdressers' series: results from 9 European centres. *Contact Dermatitis* 28: 180–183
- Gaitan E (1983) Endemic goiter in western Colombia. *Ecol Dis* 2: 295–308
- Gaitan E (1990) Goitrogens in food and water. *Annu Rev Nutr* 10: 21–39
- Gamble JF, McMichael AJ, Williams T, Battigelli M (1976) Respiratory function and symptoms: an environmental-epidemiological study of rubber workers exposed to a phenolformaldehyde type resin. *Am Ind Hyg Assoc J* 37: 499–513
- Gloor M, Thoma K, Fluhr J (2000) *Dermatologische Externtherapie* (Dermatological therapy with external agents) (German), Springer, Berlin, 15
- Gocke E, King M-T, Eckhardt K, Wild D (1981) Mutagenicity of cosmetics ingredients licensed by the European Communities. *Mutat Res* 90: 91–109
- Graham SG, Tisdall FF (1922) Poisoning from external use of resorcin. *Can Med Assoc J* 12: 730–732
- Guerra L, Bardazzi F, Tosti A (1992a) Contact dermatitis in hairdressers' clients. *Contact Dermatitis* 26: 108–111
- Guerra L, Tosti A, Bardazzi F, Pigatto P, Lisi P, Santucci B, Valsecchi R, Schena D, Angelini G, Sertoli A, Ayala F, Kokelj F (1992b) Contact dermatitis in hairdressers: the Italian experience. *Contact Dermatitis* 26: 101–107
- Haenelt M (1925) Ein Fall von perkutaner Resorzinvergiftung (A case of percutaneous resorcinol poisoning) (German). *Muench Med Wochenschr* 72: 386
- Hasegawa R, Ito N (1992) Liver medium-term bioassay in rats for screening of carcinogens and modifying factors in hepatocarcinogenesis. *Food Chem Toxicol* 30: 979–992
- Hasegawa R, Furukawa F, Toyoda K, Takahashi M, Hayashi Y, Hirose M, Ito N (1990) Inhibitory effects of antioxidants on *N*-bis(2-hydroxypropyl)nitrosamine-induced lung carcinogenesis in rats. *Jpn J Cancer Res* 81: 871–877
- Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E (1983) *Salmonella* mutagenicity test results for 250 chemicals. *Environ Mutagen, Suppl* 1: 3–142
- Hirose M, Inoue T, Asamoto M, Tagawa Y, Ito N (1986) Comparison of the effects of 13 phenolic compounds in induction of proliferative lesions of the forestomach and increase in the labelling indices of the glandular stomach and urinary bladder epithelium of Syrian golden hamsters. *Carcinogenesis* 7: 1285–1289

- Hirose M, Yamaguchi S, Fukushima S, Hasegawa R, Takahashi S, Ito N (1989) Promotion by dihydroxybenzene derivatives of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine-induced F344 rat forestomach and glandular stomach carcinogenesis. *Cancer Res* 49: 5143–5147
- Hoechst (1989) *Resorcin DS Hoechst, Prüfung auf sensibilisierende Eigenschaften an Pirbright-White-Meerschweinchen im Maximierungstest, Nr. 89.0483* (Resorcin DS Hoechst, testing for sensitizing properties in Pirbright-White guinea pigs in the maximization test, No. 89.0483) (German), unpublished report
- Holness DL, Nethercott JR (1990) Epicutaneous testing results in hairdressers. *Am J Contact Dermatitis* 1: 224–234
- Hossack DJN, Richardson JC (1977) Examination of the potential mutagenicity of hair dye constituents using the micronucleus test. *Experientia* 33: 377–378
- IVDK (Informationsverbund Dermatologischer Kliniken) (2001) *Auswertung der zwischen 1992 und 2000 vom IVDK erfassten Daten* (Analysis of the data collected by the IVDK between 1992 and 2000) (German), Göttingen, 8th June 2001
- Jansson T, Curvall M, Hedin A, Enzell CR (1986) *In vitro* studies of biological effects of cigarette smoke condensate. II. Induction of sister-chromatid exchanges in human lymphocytes by weakly acidic, semivolatile constituents. *Mutat Res* 169: 129–139
- Jarisch R, Sandor I (1978) Epicutanstandardtestung: Ergebnisse aus fünf Jahren und ihre Auswirkungen auf zukünftige Untersuchungen (Results of five years' standard patch tests and their effects on future testing) (German). *Z Hautkr* 53: 462–470
- Kalish RS, Wood JA (1995) Sensitization of mice to paraphenylenediamine and structurally-related compounds: adjuvant effects of vitamin A supplementation. *Contact Dermatitis* 33: 407–413
- Katin MJ, Teehan BP, Sigler MH, Schleifer CR, Gilgore GS (1977) Resorcinol-induced hypothyroidism in a patient on chronic hemodialysis. *Ann Intern Med* 86: 447–449
- Katsarou A, Koufou B, Takou K, Kalogeromitros D, Papanayiotou G, Vareltzidis A (1995) Patch test results in hairdressers with contact dermatitis in Greece (1985–1994). *Contact Dermatitis* 33: 347–348
- Kavlock RJ (1990) Structure-activity relationships in the developmental toxicity of substituted phenols: *in vivo* effects. *Teratology* 41: 43–59
- Kawanishi S, Inoue S, Kawanishi M (1989) Human DNA damage induced by 1,2,4-benzenetriol, a benzene metabolite. *Cancer Res* 49: 164–168
- Keil H (1962) Group reactions in contact dermatitis due to resorcinol. *Arch Dermatol* 86: 130–134
- Kim YC, Matthews HB (1987) Comparative metabolism and excretion of resorcinol in male and female F344 rats. *Fundam Appl Toxicol* 9: 409–414
- Kirchgessner M, He J, Windisch W (1999) Homeostatic adjustments of iodine metabolism and tissue iodine to widely varying iodine supply in <sup>125</sup>I labelled rats. *J Anim Physiol Anim Nutr* 82: 238–250
- Kligman AM (1966) The identification of contact allergens by human assay. III. The maximization test: a procedure for screening and rating contact sensitizers. *J Invest Dermatol* 47: 393–409
- Köhn R (1993) Allergisches Kontaktekzem durch Resorcinol nach Anwendung von *Solutio Castellani* (Allergic contact dermatitis after use of Castellani's lotion) (German). *Aktuel Dermatol* 19: 13–16
- Kurata Y, Fukushima S, Hasegawa R, Hirose M, Shibata M-A, Shirai T, Ito N (1990) Structure activity relations in promotion of rat urinary bladder carcinogenesis by phenolic antioxidants. *Jpn J Cancer Res* 81: 754–759
- Langeland T, Braathen LR (1987) Allergic contact dermatitis from resorcinol. *Contact Dermatitis* 17: 126
- Lloyd GK, Liggett MP, Kynoch SR, Davies RE (1977) Assessment of the acute toxicity and potential irritancy of hair dye constituents. *Food Cosmet Toxicol* 15: 607–610
- Lundberg P (Ed.) (1992) Scientific basis for Swedish occupational standards. Consensus report for resorcinol. *Arbete och Hälsa* 47: 16–20

- Lynch BS, Delzell E, Bechtel DB, Buchner BB (2001) Resorcinol: risk assessment with emphasis on potential for thyroidal effects. *Toxicologist* 60, Suppl: 434–435
- Marks Jr JG, West GW (1978) Allergic contact dermatitis to radiotherapy dye. *Contact Dermatitis* 4: 1–2
- Maronpot RR, Mitsumori K, Mann P, Takaoka M, Yamamoto S, Usui T, Okamiya H, Nishikawa S, Nomura T (2000) Interlaboratory comparison of the CB6F1-Tg rasH2 rapid carcinogenicity testing model. *Toxicology* 146: 149–159
- Maruyama H, Amanuma T, Nakae D, Tsutsumi M, Kondo S, Tsujiuchi T, Denda A, Konishi Y (1991) Effects of catechol and its analogs on pancreatic carcinogenesis initiated by *N*-nitrosobis(2-oxopropyl)amine in Syrian hamsters. *Carcinogenesis* 12: 1331–1334
- Massone L, Anonide A, Borghi S, Usiglio D (1993) Contact dermatitis of the eyelids from resorcinol in an ophthalmic ointment. *Contact Dermatitis* 28: 49
- McGregor DB, Brown A, Cattnach P, Edwards I, McBride D, Caspary WJ (1988) Responses of the L5178Y tk<sup>+</sup>/tk<sup>-</sup> mouse lymphoma cell forward mutation assay. II: 18 coded chemicals. *Environ Mol Mutagen* 11: 91–118
- Melby EC, Altmann NH (Eds) (1976) *Handbook of Laboratory Animal Science, Vol. III*, CRC Press, Boca Raton, FL, USA, 18–19
- Meneghini CL, Rantuccio F, Lomuto M (1971) Additives, vehicles and active drugs of topical medicaments as causes of delayed-type allergic dermatitis. *Dermatologica* 143: 137–147
- Merker PC, Yeung D, Doughty D, Nacht S (1982) Pharmacokinetics of resorcinol in the rat. *Res Commun Chem Pathol Pharmacol* 38: 367–388
- Miura T, Muraoka S, Fujimoto Y, Zhao K (2000) DNA damage induced by catechol derivatives. *Chem Biol Interact* 126: 125–136
- Miyata Y, Fukushima S, Hirose M, Masui T, Ito N (1985) Short-term screening of promoters of bladder carcinogenesis in *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine-initiated, unilaterally ureter-ligated rats. *Jpn J Cancer Res* 76: 828–834
- Mutoh M, Takahashi M, Fukuda K, Matsushima-Hibiya Y, Mutoh H, Sugimura T, Wakabayashi K (2000) Suppression of cyclooxygenase-2 promoter-dependent transcriptional activity in colon cancer cells by chemopreventive agents with a resorcin-type structure. *Carcinogenesis* 21: 959–963
- Nakagawa M, Kawai K, Kawai K (1992) Cross-sensitivity between resorcinol, resorcinol mono-benzoate and phenyl salicylate. *Contact Dermatitis* 27: 199–200
- Nakamura S-I, Oda Y, Shimada T, Oki I, Sugimoto K (1987) SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1535/pSK1002: examination with 151 chemicals. *Mutat Res* 192: 239–246
- Novák N, Kvičalová E (1985) Analysis of the results of epicutaneous tests at the dermatological clinic of faculty hospital in Prague 10 (Czech). *Cesk Dermatol* 60: 305–316
- NTP (National Toxicology Program) (1992) *Toxicology and carcinogenesis studies of resorcinol (CAS No. 108-46-3) in F344/N rats and B6C3F<sub>1</sub> mice (gavage studies)*. National Toxicology Program, Technical Report Series No. 403, NIH Publication No. 92-2858, National Institutes of Environmental Safety and Health, Research Triangle Park, NC, USA
- Okazaki S, Hoshiya T, Takahashi S, Futakuchi M, Saito K, Hirose M (1993) Modification of hepato- and renal carcinogenesis by catechol and its isomers in rats pretreated with *N*-ethyl-*N*-hydroxyethylnitrosamine. *Teratogen Carcinogen Mutagen* 13: 127–137
- Paschin YV, Bakhitova LM, Benthien TI (1986) Increased antimutagenic activity of simple substituted phenols mixed with the hindered phenolic antioxidant dibunol. *Food Chem Toxicol* 24: 881–883
- Pecegueiro M (1992) Contact dermatitis due to resorcinol in a radiotherapy dye. *Contact Dermatitis* 26: 273
- Peters K-P, Frosch PJ, Uter W, Schnuch A, Arnold R, Bahmer F, Brasch J, Diepgen TL, Elsner F, Fuchs T, Henseler T, Müller S, Przybilla B, Schulze-Dirks A, Sary A, Zimmermann J (1994) Typ IV-Allergien auf Friseurberufsstoffe (Type IV allergies to workplace substances encountered by hairdressers) (German). *Dermatosen Beruf Umwelt* 42: 50–57

- doPico GA, Rankin J, Chosy LW, Reddan WG, Barbee RA, Gee B, Dickie HA (1975) Respiratory tract disease from thermosetting resins. Study of an outbreak in rubber tire workers. *Ann Intern Med* 83: 177–184
- Probst GS, McMahon RE, Hill LE, Thompson CZ, Epp JK, Neal SB (1981) Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: a comparison with bacterial mutagenicity using 218 compounds. *Environ Mutagen* 3: 11–32
- Pschyrembel W (1994) *Klinisches Wörterbuch* (Clinical Dictionary) (German), Walter de Gruyter, Berlin, 1093
- Purchase IFH, Longstaff E, Ashby J, Styles JA, Anderson D, Lefevre PA, Westwood FR (1978) An evaluation of 6 short-term tests for detecting organic chemical carcinogens. *Br J Cancer* 37: 873–903
- Resorcinol Task Force (2000) *Resorcinol: toxicological review and risk assessment with emphasis on thyroidal effects*. Cantox Health Sciences International, Bridgewater, NJ, USA, Resorcinol Task Force, Bristol, UK
- Roberts MS, Anderson RA, Swarbrick J (1977) Permeability of human epidermis to phenolic compounds. *J Pharm Pharmacol* 29: 677–683
- Roberts FP, Wright AL, O'Hagan SA (1990) Hypothyroidism in textile workers. *J Soc Occup Med* 40: 153–156
- Rote Liste Service GmbH (Ed.) (2001) *Rote Liste® 2001*, ECV, Aulendorf
- Rudzki E, Kleniewska D (1970) The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 83: 543–545
- Sakano Y, Tsuyoshi T, Kobayashi Y, Andoh H, Masomoto Y (1985) The role of oxygen free-radicals in the mutagenesis of divalent phenols. *Mutat Res* 147: 272–273
- Samuel KC (1955) Experimental production of goiter in rats. With resorcinol and its derivatives. *Lab Invest* 4: 90–105
- Scheuer B, Rüther T, von Bülow V, Henseler T, Deing B, Denzer-Fürst S, Dreismann G, Eckstein L, Eggers B, Engelke H, Gärtner K, Hansen G, Hardung H, Heidbreder G, Hoffmann E, Kitzmann H, Kröger J, Mehnert I, Möhlenbeck F, Schlaak HE, Schmoll A, Schmoll M, Schröder I, Sipkova S, Sterry G, Trettel W, Walsdorfer U (1992) Häufige Kontaktallergene. Eine praxisorientierte Multicenterstudie (Common contact allergens. A practice-oriented multicentre study) (German). *Aktuel Dermatol* 18: 44–49
- Schubert H, Berova N, Hegyi E, Jirásek L, Kalenský J, Korossy S, Michailov P, Nebenführer L, Prater E, Rothe A, Rudzki E, Temesvári E, Ziegler V, Zschunke E (1982) Das allergische Kontaktekzem. Analyse einer Stichprobe in fünf sozialistischen Ländern Europas. 1. Mitteilung (Allergic contact dermatitis. A sample analysis from five socialist European countries. I) (German). *Dermatol Monatsschr* 168: 613–623
- Schulz R, Schwanitz G, Winterhoff H (1982) Untersuchungen zur mutagenen und klastogenen Wirkung von Resorcin (Studies of the mutagenic and clastogenic effects of resorcinol) (German). *Arzneim-Forschung* 32: 533–536
- Seffner W, Schiller F, Heinze R, Breng R (1995) Subchronic application of humic acids and associated compounds provokes histological changes of goitre in the rat. *Exp Toxicol Pathol* 47: 63–70
- Seiler JP (1977) Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens. Preliminary results in the validation of a novel short term test. *Mutat Res* 46: 305–310
- Serrano G, Fortea JM, Millan F, Botella R, Latasa JM (1992) Contact allergy to resorcinol in acne medications: report of three cases. *J Am Acad Dermatol* 26: 502–504
- Shahin MM, Bugaut A, Gilard P, Kalopissis G (1980) Studies on the mutagenicity of resorcinol and hydroxy-3-(p-amino)anilino-6,N-[(p-amino)phenol]benzoquinone-monoimine-1,4 in *Salmonella typhimurium*. *Mutat Res* 78: 213–218
- Shibata M-A, Yamada M, Hirose M, Asakawa E, Tatematsu M, Ito N (1990) Early proliferative responses of forestomach and glandular stomach of rats treated with five different phenolic antioxidants. *Carcinogenesis* 11: 425–429
- Stenbäck F (1977) Local and systemic effects of commonly used cutaneous agents: lifetime studies of 16 compounds in mice and rabbits. *Acta Pharmacol Toxicol* 41: 417–431

- Stenbäck F, Shubik P (1974) Lack of toxicity and carcinogenicity of some commonly used cutaneous agents. *Toxicol Appl Pharmacol* 30: 7–13
- Stich HF, Rosin MP, Wu CH, Powrie WD (1981) The action of transition metals on the genotoxicity of simple phenols, phenolic acids and cinnamic acids. *Cancer Lett* 14: 251–260
- Tarvainen K (1995) Analysis of patients with allergic patch test reactions to a plastics and glues series. *Contact Dermatitis* 32: 346–351
- Thomas AE, Gisburn MA (1961) Exogenous ochronosis and myxoedema from resorcinol. *Br J Dermatol* 73: 378–381
- Tush GM, Kuhn RJ (1996) Methemoglobinemia induced by an over-the-counter medication. *Ann Pharmacother* 30: 1251–1254
- Van Duuren BL, Goldschmidt BM (1976) Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. *J Natl Cancer Inst* 56: 1237–1242
- Vilaplana J, Romaguera C, Grimalt F (1991) Contact dermatitis from resorcinol in a hair dye. *Contact Dermatitis* 24: 151–152
- Waddell MM, Finn OA (1981) Sensitivity to resorcin. *Contact Dermatitis* 7: 216
- Walles SAS (1992) Mechanisms of DNA damage induced in rat hepatocytes by quinones. *Cancer Lett* 63: 47–52
- Wella (1982a) *Resorcin: oral (gavage) teratology study in the rat*. Hazelton Deutschland, Project No. 213/5, Wella, Darmstadt, unpublished report
- Wella (1982b) *Resorcin: oral (gavage) teratology study in the New Zealand White rabbit*. Hazelton Deutschland, Project No. 213/1, Report No. 60–213/1, Wella, Darmstadt, unpublished report
- West RR, Stafford DA (1997) Occupational exposures and haematological abnormalities among ordnance factory workers: a case control study. *Leuk Res* 21: 675–680
- Wild D, King M-T, Eckhardt K, Gocke E (1981) Mutagenic activity of aminophenols and diphenols, and relations with chemical structure. *Mutat Res* 85: 456
- Windhager K, Plewig G (1977) Wirkung von Schälmitteln (Resorcin, kristalliner Schwefel, Salicylsäure) auf Meerschweinchenepidermis (Effects of desquamative agents (resorcinol, crystalline sulfur, salicylic acid) on guinea pig epidermis) (German). *Arch Dermatol Res* 259: 187–198
- Woodard GDL (1951) *Initial submission: report on the toxicity, mechanism of action and metabolism of hydroquinone*, Doctoral thesis, George Washington University, Washington DC, USA
- Wüthrich B, Zabrodsky S, Storck H (1970) Perkutane Vergiftungen durch Resorcin, Salicylsäure und weiße Präcipitatsalbe (Poisoning caused by percutaneous application of resorcinol, salicylic acid and white ointment) (German). *Pharm Acta Helv* 45: 453–460
- Yamada K, Shirahata S, Murakami H, Nishiyama K, Shinohara K, Omura H (1985) DNA breakage by phenyl compounds. *Agric Biol Chem* 49: 1423–1428
- Yamaguchi S, Hirose M, Fukushima S, Hasegawa R, Ito N (1989) Modification by catechol and resorcinol of upper digestive tract carcinogenesis in rats treated with methyl-*N*-amyl nitrosamine. *Cancer Res* 49: 6015–6018
- Yeung D, Kantor S, Nacht S, Gans EH (1983) Percutaneous absorption, blood levels, and urinary excretion of resorcinol applied topically in humans. *Int J Dermatol* 22: 321–324

completed 28.02.2002