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# TOXICOLOGICAL EVALUATIONS

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**TOXICOLOGICAL EVALUATION**

last updated: 02/2005

# 2,4-Dimethyl-phenol

**No. 137**

CAS No. 105-67-9

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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# 2,4-Dimethylphenol

In addition to the present TOXICOLOGICAL EVALUATION, there are also TOXICOLOGICAL EVALUATIONS on the isomers 2,6-dimethylphenol (No. 138) and 3,5-dimethylphenol (No. 139). These can be consulted for comparison.

## 1 Summary and assessment

The results from single-dose and multiple-dose studies show that 2,4-dimethylphenol is absorbed by the body upon dermal exposure or intragastric administration to experimental animals. Permeation of 2,4-dimethylphenol through the abdominal skin of mice, as determined in vitro by means of a two-compartment diffusion cell, is relatively rapid, taking 10 minutes, and the permeability coefficient is 110 x $10^3$ cm/hour. Once in the body, 2,4-dimethylphenol is distributed very rapidly in the tissues and organs and subsequently undergoes rapid and almost complete metabolism to glucuronide and sulphate conjugates. In rats, 2,4-dimethylphenol levels detected in the liver and brain immediately upon intravenous injection are higher than in the blood. The highest concentration is found in the brain. At 30 minutes, levels of 2,4-dimethylphenol are low and at one hour the compound is no longer detectable in the blood plasma, liver or fat. Brain levels of 2,4-dimethylphenol are still 10% of those measured 5 minutes after administration. After only 30 minutes, the administered 2,4-dimethylphenol has been almost completely metabolically converted to water-soluble and renally excretable (glucuronide and sulphate) conjugates and as such undergoes rapid excretion. Accumulation of 2,4-dimethylphenol in the body is unlikely. The finding that 2,4-dimethylphenol is essentially excreted in the urine as the glucuronide and sulphate conjugates was also demonstrated in a rabbit study. Upon oral administration, only 1% of the 2,4-dimethylphenol dose is excreted as unchanged compound, whereas 64% is excreted as the glucuronide conjugate and 13% as the sulphate conjugate. Further treatment of urine samples yields indications as to the presence of small amounts of phenolic and other metabolites, but their structures remain unelucidated.

The poorly documented and incomplete findings on the acute toxicity of 2,4-dimethylphenol demonstrate that the chemical is to be considered

harmful. The oral $LD_{50}$ values for the rat and the mouse are given as 3200 mg/kg body weight and 809 mg/kg body weight, respectively. Reportedly, the dermal $LD_{50}$ for the rat is 1040 mg/kg body weight while intraperitoneal $LD_{50}$ values for the mouse are between 100 and 182 mg/kg body weight. There is no known $LC_{50}$ for inhalation exposure. Clinical signs of intoxication initially consist in CNS impairments and severe signs of irritation. Death results from respiratory arrest. When injected intravenously as a solution in aqueous Cremophor, 2,4-dimethylphenol produces an anaesthetic effect in mice. The $LD_{50}$ has been found to be 100 to 120 mg/kg body weight. 2,4-Dimethylphenol has also been found to be of low toxicity following repeated oral administration. A dose of 1000 mg/kg body weight gives rise to slight to moderate salivation, rough coat and lethargy from day 4 of treatment. When treated at dose levels of 60, 120, 600 or 1200 mg/kg body weight for 10 days, rats exhibit dose-dependent lesions of the gastric mucosa in all dose groups. At the top dose level, all animals die. No further relevant effects of 2,4-dimethylphenol treatment are observed. In a subacute toxicity study conducted in accordance with OECD guideline No. 407, 4-week daily oral administration of 2,4-dimethylphenol to rats at dose levels of 30, 100 or 300 mg/kg body weight resulted in statistically significant increases in creatinine levels in male rats from the highest dose group as well as causing increased absolute and relative weights of the testes and epididymides in the absence of corresponding histopathological changes. Females treated at the highest dose level exhibited increased absolute liver weights together with sinusoidal dilatation and congestion, and those treated at 100 mg/kg body weight and above had increased absolute kidney weights without any corresponding histopathological changes. The *no-effect level* was 30 mg/kg body weight.

It appears from the very incomplete skin irritancy data available for 2,4-dimethylphenol that the chemical is corrosive to the skin of the rat and the mouse. Tests on guinea pig skin have shown 5% in Lutrol E 400 to be the maximum non-irritant concentration.

A clear skin-sensitising effect was noted for 2,4-dimethylphenol when investigated in guinea pigs in the Magnusson and Kligman maximisation test conducted in accordance with OECD guideline for testing, No. 406. Upon intradermal induction with a 0.5-percent solution of 2,4-dimethylphenol in physiological saline solution and percutaneous induction with a 25-percent solution of 2,4-dimethylphenol in Lutrol 400, the first challenge with a 5-per-

cent solution of 2,4-dimethylphenol in Lutrol 400 caused allergic reactions in 11 out of 20 test animals. Following a second challenge with the same 2,4-dimethylphenol solution one week later, 8 out of 20 animals showed a positive reaction. Based on a further study, it is suspected that 2,4-dimethylphenol is also capable of allergic cross-reactions with 2-methylol phenol.

The *no observed adverse effect level* for 3-month subchronic oral administration to rats has been given as 60 mg/kg body weight. Dose levels of 180 mg/kg body weight and above primarily led to inflammatory lesions in the forestomach that were dose- and concentration-dependent. Again, no further marked systemic toxicity was observed at the administered 2,4-dimethylphenol dose levels of 60, 180 and 540 mg/kg body weight. However, due to the strength of the 2,4-dimethylphenol suspension administered, there were deaths in the highest dose group so that the top concentration had to be diluted to half its original strength. Repeated exposure of mice to 2,4-dimethylphenol vapours at a concentration level of 23 mg/m³ for 2 hours/day for one month only caused a slight decrease in body weight gain but no other functional or morphological effects. In a 90-day study in mice, 2,4-dimethylphenol was administered by gavage at dose levels of 5, 50 or 250 mg/kg body weight/day. Only the top dose level caused treatment-related, statistically significant haematological changes in the females (reduced mean corpuscular volume and reduced mean corpuscular haemoglobin concentration) and clinical signs of toxicity (lethargy, prostration and ataxia) in both sexes, but these occurred only after 6 weeks of treatment. Treatment at dose levels of up to 250 mg/kg body weight/day did not affect body weight gain, food consumption or organ weights. Ophthalmological, macroscopic and histopathological examinations were also without abnormal findings. The *no observed adverse effect level* (NOAEL) was 50 mg/kg body weight and the *low observed adverse effect level* (LOAEL) was 250 mg/kg body weight.

The available studies do not demonstrate genotoxic potential for 2,4-dimethylphenol, either in vitro or in vivo. Various Salmonella/microsome assays have given negative results both with and without metabolic activation, a test for sister chromatid exchange in human lymphocytes was negative and a mouse micronucleus test that was conducted in accordance with OECD guideline No. 474 failed to demonstrate any clastogenic or spindle poison

effects. Based on these data, 2,4-dimethylphenol is to be considered non-mutagenic.

The available carcinogenicity studies on 2,4-dimethylphenol involved the application of 2.5 and 5 mg/animal to the skin of mice for 28 and 39 weeks, respectively. They are inadequate (insufficient numbers of animals, lack of data on historical controls in the very tumour-susceptible strain of mouse used, study duration too short, diagnosis primarily only by macroscopic examination and use of benzene as a solvent) and of limited use for assessment of the possible carcinogenic potential of 2,4-dimethylphenol, despite the finding that the incidence of papillomas and carcinomas of the skin increased in a dose-dependent manner under 2,4-dimethylphenol treatment. The same applies to a dermal promotion study in mice with DMBA as the initiator. The results of these studies support neither the conclusion that 2,4-dimethylphenol is carcinogenic nor the conclusion that it is not. However, they do give an indication as to a possible carcinogenic or tumour-promoting action following dermal exposure.

Based on the results obtained in different in-vitro systems, 2,4-dimethylphenol possesses marked cytotoxicity. In a screening study employing four short-term assays (for cell growth, oxidative metabolism, cell membrane damage and ciliotoxicity in isolated tracheal rings from chicken embryos) 2,4-dimethylphenol proved to be highly active compared with a further 304 chemicals tested in that study. In a number of mammalian cell cultures, studies on the effects of 2,4-dimethylphenol on cell viability, intracellular adenosine triphosphate content and inhibition of protein and DNA synthesis have shown the chemical to be moderately cytotoxic.

There are indications from studies in patients with contact allergies to methylol phenols that 2,4-dimethylphenol exhibits contact-allergic cross-reactivity with methylol phenols. Olfactory and taste threshold concentrations for 2,4-dimethylphenol in aqueous solution have been ascertained as 400 ppb (400 µg/l) and 500 ppb (500 µg/l), respectively, in volunteers.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) has listed 2,4-dimethylphenol in the “Yellow Pages” of the List of MAK and BAT Values 2004 on the suggestion of BG Chemie in order that a MAK value be established for the chemical and that it be classified according to its sensitising potential.

## 2 Name of substance

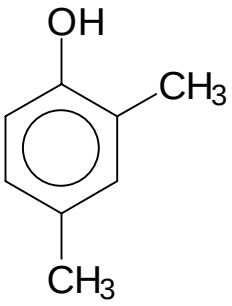
| | | |
|---|---|---|
| 2.1 | Usual name | 2,4-Dimethylphenol |
| 2.2 | IUPAC name | 2,4-Dimethylphenol |
| 2.3 | CAS No. | 105-67-9 |
| 2.4 | EINECS No. | 203-321-6 |

## 3 Synonyms, common and trade names

Benzene, 2,4-dimethyl-1-hydroxy-
2,4-Dimethyl-1-hydroxybenzene
4,6-Dimethylphenol
2,4-DMP
1-Hydroxy-2,4-dimethylbenzene
1-Hydroxy-2,4-dimethylbenzol
4-Hydroxy-1,3-dimethylbenzol
4-Hydroxy-m-xylene
2,4-Hydroxyxylol
4-Hydroxy-m-xylol
Phenol, 2,4-dimethyl-
2,4-Xylenol
asym.-m-Xylenol
m-Xylenol
1,3,4-Xylenol

## 4 Structural and molecular formulae

4.1 Structural formula




4.2 Molecular formula $C_8H_{10}O$

## 5 Physical and chemical properties

| | | | |
|---|---|---|---|
| 5.1 | Molecular mass, g/mol | 122.17 | |
| 5.2 | Melting point, °C | 24.5 | (Lide and Frederikse, 1997) |
| | | 24.54 | (Fiege, 2001) |
| | | 26 | (Falbe and Regitz, 1997) |
| 5.3 | Boiling point, °C | 137.12 (at 100 hPa) | (Fiege, 2001) |
| | | 210.9 | (Lide and Frederikse, 1997) |
| | | 210.93 (at 1013 hPa) | (Fiege, 2001) |
| | | 211 | (Falbe and Regitz, 1997) |
| 5.4 | Vapour pressure, hPa | < 0.1 (at 20 °C) | (UK, 1984) |
| 5.5 | Density, g/cm³ | 0.9650 (at 20 °C) | (Lide and Frederikse, 1997) |
| | | 1.0160 (at 25 °C) | (Fiege, 2001) |
| 5.6 | Solubility in water | 0.61% (at 25 °C) | (Fiege, 2001) |
| 5.7 | Solubility in organic solvents | Soluble in ethanol, acetone and other solvents | (Fiege, 2001) |
| | | Soluble in alcohol | (Falbe and Regitz, 1997) |
| 5.8 | Solubility in fat | No information available | |
| 5.9 | pH value | No information available | |
| 5.10 | Conversion factor | 1 ml/m³ (ppm) ≙ 4.99 mg/m³<br>1 mg/m³ ≙ 0.20 ml/m³ (ppm)<br>(at 1013 hPa and 25 °C) | |

## 6 Uses

As a solvent for electrical wire enamels and as a disinfectant; in the manufacture of trixylenyl phosphates for heat-resistant hydraulic fluids, of xylenol-formaldehyde resins and of textile auxiliaries; intermediate in the manufacture of antioxidants and chemical syntheses (Fiege, 2001).

# 7 Experimental results

## 7.1 Toxicokinetics and metabolism

The results from single-dose and multiple-dose studies show that 2,4-dimethylphenol is absorbed by the body upon dermal exposure or intragastric administration to experimental animals.

Permeation through the abdominal skin of hairless mice (SKH-hr-1 strain) aged 60 to 100 days was studied in vitro by means of a two-compartment diffusion cell. The skin sections were mounted between the half-cells of the diffusion cell, thus separating the two compartments which were filled with buffer (donor pH 6.31, receiver pH 6.2). Upon addition of 2,4-dimethylphenol at a concentration of 500 µg/ml to the medium in the chamber facing the skin surface (donor chamber), penetration of the chemical through the skin was determined by measuring its concentration in the receiver chamber with the aid of spectrophotometry at intervals. The permeability coefficient at steady state was calculated as 110 x $10^3$ cm/hour for 2,4-dimethylphenol. The average delay in permeation through the skin (lag time) was 10.1 minutes, i.e. permeation was relatively rapid (Huq et al., 1986).

A series of studies were conducted in male Sprague-Dawley rats (weighing 150 to 200 g) in order to investigate the metabolism and tissue distribution of 2,4-dimethylphenol upon administration. First, a group of 3 rats received an infusion of the chemical (infusion medium not specified) at a rate of 17 mg/hour into the tail vein for 6 hours by means of an infusion pump. Blood samples were subsequently withdrawn via cardiac puncture, the animals were then sacrificed and the brain, the liver and fat were removed. The concentration of 2,4-dimethylphenol was determined by gas chromatography in the blood plasma and the three types of tissue obtained. The experiments were carried out three times. The mean concentration levels of 2,4-dimethylphenol as obtained from the 9 animals used in total were 2.14, 6.45, 2.66 and 4.46 µg/g in plasma, brain, liver and fat, respectively. The data demonstrated that 2,4-dimethylphenol was widely distributed in the body and that following 6-hour infusion the concentrations found in the analysed tissues, particularly in the brain, were higher than in the blood. In further studies, groups of 3 rats were given single intravenous injections of 2,4-dimethylphenol at 30 mg/kg body weight into the tail vein. At 5, 10, 20 or 30 minutes, blood samples were collected by cardiac puncture from one

group per time interval. The animals were subsequently sacrificed and the brain, the liver and fat removed for analysis. The blood plasma and the three types of tissue were analysed by gas chromatography for unchanged 2,4-dimethylphenol and, subsequent to hydrolysis, for glucuronide conjugates and total conjugates of the compound. The results showed that plasma levels of 2,4-dimethylphenol, after peak levels at 5 minutes, declined very rapidly within 30 minutes, with levels having dropped below the detection limit of 0.1 µg/ml extract solution at one hour. A similar time course was observed in liver and fat tissue. Brain showed a markedly slower decline in 2,4-dimethylphenol concentration levels so that at one hour about 10% of the initial concentration was still observed. At 30 minutes after administration, the level of total conjugated 2,4-dimethylphenol was about 70 times higher than the level of unchanged compound. About half the total conjugate was accounted for by the glucuronide, while the other half presumably represented the sulphate. An additional study was carried out, in which rats were administered the same dose of 2,4-dimethylphenol by intraperitoneal injection under otherwise identical conditions as in the intravenous study, except that investigation was limited to analysis of blood plasma at 30 minutes after dosing. The results were comparable. Once absorbed into the bloodstream, 2,4-dimethylphenol thus underwent very rapid distribution throughout the body and very rapid and complete metabolism, the predominant metabolites being glucuronide and sulphate conjugates. On the basis of these findings, the investigators considered the probability of 2,4-dimethylphenol accumulation in tissues to be minimal (Kaka et al., 1982).

A study was conducted in rabbits (weighing 2 to 3 kg) in order to investigate the form in which the animals excreted 2,4-dimethylphenol in the urine upon oral administration by gavage. The administered dose was 850 mg/kg body weight. No details were given as to the frequency and times of treatment or the times of urine collection. Reference was made only to average daily and weekly excretion. Determinations were carried out for the excreted quantities of unchanged 2,4-dimethylphenol and of glucuronide and sulphate conjugates. Whereas the 2,4-dimethylphenol portion excreted in the urine was very small, on average 1% of the administered dose, the average urinary recoveries of the glucuronide and sulphate conjugates of 2,4-dimethylphenol were 64% and 13%, respectively. Further treatment of urine samples and analysis of the extracts by paper chromatography yielded indications as to the presence of small amounts of phenolic and other

metabolites of 2,4-dimethylphenol, but these were not further investigated. The data demonstrated that the major metabolic route for 2,4-dimethylphenol in the body was glucuronide or sulphate conjugation, which permitted excretion in the urine (Bray et al., 1950).

## 7.2 Acute and subacute toxicity

The acute toxicity data for 2,4-dimethylphenol are summarised in Table 1. Based on the data presented below, the chemical is to be considered harmful.

**Table 1. Acute toxicity of 2,4-dimethylphenol**

| Species, strain, sex[1] | Route | Dose (mg/kg body weight) | Effects | Observation period | References |
|---|---|---|---|---|---|
| Rat | oral | 3200 | $LD_{50}$; apathy, lying on the side, respiratory arrest (no further details) | no data | Uschdavini et al., 1974, 1979 |
| Mouse | oral | 809 | $LD_{50}$; apathy, lying on the side, respiratory arrest | no data | Uschdavini et al., 1974, 1979 |
| Mouse, NMRI, male and female | oral | 1000 and 1250 | no deaths; curved position and reeling at 1000 mg/kg body weight; deaths at 1250 mg/kg body weight | no data | BASF, 1998 b |
| Rat | dermal | 1040 | $LD_{50}$ | no data | Uschdavini et al., 1974, 1979 |
| Rat | dermal | 2000 | all animals died; no animal died when the chemical was applied for 5 minutes and the washed off with aqueous ethanol for 10 minutes; when the chemical was washed off with glycerine or sunflower oil mortality was 1/5 in each case | no data | Uschdavini et al., 1979 |
| Rat | inhalation | 30 mg/m³ | no deaths; mucosal irritation, threshold concentration for changes in CNS function (performance in the maze test) | no data | Uschdavini et al., 1979 |
| Rat | inhalation | vapours and aerosols generated by heating | lethal outcome following absorption also via the skin | no data | Uschdavini et al., 1979 |
| Mouse | intraperitoneal | 182 in dimethyl sulphoxide | $LD_{50}$ | 24 hours | Biagi et al., 1975 |
| Mouse, Alderley Park strain | intravenous within 20 seconds | 100–120 (administered as a 10% aqueous Cremophor solution) | $LD_{50}$; median hypnotic dose 30 to 40 mg/kg body weight | 10 days | James and Glen, 1980 |

[1] where specified

Clinical signs of intoxication initially consisted in effects on CNS function and severe signs of irritation. Death resulted from respiratory arrest. The toxicity of 2,4-dimethylphenol following oral or dermal administration depended on whether the chemical was administered undiluted or as a solution or suspension and what solvent or suspension agent was used (Uschdavini et al., 1974). Table 1 also gives details, where known, of the dosage forms and doses administered. Overall, the poorly documented and incomplete findings none the less provide a workable estimate as to the magnitude of the acute toxicity of 2,4-dimethylphenol, according to which the chemical is to be considered harmful.

Groups of 10 male and 10 female Sprague-Dawley rats (initial age 80 days) received daily doses of 2,4-dimethylphenol (99.2 percent) by gavage at levels of 0 (controls), 60, 120, 600 or 1200 mg/kg body weight in corn oil for 10 consecutive days. Following 1200 mg/kg body weight, all animals died with severe irritation of the gastric mucosa. There was no mortality in other dose groups. Food and water consumption was not significantly affected. The female rats in the 600 mg/kg dose group exhibited elevated values for white blood cell count and haemoglobin. Clinical chemistry analyses revealed elevated serum glucose and cholesterol levels in the female rats of the 600 mg/kg group while aspartate aminotransferase levels were decreased in animals from the dose groups treated at 600 and 60 mg/kg body weight. The males in the 120 and 600 mg/kg dose groups exhibited a decrease in serum calcium while those in the 600 mg/kg dose group had decreased aspartate aminotransferase levels and mildly increased cholesterol levels. Necropsy and histopathology revealed an increase in relative liver weights without any histopathological correlates in female rats from the 600 mg/kg dose group, and dose-dependent mucosal lesions in the forestomach, including epithelial hypertrophy, hyperkeratosis and vacuolar degeneration, were noted in both sexes at all dose levels. The findings were considered to be linked with the local irritant effect of 2,4-dimethylphenol (Daniel et al., 1993).

In a dose-finding study, groups of 3 male and 3 female Sprague-Dawley rats were given 7 days of daily treatment with 2,4-dimethylphenol at dose levels of 0 (controls), 250, 500 or 1000 mg/kg body weight, administered by gavage as a suspension in corn oil. The top dose group exhibited salivation, rough coat and lethargy from day 4. The effects were generally slight to moderate. For the intermediate dose group, slight salivation was obser-

ved from day 4. The low dose group showed no treatment-related effects. None of the treated animals exhibited any notable changes in body weights or food consumption. There were no macroscopic organ changes noted during necropsy of treated rats and organ weights were comparable with those of the controls (HRC, 1993).

The subacute oral toxicity of 2,4-dimethylphenol was investigated in accordance with OECD guideline No. 407. Groups of 5 male and 5 female Sprague-Dawley rats (Charles River Crl:CD SD BR VAF Plus strain, mean initial weights 149.5 and 138.3 g, respectively) received by gavage daily doses of 2,4-dimethylphenol (99.6 percent) at levels of 0 (controls), 30, 100 or 300 mg/kg body weight for 4 weeks as a suspension in corn oil. No deaths occurred. Body weights and food and water consumption did not differ significantly from controls. The rats from the top dose group displayed increased salivation and wet fur. The 100 mg/kg dose caused the same clinical signs, but to a lesser degree and less frequently. There were no treatment-related haematological changes in any of the groups. Clinical chemistry tests revealed a statistically significant increase in creatinine levels for male rats from the 300 mg/kg group and a nonsignificant increase in alkaline phosphatase activity. All other parameters were within normal ranges. Necropsy revealed significant increases in the absolute and relative weights of the testes and epididymides in the males at the top dose level (300 mg/kg body weight). The female rats from that group were noted to have statistically significant increases in relative liver weights while females from the top and intermediate dose groups (given 300 and 100 mg/kg body weight, respectively) had significantly increased relative kidney weights. There were no macroscopic changes. Microscopic examination revealed sinusoidal dilatation and congestion of the liver in rats dosed at 300 mg/kg body weight. The testes and epididymides were without abnormal histopathological findings in the male rats from all three dose groups. The kidneys of the female rats in the 300 and 100 mg/kg dose groups were also without treatment-related histopathological findings. The other organs showed no treatment-related histopathological changes. All effects observed upon treatment with 2,4-dimethylphenol were considered by the investigators to be of no toxicological importance. The *no-effect level* was thus 30 mg/kg body weight/day (HRC, 1993).

Repeated inhalation exposure of mice to 2,4-dimethylphenol vapours at concentration levels of 23 mg/m³ for 2 hours/day for one month caused a

slight decrease in body weight gain. Functional and morphological parameters, metabolism and body temperature, spontaneous motor activity, peripheral blood and internal organs weights remained unchanged (no further details; Uschdavini et al., 1979).

## 7.3 Skin and mucous membrane effects

Undiluted 2,4-dimethylphenol caused necrosis upon application to the skin of rats (no further details; Uschdavini et al., 1974).

As a preliminary test to a skin sensitisation study, groups of 4 guinea pigs (Pirbright White Dunkin Hartley Crl:(HA)BR[SPF]) had various concentrations of 2,4-dimethylphenol applied to the clipped dorsal skin as solutions in Lutrol E 400 in order to determine a non-irritant concentration. The 2,4-dimethylphenol solutions were applied by means of strips of filter paper sized 2 cm x 2 cm and left on the skin for 24 hours under occlusive cover. Treatment was repeated after 2 days. The maximum non-irritant concentration was 5% and the minimum irritant concentration was 10%. The 25% concentration caused slight to well-defined skin reactions (BASF, 1998 a).

## 7.4 Sensitisation

The skin-sensitising potential of 2,4-dimethylphenol was investigated in guinea pigs in the Magnusson and Kligman maximisation test conducted in accordance with OECD guideline for testing, No. 406. The test group comprised 20 guinea pigs (Pirbright White Dunkin Hartley Crl:(HA)BR[SPF] strain, weighing 322 to 399 g), while the two control groups each comprised 10 guinea pigs. Intradermal induction with a solution of Freund's adjuvant in physiological saline solution containing 0.5% 2,4-dimethylphenol (99.5% pure) caused swelling and moderate erythema at the application site. The two control groups were treated with Freund's adjuvant solution which did not contain 2,4-dimethylphenol. One week later, percutaneous induction was carried out using a 25-percent solution of 2,4-dimethylphenol in Lutrol E 400. The controls were treated with Lutrol alone. The induction with 2,4-dimethylphenol gave rise to swelling and necrotic skin changes. Fourteen days later, the animals in the test group and in one control group had a 5-percent solution of 2,4-dimethylphenol in Lutrol E 400 applied to the skin in order to elicit skin-sensitising effects. The second control group

was treated with Lutrol alone. Of the 20 animals in the test group, 11 showed a positive allergic reaction. A second challenge was carried out one week later, when all animals including the two controls were treated with a 5% solution of 2,4-dimethylphenol in Lutrol. Of the 20 animals, 8 were positive. None of the controls were observed to develop an allergic reaction. The 5-percent solution of 2,4-dimethylphenol was tolerated without any effects. 2,4-Dimethylphenol thus showed a clear skin sensitisation potential in the test as conducted (BASF, 1998 a).

In the context of a skin sensitisation study of 2-methylol phenol (o-hydroxybenzylalcohol), 4-methylol phenol (p-hydroxybenzyl alcohol) and 2,4,6-trimethylol phenol a number of structural congeners, including 2,4-dimethylphenol, were tested for cross-reactions with the three principal chemicals investigated in the study. Groups of 24 guinea pigs (Dunkin Hartley strain, weighing 300 to 400 g) were studied in the maximisation test according to Magnusson and Kligman. Intradermal induction was performed with a 5-percent solution of 2-methylol phenol or 4-methylol phenol or with a 7.4-percent solution of 2,4,6-trimethylol phenol. Percutaneous induction was performed with a 25-percent solution of 2-methylol phenol or 4-methylol phenol or with a 37.1-percent solution of 2,4,6-trimethylol phenol. The first challenge was carried out 2 weeks later by means of a 15-percent solution of 2-methylol phenol or 4-methylol phenol or a 22.3-percent solution of 2,4,6-trimethylol phenol. Marked allergic skin reactions were noted in 20 out of 24 animals in the 2-methylol phenol group and in 19 out of 24 animals in the 4-methylol phenol group. Nine out of 24 animals in the group treated with 2,4,6-trimethylol phenol also showed a positive reaction. At rechallenge one week later, all 24 animals were again treated with the corresponding principal test compound, and 4 animals each had one of the compounds to be tested for cross-reactivity applied to the untreated side. 2,4-Dimethylphenol was administered as a 14.8-percent solution in ethanol (99.5%). 2-Methylol phenol gave a positive reaction in 13 out of 24 animals. When 2,4-dimethylphenol was additionally applied, 12 out of 24 animals showed positive allergic reactions at the site of application. However, 4 of the 12 controls also showed a positive reaction to both 2-methylol phenol and 2,4-dimethylphenol so that the result was not significant. The investigators evaluated the result as a possible cross-reaction between 2-methylol phenol and 2,4-dimethylphenol. No such effect was demonstrated with 4-methylol phenol or 2,4,6-trimethylol phenol (Bruze, 1986).

## 7.5 Subchronic and chronic toxicity

Groups of 10 male and 10 female Sprague-Dawley rats (initial age 80 days) received daily doses of 2,4-dimethylphenol (99.2 percent) by gavage at levels of 0 (controls), 60, 180 or 540 mg/kg body weight in corn oil for 90 consecutive days. In the top dose group, 6 of 10 male rats and all female rats died after 5 days with burns to the oesophagus and stomach. Therefore, 6 male and 6 female rats were added to this group as replacements, and the concentration of 2,4-dimethylphenol was halved by increasing the volume administered. By the end of the study, several of the additional rats in the high dose group had died so that only 3 female and 7 male rats survived. The animals in the other dose groups showed no significant clinical signs of toxicity. At the end of the study, there were statistically significant reductions in body weight gain in the males in the top dose group and the females in the intermediate dose group. There were no biologically significant changes in haematology parameters. Clinical chemistry analyses revealed statistically significant decreases in creatinine levels and increases in cholesterol levels in both sexes in the top dose group, with elevated triglycerides and reduced aspartate aminotransferase activities in the male rats in this group. At necropsy, there were some changes in organ weights, but these showed no uniform trend and no dose-dependency. Histopathology revealed hyperplasia and hyperkeratosis of the forestomach in all surviving male rats from the 540 and 180 mg/kg groups. The same findings were evident in the surviving female rats in the 540 mg/kg group while 6 out of 10 in the 180 mg/kg group showed epithelial hyperplasia. Various changes in the liver, heart and kidneys in the high dose group corresponded with those seen in the controls and were therefore considered not to be treatment-related. Histological findings in the reproductive organs were not reported. A *no observed adverse effect level* (NOAEL) of 60 mg/kg body weight/day was given (Daniel et al., 1993).

Groups of 30 male and 30 female albino mice received 2,4-dimethylphenol dissolved in corn oil at dose levels of 5, 50 or 250 mg/kg body weight by gavage daily for 90 days. One control group remained untreated while a second control group received pure corn oil. The study assessed mortality, clinical signs of toxicity, body weight, food consumption, various organ weights, histopathological examination and haematological and clinical chemistry parameters. The eyes were examined in addition. Although 15 deaths occurred during the study (mostly due to dosing errors), only the

death of one animal, which had received 2,4-dimethylphenol at 5 mg/kg body weight and died during the first 30 days of treatment, was considered by the investigators to have been possibly treatment-related and caused by the test substance. In respect of body weight, body weight development, food consumption and ophthalmological examinations, all treated animals showed no significant differences in comparison with the controls. Clinical signs of toxicity (lethargy, prostration, ataxia and squinting) were observed in both sexes but only in the highest dose group and after treatment week 6. Statistically significant haematology changes included lower mean corpuscular volume and mean corpuscular haemoglobin concentration in females at the end of treatment. At the interim sacrifice, the blood urea nitrogen levels for females in the intermediate and high dose groups were significantly lower than the controls, while at the end of treatment, the blood urea nitrogen levels for females in the intermediate dose group were significantly increased. For the low-dose males at the interim sacrifice, blood cholesterol levels were significantly increased. No significant differences between treated and untreated animals were noted at necropsy or in respect of organ weight determination and histopathological findings, except that females from the lowest dose group showed increased adrenal weights. The *no observed adverse effect level* (NOAEL) for 2,4-dimethylphenol as given by the investigators for the study described above was 50 mg/kg body weight. The highest dose, 250 mg/kg body weight, was given as the *low observed adverse effect level* (LOAEL; no further details; Dynamac Corporation, 1989).

## 7.6 Genotoxicity

### 7.6.1 In vitro

The available data on the in-vitro genotoxicity of 2,4-dimethylphenol in bacteria are summarised in Table 2. The Salmonella/microsome assays referred to below were all negative and there were no indications that 2,4-dimethylphenol had any genotoxic potential. A test for sister chromatid exchange (SCE) induction, which was carried out with human lymphocyte suspensions treated with 0.1 mM 2,4-dimethylphenol (equivalent to 12.2 µg/ml, 98.6% pure), yielded a negative result (Jansson et al., 1986).

| Table 2. In-vitro genotoxicity tests with 2,4-dimethylphenol in bacteria | | | | | |
|---|---|---|---|---|---|
| Test system | Concentration range tested (µg/plate)[1] | Metabolic activation system | Result | | Reference |
| | | | with metabolic activation | without metabolic activation | |
| *Salmonella typhimurium* TA 98, TA 100, standard plate incorporation test | no data | S-9 mix from Aroclor-induced rat liver | negative | negative | Epler et al., 1979 |
| *Salmonella typhimurium* TA 100, standard plate incorporation test | 3.67–3665, toxic at the highest concentration (99% pure) | S-9 mix from Aroclor-induced rat liver | negative | negative | Florin et al., 1980 |
| *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538, standard plate incorporation test | 0.5–5000, toxic at the highest concentration, 90% pure with 5–7% dimethylcresol | S-9 mix from Aroclor-induced rat liver | negative | negative | Pool and Lin, 1982 |
| *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, preincubation test | 0.33–33, 99% pure | S-9 mix from Aroclor-induced rat and hamster liver | negative | negative | Mortelmans et al., 1986 |

[1] Unless stated otherwise, publications give no details of cytotoxic effects or of the purity of the 2,4-dimethylphenol used and/or any impurities it may have contained.

### 7.6.2 In vivo

The clastogenic potential (induction of chromosome mutations) and mitotic spindle poison effects of 2,4-dimethylphenol were investigated in a micronucleus assay performed in accordance with OECD guideline No. 474. Groups of 5 male and 5 female mice (NMRI strain, mean weight 26.8 g) were treated by gavage with a single oral dose of 0 (controls), 250, 500 or 1000 mg/kg body weight. As a positive control for the clastogenic effect, an additional group was dosed orally with an aqueous solution of cyclophosphamide at 20 mg/kg body weight. A further positive control group, included to identify spindle poison effects, was treated intraperitoneally with an aqueous solution of vincristine at 0.15 mg/kg body weight. Except for those in the highest dose group, the mice exhibited no evident clinical signs of toxicity. Following administration, animals treated with 2,4-dimethylphenol at 1000 mg/kg body weight were in very poor general condition with squatting posture, closed eyelids and piloerection. One male from an additional group which was scheduled for sacrifice at 48 hours after dosing together with a further control group, died 2 days after treatment. All other animals were sacrificed at 24 hours. The bone marrow was removed from the femurs, spread onto slides and stained. The additional groups underwent the

same procedure at 48 hours. For each animal, 2000 polychromatic erythrocytes were scored and the number of cells with micronuclei was recorded. A distinction was also made as to whether the micronuclei were small or large, and the numbers of normochromatic erythrocytes were ascertained. Whereas the groups treated with the positive control agents yielded the expected results, 2,4-dimethylphenol showed no effect on any of the parameters under investigation and therefore was completely devoid of clastogenicity and spindle poison effects under the conditions of the study (BASF, 1998 b).

## 7.7 Carcinogenicity

The potential of 2,4-dimethylphenol to elicit skin cancer was investigated in 2- to 3-month-old female albino mice (of the Sutter strain, which is particularly susceptible to tumours). A group of 29 mice was treated with 2.5 mg 2,4-dimethylphenol dissolved in benzene (25 µl of a 10-percent solution), which was applied to their clipped dorsal skin twice weekly, while 24 further mice were treated in the same manner with 5 mg (25 µl of a 20-percent solution). The study durations were 28 and 39 weeks, respectively. A solvent control group was treated with benzene for 24 weeks. Papillomas and carcinomas were primarily diagnosed macroscopically. The tumour incidences are shown in Table 3. Microscopic examinations were only carried out in certain cases. 2,4-Dimethylphenol caused marked damage to the skin, and hair loss (no further details).

**Table 3. Tumour incidences following dermal application of 2,4-dimethylphenol**

| | 2,4-Dimethylphenol | | Controls (benzene) Examination at study week 24 |
|---|---|---|---|
| | 2.5 mg/animal Examination at study week 20 | 5 mg/animal Examination at study week 24 | |
| Survival rate (survived/used) | 26/29 | 19/24 | 27/32 |
| Average number of papillomas/survivor | 0.66 | 1.42 | 0.15 |
| % of survivors with papillomas[1] | 31 | 63 | 11 |
| % of survivors with carcinomas[1] | 0 | 5 | 0 |
| | (at study week 28) | (at study week 39) | |
| % of survivors with carcinomas[1] | 12 | 42 | |

[1] animal numbers not stated in the original publication

Thus in these studies, 2,4-dimethylphenol led to a dose-dependent increase in the incidence of papillomas and carcinomas of the skin (Boutwell and Bosch, 1959).

In addition, the same strain of mouse was employed to investigate the activity of 2,4-dimethylphenol as a tumour promoter. Females aged 2 to 3 months were first treated with 9,10-dimethyl-1,2-benzanthracene (DMBA) at a dose of 75 µg/animal, dissolved in benzene (25 µl of a 0.3-percent solution), which was applied once to their clipped dorsal skin. This dose did not result in any increase in tumour incidence as compared with the historical controls, of which no details were given, however. After a rest period of 7 days, 30 animals thus treated received twice-weekly applications of 5 µg 2,4-dimethylphenol/animal (25 µl of a 20-percent solution in benzene) to the clipped dorsal skin for 15 weeks. An additional 20 animals that had been pretreated with DMBA received no further 2,4-dimethylphenol applications and served as controls. 2,4-Dimethylphenol caused marked damage to the skin, and hair loss (no further details). The findings noted after 15 weeks of treatment are summarised in Table 4. In total, the controls and 2,4-dimethylphenol-treated animals were kept in the study for 53 and 23 weeks, respectively.

**Table 4. Tumour promoting action of 2,4-dimethylphenol for mouse skin upon initiation treatment with DMBA**

| | Controls | 2,4-Dimethylphenol |
|---|---|---|
| Survival rate (survived/used) | 16/20 | 28/30 |
| Average number of papillomas/survivor | 0.13 | 1.21 |
| % of survivors with papillomas[1] | 13 | 50 |
| % of survivors with carcinomas[1] | 0 | 11 |
| | (at study week 53) | (at study week 23) |
| % of survivors with carcinomas[1] | 6 | 18 |

[1] animal numbers not stated in the original publication

Table 4 demonstrates the markedly increased incidences of papillomas and carcinomas of the skin after additional application of 2,4-dimethylphenol as compared with the controls treated with DMBA only. The investigators concluded that 2,4-dimethylphenol possessed marked tumour-promoting properties comparable with those of phenol, which was tested in parallel (Boutwell and Bosch, 1959).

Neither the carcinogenicity study nor the study on the tumour-promoting actions of 2,4-dimethylphenol permits a conclusive evaluation of the chemical's carcinogenic potential for the following reasons:

The low number of animals limits evaluation of the results.

Data on tumour incidences in historical controls of the chosen strain are not available. It is only stated that this strain is particularly tumour-susceptible (EPA, 1980).

The doses and concentrations used evidently had a corrosive effect, so that it is suspected that they were above the maximum tolerated levels for carcinogenicity studies.

The use of benzene as a solvent can be considered problematic because of its carcinogenic and irritant effects. A possible combined effect of benzene, 2,4-dimethylphenol and/or the corrosive effect of 2,4-dimethylphenol that occurred during the study could be of significance.

There was no rigorous histopathological examination of the tumours.

The United States Environmental Protection Agency took the view that the results were not conclusive of 2,4-dimethylphenol having carcinogenic activity. None the less, they did give an indication of a possible carcinogenic effect, particularly a promoting effect, of 2,4-dimethylphenol upon dermal exposure (EPA, 1980).

## 7.8 Reproductive toxicity

No information available.

## 7.9 Effects on the immune system

No information available.

## 7.10 Neurotoxicity

No information available.

## 7.11 Other effects

The oral administration of 2,4-dimethylphenol at 1.5 mmol/kg body weight/day (equivalent to 183 mg/kg body weight/day) to female weanling rats for 6 days led to induction of hexobarbitone oxidase and aminopyrine demethylase in the liver. The degree of induction was equivalent to that caused by BHT (2,6-di-tert.-butyl-4-methylphenol; no further details; Gilbert et al., 1967).

A study in rats was carried out to investigate a series of phenol derivatives, including 2,4-dimethylphenol, for their potential to induce hyaline droplet nephropathy (nephropathy due to accumulation of $\alpha_2$-microglobulin). A group of 5 male Wistar rats (Bor:WISW(Spf,Cpb) strain, Harlan-Winkelmann), aged 10 to 12 weeks, were dosed by gavage with 2,4-dimethylphenol at 1 mmol/kg body weight (equivalent to 122 mg/kg body weight, formulated in polyethylene glycol 400, 200 mmol/l). On day 7, the kidneys were removed, fixed, sliced into 5 µm sections and stained with Azan staining to make hyaline droplets visible. 2,4-Dimethylphenol did not cause hyaline droplet accumulation, as shown by semiquantitative comparison with the control (Hildebrand et al., 1997).

A study was conducted in isolated, perfused lungs of Sprague-Dawley rats in order to assess the effect of 2,4-dimethylphenol on vasoconstriction induced by hypoxia or adenosine triphosphate. 2,4-Dimethylphenol, when added in quantities of 1 to 10 mg to 35 ml of rat blood as the perfusate, had no effect on vasoconstriction induced by hypoxia (ventilation with 2% $O_2$). Adenosine triphosphate-induced vasoconstriction was reduced by 10 to 70% by the same amount of 2,4-dimethylphenol (no further details; Hauge, 1968).

In the perfused ventilated lungs of a female rabbit weighing 2.9 kg, vasoconstriction induced by repeated administration of 50 µg adenosine triphosphate was almost completely inhibited by a single addition of 1 mg 2,4-dimethylphenol to the perfusate (rabbit blood, 264 ml/minute; Lunde et al., 1968).

2,4-Dimethylphenol was tested in vitro on rat erythrocytes for haemolytic activity. One to 10 µl 2,4-dimethylphenol in ethanolic solution was added to a suspension consisting of 0.2 ml erythrocyte suspension and 3.8 ml phosphate-buffered saline and incubated for 3 hours at 37 °C. The haemoglobin liberated was determined colorimetrically at 540 nm. The $ED_{50}$ for haemolysis was 2 mM, or 244 µg/ml (Biagi et al., 1975).

In isolated tracheal rings obtained from 16- to 17-day-old chicken embryos, a 5 mM concentration of 2,4-dimethylphenol (equivalent to 611 µg/ml) in the culture medium caused ciliostasis in vitro after 7 minutes. The investigators regarded this response time as a measure of ciliotoxicity and assigned 2,4-dimethylphenol 8 points on a scale from 0 to 9 (Pettersson et al., 1982; Curvall et al., 1984).

The results of 4 short-term in-vitro assays, including tests with 2,4-dimethylphenol, were used as measures of the cytotoxicity of chemicals. Measurements were carried out on the inhibition of cell growth in a stationary culture of ascites sarcoma cells (BP8) after 48-hour incubation of 3 ml cell suspension (4000 cells/ml) to which 1 mM 2,4-dimethylphenol (equivalent to 122 µg/ml) had been added. Next, the effect of the same concentration of 2,4-dimethylphenol on oxidative metabolism was measured in suspended, freshly isolated brown fat cells from adult hamsters (10000 cells/ml) within 5 minutes of stimulating metabolism by addition of norepinephrine (0.6 mM). Polarography was employed to determine oxygen consumption in the cell suspension. Furthermore, cultures of human embryonic lung fibroblast between the 20th and 35th generation were used in order to determine the potential of 2,4-dimethylphenol to cause membrane damage. The cells were incubated with $^{3}$H-uridine to label the cytoplasmic uridine nucleotides. The confluent monolayers with a cell density of 10000 cells/cm² were incubated for 30 minutes at 37 °C with medium containing 25 mM 2,4-dimethylphenol (equivalent to 3050 µg/ml). The radioactivity measured in the supernatant upon centrifugation was taken as a measure of membrane damage. The fourth short-term assay, described above, assessed ciliotoxicity in isolated tracheal rings from chicken embryos (see above; Pettersson et al., 1982). 2,4-Dimethylphenol inhibited cell growth by 90 to 99%, decreased oxidative metabolism by 70 to 79% and caused damage to the membranes of lung fibroblasts to a degree of 80 to 89%. The onset of ciliostasis was after 7 minutes, a finding that was also evaluated as representing 80 to 89% ciliotoxicity. The investigators evaluated 2,4-dimethylphenol as highly cytotoxic compared with a further 304 chemicals they investigated (Curvall et al., 1984).

The in-vitro toxicity of 2,4-dimethylphenol was also investigated in Chinese hamster ovary (CHO) cells. For each of various concentrations of 2,4-dimethylphenol tested, 1 ml cell suspension (1 to 2 x $10^{6}$ cells) was mixed with 1 ml suspension medium to which the appropriate amount of the test chemi-

cal had been added. The cell suspension was then incubated for 20 hours at 37 °C. Per concentration of 2,4-dimethylphenol tested, 3 replicate samples were treated with the chemical and 5 replicate samples for controls were not. Following incubation, cell samples were assayed for viability by the trypan blue exclusion method (dead cells are stained, while viable cells are not) and for intracellular adenosine triphosphate by the luciferin-luciferase method. Moreover, in a second set of experiments 1 µCi $^{3}$H-leucine and 0.5 µCi $^{14}$C-thymidine were added to the cell suspensions prior to incubation in order to measure protein and DNA synthesis. Quantification was achieved by measuring the amount of radioactivity retained on glass-fibre filters after cell lysis and trichloroacetic acid precipitation. At the 500 µg/ml level, 2,4-dimethylphenol killed more than 90 percent of cells. Adenosine triphosphate and DNA synthesis were absent in dead cells. In addition, inhibition of protein synthesis exceeded 90%. When 2,4-dimethylphenol was added to the cell suspension at levels of 10, 50, 100 or 250 µg/ml, concentrations producing a 50-percent effect on cell viability, adenosine triphosphate content, DNA synthesis and protein synthesis were found to be 176, 68, 34 and 94 µg/ml, respectively. The investigators evaluated this result as indicating moderate cellular toxicity (Garrett and Lewtas, 1983).

A further study based on exactly the same methodology as that described above (see Garrett and Lewtas, 1983) investigated Chinese hamster ovary (CHO) cells in addition to 4 other cell culture types. These were rabbit alveolar macrophages (RAM), Syrian hamster embryo (SHE) cells, mouse embryo fibroblasts (BALB 3T3 cells) and human neonatal fibroblasts (HNF). 2,4-Dimethylphenol was added to the various cell cultures at a concentration of 40 µg/ml. At that level, inhibition of DNA synthesis was 49.5 and 60.8% in CHO cells and HNF cells (with no significant difference between the two cell types) while it was 98.6 and 97.6% in SHE cells and BALB cells, respectively. Inhibition of protein synthesis in CHO, RAM and HNF was 11.2, 11.3 and 2.2%, respectively, with the differences being statistically nonsignificant. Inhibition was 35.2 and 82.3% in BALB and SHE cells, respectively. No data were reported on the effect of incubation with 2,4-dimethylphenol on cell viability and cellular adenosine triphosphate levels (Garrett et al., 1983).

# 8 Experience in humans

A study was conducted to investigate whether or not 2,4-dimethylphenol was capable of cross-reacting with methylol phenols to elicit allergic contact dermatitis in humans. Ten patients with allergic hand dermatitis and hypersensitivity to at least one of 6 methylol phenols under investigation were patch-tested on the back for 2 days with equimolar concentrations of the chemicals (81 x $10^{-3}$ mol/l). In the event of positive results, the tests were repeated at $^1/_{10}$ of the concentration until a concentration was reached at which an allergic reaction no longer occurred. All patients were additionally tested with 2,4-dimethylphenol at 81 x $10^{-3}$ mol/l (equivalent to 9.90 mg/ml) and dilutions thereof, as appropriate. Three patients exhibited a positive reaction to 2,4-dimethylphenol at the highest concentration, and one of these patients even reacted to $^1/_{10}$ of the highest concentration. All 3 patients were hypersensitive to the same 4 out of 6 methylol phenols tested, with one patient also reacting to a fifth compound of that group. In a control group of 20 subjects, no allergic reactions were elicited either by methylol phenols or by 2,4-dimethylphenol. The investigators concluded that the reactions to 2,4-dimethylphenol possibly represented cross-reactions to methylol phenols (Bruze and Zimerson, 1997).

In order to determine the olfactory threshold, dilutions of an ethanolic solution of 2,4-dimethylphenol were prepared in odour- and taste-free dam water. The concentrations prepared were 0.1, 1.0 and 10 mg/l and where necessary these were diluted further to less than 0.1 mg/l. The solutions were placed in wide-necked bottles, shaken for about 5 seconds and given to the volunteers (9 to 12 subjects) to “sniff”. Additive-free water was used for comparison. The study was carried out at 20 to 22 °C. The olfactory threshold concentration determined under these conditions was 400 µg/l, equivalent to 400 ppb (Dietz and Traud, 1978).

The taste threshold for 2,4-dimethylphenol was tested in 4 subjects, with sample preparation being carried out as for the olfactory threshold tests. A taste threshold concentration of 500 µg/l, equivalent to 500 ppb, was determined (Dietz and Traud, 1978).

In other studies, each conducted with 2 to 4 volunteers, the olfactory threshold was determined at 30 and 60 °C. The olfactory thresholds were 55.5 ppb and 100 ppb at 30 °C and 60 °C, respectively (Hoak, 1957).

# 9 Classifications and threshold limit values

A TLV of 2 mg/m³ was given for 2,4-dimethylphenol in the former USSR (Sidorov and Golubovich, 1991).

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") has listed 2,4-dimethylphenol in the "Yellow Pages" of the List of MAK and BAT Values 2004 on the suggestion of BG Chemie in order that a MAK value be established for the chemical and that it be classified according to its sensitising potential (DFG, 2004).

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