ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

PHENOL (CAS Reg. No. 108-95-2)

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PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

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EXECUTIVE SUMMARY

Phenol is a colorless to pink, hygroscopic solid with a characteristic, sweet, tarry odor. Pure phenol consists of white to clear acicular crystals. In the molten state, it is a clear, colorless liquid with a low viscosity.

Human fatalities by phenol have been reported after ingestion and skin contact. Few studies after inhalation of phenol are available: one occupational study reported slight changes in liver and blood parameters (increased serum transaminase activity, increased hemoglobin concentration, increased numbers of basophils and neutrophils and lower levels of monocytes) after repeated exposure to a mean time-weighted average concentration of 5.4 ppm (Shamy et al., 1994). Piotrowski (1971) did not report symptoms or complaints in a toxicokinetic study, in which subjects were exposed at 6.5 ppm for 8 hours. Likewise, Ogata et al. (1974) in a toxicokinetic field study did not mention any effects on workers exposed to mean workshift concentrations of 4.95 ppm. Among persons exposed to >1 mg/l phenol in contaminated drinking water for several weeks, gastrointestinal symptoms (diarrhea, nausea, burning pain in the mouth and sores in the mouth) and skin rashes occurred (Baker et al., 1978). A geometric mean odor detection threshold of 0.060 ppm (range of all critiqued odor thresholds 0.0045-1 ppm) has been reported (AIHA, 1989). Don (1986) reported an odor detection threshold of 0.010 ppm in an EN13725:2003-comparable study.

No studies reporting LC_{50} values for phenol in animals are available. Oral LD_{50} values were reported as 420 mg/kg for rabbits, 400-650 mg/kg for rats and 282-427 mg/kg for mice. In rats, exposure to a phenol aerosol concentration of 900 mg/m³ for 8 hours resulted in ocular and nasal irritation, incoordination and prostration in one of six rats (Flickinger, 1976). After 4 hours exposure at 211 or 156 ppm phenol vapor, a decrease of the number of white blood cells, but no signs of toxicity were reported (Brondeau et al., 1989). After vapor exposure of rats at 0.5, 5 or 25 ppm for 6 hours/day, 5 days/week for 2 weeks no clinical, hematological or histopathological effects were found (CMA, 1998; Hoffmann et al., 2001). Continuous exposure at 5 ppm phenol vapor for 90 days caused no hematological or histological effects in rhesus monkeys, rats and mice. A vapor concentration of 166 ppm (for 5 min) resulted in a 50 %-decrease of respiration (RD_{50}) in female Swiss OF_1 mice. No teratogenic effects were found in studies using repeated oral gavage and doses of up to 120 mg/kg in CD rats and 140 mg/kg in CD-1 mice. In a two-generation drinking water study in Sprague-Dawley rats, decreased pup survival linked to decreased maternal body weight was observed at the highest dose of 5000 ppm; the NOAEL was 1000 ppm (equivalent to 70 mg/kg/day for males and 93 mg/kg/day for females). In an oral carcinogenicity study B6C3F1 mice and F344 rats received 2500 or 5000 mg/l phenol in drinking water (corresponding to 281 and 412 mg/kg/day for mice and 270 and 480 mg/kg/day for rats). No increased incidence of tumors was observed in mice and female rats; a significant incidence of tumors (pheochromocytomas of the adrenal gland, leukemia or lymphoma) occurred in male rats of the low exposure group. Phenol had tumor promoting activity when applied repeatedly on the skin after induction using benzene. It can cause clastogenic and possibly very weak mutagenic effects. IARC evaluated the findings on carcinogenicity and concluded that there is inadequate evidence in both humans and experimental animals for the carcinogenicity of phenol. Consequently, phenol was found “not classifiable as to its carcinogenicity to humans (Group 3)”. EPA concluded that, “the data regarding the carcinogenicity of phenol via the oral, inhalation, and dermal exposure routes are inadequate for an assessment of human carcinogenic potential. Phenol was negative in oral carcinogenicity studies in rats and mice, but questions remain regarding increased leukemia in male rats in the bioassay as well as the positive gene mutation data and the positive

results in dermal initiation/promotion studies at doses at or above the maximum tolerated dose (MTD). No inhalation studies of an appropriate duration exist. Therefore, no quantitative assessment of carcinogenic potential via any route is possible." Therefore, carcinogenicity was not an endpoint in the derivation of AEGL values.

The AEGL-1 was based on a repeat inhalation study of phenol in rats (CMA, 1998; Hoffmann et al., 2001), which found no clinical, hematological or histopathological effects after exposure at 25 ppm phenol (highest concentration used) for 6 hours/day, 5 days/week for 2 weeks. An uncertainty factor of 1 was applied for interspecies variability: the toxicokinetic component of the uncertainty factor was reduced to 1 because toxic effects are mostly caused by phenol itself without requirement for metabolism, moreover, possible local irritation effects depend primarily on the phenol concentration in inhaled air with little influence of toxicokinetic differences between species. The starting point for AEGL derivation was a NOAEL from a repeat exposure study and, thus, the effect level was below that defined for AEGL-1. The human experimental and workplace studies (Piotrowski, 1971; Ogata et al., 1986) support the derived values. Based on these reasons, the interspecies factor was reduced to 1. An uncertainty factor of 3 was applied for intraspecies variability because for local effects, the toxicokinetic differences do not vary considerably within and between species. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 while the factor of 3 for the toxicodynamic component, reflecting a possible variability of the target-tissue response in the human population was retained. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent. For the 10-minute AEGL-1 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

A level of distinct odor awareness (LOA) for phenol of 0.25 ppm was derived on the basis of the odor detection threshold from the study of Don (1986). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

The AEGL-2 was based on a combination of the Flickinger (1976) and Brondeau et al. (1990) studies. Aerosol exposure at 900 mg/m³ phenol (equivalent to 234 ppm phenol vapor) for 8 hours resulted in ocular and nasal irritation, slight loss of coordination and spasms of the muscle groups at 4 hours into the exposure, after 8 hours additional symptoms (tremor, incoordination and prostration) were observed in one of the six animals. No deaths occurred. Since the aerosol concentration was below the saturated vapor concentration at room temperature of about 530 ppm, it was assumed that much phenol had evaporated from the aerosol so that a mixed aerosol/vapor exposure prevailed. This study is supported by the study of Brondeau et al. (1990), which did report only slight effects after exposure at 211 ppm phenol vapor for 4 hours. Although both studies had shortcomings, i.e., aerosol exposures, nominal concentrations, and no description of toxic signs in one study, taken together, they had consistent results. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 hours. An uncertainty factor of 3 was applied for interspecies variability because oral lethal data did not indicate a high variability between species (cf. Section 4.4.1.) and because application of a higher uncertainty factor would have resulted in AEGL-2 values below levels that humans can stand without adverse effects (Piotrowski, 1971;

Ogata et al., 1986). An uncertainty factor of 3 was applied for intraspecies variability because the study of Baker et al. (1978) that investigated health effects in members of 45 families (including children and elderly), that were exposed to phenol through contaminated drinking water for several weeks, did not indicate that symptom incidence or symptom severity was higher in any specific subpopulation. Moreover, newborns and infants were not considered more susceptible than adults because of their smaller metabolic capacity to form toxic phenol metabolites (cf. Section 4.4.2.). Based on the small data base and study shortcomings, a modifying factor of 2 was applied. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent. For the 10-minute AEGL-1 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

Although phenol is a high-production-volume chemical, no acute inhalation studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended.

The calculated values are listed in the table below.

SUMMARY TABLE OF AEGL VALUES FOR PHENOL [a]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	19 ppm (73 mg/m³)	19 ppm (73 mg/m³)	15 ppm (58 mg/m³)	9.5 ppm (37 mg/m³)	6.3 ppm (24 mg/m³)	No effects in rats (CMA, 1998; Hoffmann et al., 2001)
AEGL-2 (Disabling)	29 ppm (110 mg/m³)	29ppm (110 mg/m³)	23 ppm (90 mg/m³)	15 ppm (57 mg/m³)	12 ppm (45 mg/m³)	Irritation and CNS depression in rats (Flickinger, 1976; Brondeau et al., 1990)
AEGL-3 (Lethal)	N.R. [b]	N.R.	N.R.	N.R.	N.R.	

[a] Skin contact with molten phenol or concentrated phenol solutions should be avoided; dermal penetration is rapid and fatal intoxications have been observed when a small part of the body surface was involved.
[b] not recommended due to insufficient data

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1. INTRODUCTION

Phenol is a colorless to pink, hygroscopic solid with a characteristic, sweet, tarry odor. Pure phenol consists of white to clear acicular crystals. In the molten state, it is a clear, colorless liquid with a low viscosity. A solution with approximately 10 % water is called phenolum liquefactum, as this mixture is liquid at room temperature (WHO, 1994).

Phenol is produced either by oxidation of cumene or toluene, by vapor-phase hydrolysis of chlorobenzene or by distillation from crude petroleum (WHO, 1994). Worldwide phenol production has been reported at about 500,000 to 1,000,000 metric tons per year (IUCLID, 1996). Newer data report a production of 1,800,000 metric tons per year in Europe (ECB, 2002) and about 1,500,000 metric tons for 1994 in the USA (HSDB, 2004).

Phenol is pumped in molten form (about 50 °C) or in liquefied form (containing 10 % water) through pipes on industrial sites and is also transported in molten form in tank trucks and rail tank cars between industrial sites. Therefore, inhalation exposure during accidental release cannot be ruled out.

Phenol is principally used in production of various phenolic resins, biphenol A, caprolactam and a wide variety of other chemicals and drugs. It is also used as a disinfectant and in germicidal paints and slimicides (ACGIH, 1996). The TRI database (DHHS, 2004) lists 649 sites in the US where production and/or use of phenol causes emissions to the air.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No relevant studies documenting lethal effects in humans after inhalation exposure to phenol were identified. During the second half of the 19th century, several hundred cases of intoxication occurred from inhalation, oral or dermal exposure (Lewin, 1992). Contemporary reports concerning fatalities after oral or dermal exposure are available, however for dermal exposures very often information about the absorbed dose is not reported (WHO, 1994). Lethality data in humans are summarized in Table 2.

TABLE 1: CHEMICAL AND PHYSICAL DATA

Parameter	Value	Reference
Molecular formula	C_6H_6O; C_6H_5OH	WHO, 1994
Molecular weight	94.11	WHO, 1994
CAS Registry Number	108-95-2	WHO, 1994
Physical state	solid a solution with approx. 10 % water (phenolum liquefactum) is liquid at room temperature	ACGIH, 1996 WHO, 1994
Color	colorless assumes a pink to red discoloration on exposure to air and light	ACGIH, 1996
Synonyms	carbolic acid; hydroxybenzene; phenyl hydroxide; Phenol	ACGIH, 1996
Vapor pressure	0.48 hPa at 20 °C 0.357 mm Hg at 20 °C 1 mm Hg at 40.1 °C 3.5 hPa at 25 °C 2.48 mm Hg at 50 °C 10 mm Hg at 73.8 °C 18.39 hPa at 80.1 °C 40 mm Hg at 100.1 °C 100 mg Hg at 121.4 °C	IUCLID, 1996 WHO ,1994 Weast, 1984 IUCLID, 1996 WHO, 1994 Weast, 1984 IUCLID, 1994 Weast, 1984 Weast, 1984
Density	1.0719 g/cm^3	ACGIH, 1996
Melting point	43 °C	Weast, 1984
Boiling point	181.75 °C	Weast, 1984
Solubility	very soluble in chloroform, alcohol, ether and aqueous alkali hydroxides; 67 g/l in water at 16 °C	ACGIH, 1996 WHO, 1994
Odor	sweet, tarry odor sweet and acrid	ACGIH, 1996 IARC, 1999

TABLE 1: CHEMICAL AND PHYSICAL DATA		
Parameter	**Value**	**Reference**
Explosive limits in air	1.7 % (lower), 8.6 % (upper)	ACGIH, 1996
Conversion factors	1 ppm = 3.84 mg/m³ 1 mg/m³ = 0.26 ppm	WHO, 1994

2.1.1. Case Studies

Heuschkel and Felscher (1983) reported death of a newborn (weight 3 kg) that was exposed through a contaminated continuous positive airway pressure system of an incubator. Instead of distilled water, the system contained a disinfection fluid, composed of 2 % formalin (30 % formaldehyde), 1.5 % sodium tetraborate and 0.5 % phenol. This solution was removed after 5-6 hours. However, exposure was continued since disinfection fluid was also used for filling up the reservoir for humectation of the air. The newborn developed severe symptoms after 20 hours of exposure. It showed a gray-pale skin color, edema on the head and legs, tachypnea and died on the fifth day from progressive respiratory insufficiency. On experimental reconstitution of the exposure conditions, about 20 mg/m³ (5.2 ppm) phenol and about 30 mg/m³ (24.9 ppm) formaldehyde were measured in the incubator after 2 hours (with lower concentrations of phenol and formaldehyde after 5 hours, not reported) when disinfection solution was present in the evaporation container, and about 5 mg/m³ (1.3 ppm) phenol, 50 mg/m³ (41.5 ppm) formaldehyde and 350 mg/m³ (267 ppm) methanol were found (with decrease of the formaldehyde and methanol concentrations within the first hour) with disinfection fluid in the water reservoir. It should be noted that concentrations in the incubator were measured using simple solid sorbent test tubes. Autopsy revealed hypoxemia-caused organ alterations. The authors contributed these to two causes: 1) central respiratory depression by the intoxication and 2) congenital pulmonary adaptation disorder, expressed in an immature tissue structure of the lung.

Studies with non-inhalation exposure

A 65-year-old Japanese woman ingested 70 ml of 42-52 % phenol in a suicidal attempt. Upon hospital admission, about 1 hour after ingestion, respiration had arrested and the patient was comatose. The patient survived due to intensive medical care (Kamijo et al., 1999).

Bennett et al. (1950) reported two suicide cases. The first cases involved a 50-year-old morphine addict who swallowed approximately 60 ml of an 88 % aqueous phenol emulsion. Forty-five minutes later, he was stuporous with cold and clammy skin and had a rapid and weak pulse, stertorous breathing with a phenol odor on the breath, constricted pupils which did not react to light (probably due to morphine injection prior to phenol ingestion), and rales in the lungs. An electrocardiogram showed auricular flutter with a variable auriculoventricular block. His urine was greenish with no albumin, but 12 hours later there was a marked albuminuria and cylindruria. Albuminuria persisted for 10 days. The patient responded to medical treatment and recovered in 20 days. The second case involved a 19-year-old woman who had ingested 15 ml liquefied phenol. Ninety minutes later, she complained of severe nausea and burning in the throat and epigastrium. Laryngoscopic examination revealed superficial burns and slight edema of the hypopharynx. Despite gastric lavage with olive oil and intravenous saline administration, she continued to be nauseated. One hour later, she began to vomit blood and to have

diarrhea, passing copious amounts of blood with clots. She gradually became cyanotic and stuporous and died 17.5 hours after ingestion.

Stajduhar-Caric (1968) described a woman who committed suicide by ingesting 10-20 g of phenol. She became comatose with partial absence of reflexes, pallor of the skin, accelerated respiration, weak and rapid pulse and dilated pupils which did not react to light. Almost one hour after the ingestion, her heart and respiration stopped and, in spite of repeated attempts at resuscitation for two hours, she died. Autopsy revealed marked hyperemia of the tracheal and bronchial mucous membranes. Histological examination revealed pulmonary and liver edema as well as hyperemia of the intestine.

Tanaka et al. (1998) reported the case of a 27-year-old male student, who died after ingestion of a DNA extraction fluid containing phenol. He was found in the laboratory the next day lying on the floor with his trousers soaked. At autopsy on the same day, the body surface was grayish in color; the skin in the large area extending from the right arm to both legs had changed color to dark brown, and some parts of its surroundings were chemically burned. There were also blisters in the skin across the burned area. The lips, oral mucous membranes and the walls of the orsopharynx, larynx, bronchus, esophagus and stomach were dark brown and inflamed. Histology revealed inflammatory changes in the lungs, interstitial edema and renal tubular hemorrhage in the kidneys, interstitial hemorrhage in the pancreas and adrenal glands. Analysis of free phenol was performed by gas chromatography/mass spectroscopy on ethyl acetate extracts of tissues. The following phenol concentrations were found: 60 mg/l free phenol in the blood, 208 mg/l in urine, 106 mg/l in the brain, 116 mg/l in the lung and 874 mg/l in the kidney.

Upon skin contact with liquefied phenol or phenol solutions, symptoms can develop rapidly leading to shock, collapse, coma, convulsions, cyanosis and death (NIOSH, 1976; Lewin, 1992).

Horch et al. (1994) described a healthy, 22-year old male worker who was splashed with aqueous phenol (concentration not reported) over his face, chest, one hand and both arms (20.5 % of the body surface). Extensive water showering and topical treatment with polyethylene glycol was carried out before hospital admission. Affected skin areas looked swollen and reddish like partial skin thickness burn wounds. Blood gas analysis revealed that oxygen saturation dropped from 99 % on admission to 72 % 6 hours after exposure. During this period cardiac arrhythmia and bradycardia were noted. Serum levels of phenol were 11.4 mg/l at 1 hour, 17.4 mg/l at 4 hours, 6.0 mg/l at 8 hours, 0.37 mg/l at 22 hours, and 0.07 mg/l at 28 hours postexposure. The man survived and his skin healed completely within 12 days.

Bentur et al. (1998) reported the case of a 47-year-old male who had 90 % phenol spilled over his left foot and shoe (3 % of the body surface). After 4.5 hours of exposure, with no attempt to remove the phenol, confusion, vertigo, faintness, hypotension, ventricular premature beats and atrial fibrillation developed and the affected skin area showed swelling and blue-black discoloration and was diagnosed as a second degree burn. Peak serum phenol was 21.6 mg/l and was eliminated with a half-life of 13.9 hours.

Lewin and Cleary (1982) described a 24-year-old male who died shortly after being painted with benzyl benzoate as a scrabicide with a brush that had been steeped in 80 % phenol and not thoroughly washed before use.

Hinkel and Kintzel (1968) described two newborns having cutaneous contact with phenol-containing disinfectants. A 1-day-old newborn died 11 hours after application of an umbilical bandage

which was accidentally soaked with 2 % phenol instead of saline. After 6 hours, the baby developed severe cyanosis and died at 11 hours from central respiratory depression. Autopsy revealed edematous swelling of all parenchymal organs. Phenol concentrations of 125 mg/kg blood, 144 mg/kg liver and 202 mg/kg kidney were measured. Another baby, 6 days old, was treated for skin ulcer with Chlumsky‘s solution (phenol-camphor complex) and developed life-threatening methemoglobinemia, vomiting, cyanosis, muscle twitchings and tremors, central circulatory collapse, mimic rigidity, muscular hypertonia, and tenderness to touch. These symptoms persisted for 3 days. The baby survived following intensive care and blood-exchange transfusion.

Schaper (1981) reported the case of a 19-year-old woman who was accidentally splashed with molten phenol (80-90 °C) on the face, left arm and left leg (about 35-40 % of the body surface). Five minutes later the patient lost consciousness and upon hospital admission 15 minutes after the accident she was comatose. The patient developed bradypnea and tachycardia, brownish necrosis of the affected skin and massive intravasal hemolysis. After intensive medical care, the patient regained consciousness after 6 hours; cardiac activity normalized after 8 hours. No sign of organ damage was observed and the patient was discharged after 33 days. The peak phenol concentration in urine was about 600 mg/l 2 days after the accident; the urinary concentration decreased to 100-150 mg/l during the first week and second weeks.

TABLE 2: SUMMARY OF DATA ON LETHAL EFFECTS IN HUMANS

Subject information	Exposure route	Exposure information	Estimated dose	Effect	Reference
1-day-old newborn	inhalation	about 5.2 ppm for 5-6 h, subsequently about 1.3 ppm for 14-15 h	unknown	cyanosis, tachypnea, death 4 days later; additional formaldehyde exposure	Heuschkel and Felscher, 1983
65-year-old female	oral	70 ml of 42-52 % phenol solution	490-606 mg/kg assuming a density of 1 g/ml and a body weight of 60 kg	after 1 h respiratory arrest, coma, survived due to intensive care	Kamijo et al., 1999
50-year-old male	oral	approx. 60 ml of an 88 % phenol emulsion	754 mg/kg assuming a density of 1 g/ml and a body weight of 70 kg	after 45 min stuporous, tachycardia, stertorous breathing, rales in the lungs, survived with medical treatment	Bennett et al., 1959
19-year-old female	oral	15 ml liquefied phenol	250 mg/kg assuming a density of 1 g/ml and a body weight of 60 kg	90 min later nausea, vomiting, diarrhea, cyanosis, stuporous, death after 17.5 h	Bennett et al., 1959
adult female	oral	10-20 g phenol	166-333 mg/kg assuming a body weight of 60 kg	coma, absence of reflexes, tachypnea, tachycardia, death after 1 h due to cardiac and respiratory arrest	Stajduhar-Caric, 1968

Subject information	Exposure route	Exposure information	Estimated dose	Effect	Reference
27-year-old male	oral (+ dermal)	unknown	106-874 mg/kg, based on tissue concentration	found dead next day; at autopsy tissue phenol concentrations between 106 and 874 mg/kg, 60 mg/kg in blood	Tanaka et al., 1998
1-day-old newborn	dermal	2 % phenol solution in umbilical bandage	125-202 mg/kg based on tissue concentration, assuming uniform distribution and no elimination	cyanosis, death after 11 h, at autopsy tissue phenol concentrations between 125 and 202 mg/kg	Hinkel and Kintzel, 1968

2.2. Nonlethal Toxicity

While some studies describe odor thresholds for phenol, no studies are available reporting adverse health effects after single inhalation exposures.

2.2.1. Experimental Studies

Piotrowski (1971) published a toxicokinetic study on phenol. Eight healthy volunteers (7 men aged 25-42 and one woman aged 30) were exposed by face mask to phenol concentrations between 5 and 25 mg/m³ (1.3-6.5 ppm) for 8 hours, with two breaks of 0.5 hours each after 2.5 and 5.5 hours. The author did not report any complaints concerning adverse effects of phenol exposure on the subjects neither did he explicitly state the absence of any effects.

(Don, 1986) reported an odor detection threshold of 0.010 ppm for phenol in a study which is considered to be equivalent to an EN13725:2003-compliant study. The study methodology has been described in TNO (1985). In this study, the odor threshold for the reference chemical n-butanol was determined as 0.026 ppm.

Leonardos et al. (1969) used a combination of a test room and an antechamber, which was held odor-free using an air filter system. A trained panel of four staff members of the Food and Flavor Section of Arthur D. Little, Inc., determined the odor threshold for various compounds. At least 5 different concentrations of phenol were tested. The individual concentrations tested were not reported. An odor recognition threshold of 0.047 ppm phenol was determined for all four subjects.

Mukhitov (1964) determined the odor perception threshold in 14 subjects. Each subject was tested between 33 an 43 times over a period of 2-3 days. The odor perception threshold concentration ranged between 0.022-0.14 mg/m³ (0.0057-0.036 ppm); in 11/14 subjects, the odor perception threshold was 0.029 mg/m³ (0.0075 ppm) or lower.

The geometric mean of 16 air odor detection thresholds was reported by Amoore and Hautala (1983) to be 0.16 mg/m³ (0.040 ppm, with a standard error of 0.026 ppm). The American Industrial Hygiene Association reported a geometric mean odor detection threshold of 0.060 ppm (the range of all critiqued odor threshold studies was 0.0045-1 ppm) (AIHA, 1989).

Ruth (1986) listed an irritation threshold of 182.4 mg/m³ (47 ppm) in humans. The author tabulated odor and irritation threshold for a large number of chemicals, but did not indicate the source for the values.

2.2.2. Case Studies

Spiller et al. (1993) reported a 5-year retrospective review of all exposures to a high concentration phenol disinfectant (26 % phenol) reported to a regional poison control center. Of a total of 96 located cases,16 cases were lost to follow-up, leaving 80 cases for evaluation. Ages ranged from 1 to 78 years, with a mean of 10 years; 75 % of the patients were <5 years. There were 60 oral-only exposures, 7 dermal-only exposures, 12 oral/dermal exposures and 1 case was inhalation exposure. 52 cases were evaluated in a hospital. 11 patients (all oral exposures) experienced some form of central nervous system depression. Nine patients experienced lethargy (the time to onset was 15 minutes to 1 hour, with a mean time of 20 minutes); lethargy progressed to unresponsiveness within 1 hour. Coma developed in two patients (information on the ingested dose was not available). Burns were noted in 17 patients with oral exposure and 5 patients with dermal exposure. No cardiovascular complications were noted. A distinct change in urine color to dark green/black was noted in 5 patients with oral exposure; oliguria or anuria were not seen. Recovery was complete in all cases. By history, the oral dose of exposure ranged from 2 to 90 ml disinfectant (520 mg to 23.4 g phenol). The largest ingested dose without effect was 30 ml (7.8 g phenol) and the smallest dose with any effect was 5 ml (1.3 g phenol). The dose was unknown in 14 exposures. No details were provided for the case involving inhalation exposure.

Baker et al. (1978) described an incidence in which residents drank contaminated well water for several weeks following an accidental spill of 37,900 liters of phenol. Due to incomplete removal and flushing of the site with water seepage into the underground water system developed. In a retrospective study, the population was divided into three groups based on residential location relative to the spill site and results of water testing: Group 1 (39 persons, mean age 26.5 years) consisted of all those living 120-310 m from the spill site having at least one water test which revealed more than 0.1 mg phenol/l in their drinking water. Group 2 (61 persons, mean age 26.7 years) was composed of families living adjacent to Group 1, i.e. 210-670 m from the spill who had 0.1-0.001 mg phenol/l in their water. Group 3 (58 persons, mean age 19.5 years) lived 1.9 km from the spill site in houses where well water testing had detected no phenol in the water. Upon medical evaluation no significant differences were noted in symptom rates between Groups 2 and 3, therefore, the two groups were combined and symptom rates for this group were compared with rates in Group 1. Diarrhea, nausea, burning pain in the mouth and sores in the mouth developed in 17 of the 39 individuals of group 1, 5 individuals of Group 2 and 2 cases in Group 3. In Group 1, affected persons were slightly younger than those not affected (21.7 vs. 30.2 years) and tended to live closer to the spill site. Skin rashes were also increased in Group 1, which might have been caused by dermal exposure to phenol-contaminated water. Ill individuals had significantly more frequent complaints of bad tasting or smelling water during two months after the spill than did their neighbors who were not ill. Routine blood chemistry analyses and urinalysis performed on samples obtained half a year after the spill showed no significant abnormalities in liver function tests or other

measured parameters. Mean urinary phenol levels were normal by that time because drinking water was supplied by tanks. Measured concentrations were 12±12 and 12±11 mg/l for Group 1 and the combined control group, respectively. The phenol concentrations in drinking water for the persons in Group 1 who had symptoms were >1 mg/l (the authors estimated an intake of phenol of 10-240 mg/d).

2.2.3. Occupational Exposure

Ogata et al. (1986) carried out a toxicokinetic study in 20 adult male employees engaged in treatment of fibers with phenol. The authors provided no information on age and health status of the employees or on time on the job. The workers were not equipped with protection masks and the workshops were closed rooms with phenol concentrations from 1.22 to 4.95 ppm. The study investigated the correlation between workplace exposure to phenol and the concentration of phenol metabolites in urine. The number of men in each workshop exposed to phenol (time-weighted average concentrations during workshift measured by personal samplers) were: 2 subjects at 1.22±0.52 ppm, 5 at 1.95±0.47 ppm, 5 at 2.52±0.49 ppm, 2 at 2.73±0.45 ppm, 2 at 3.81±0.26 ppm and 4 at 4.95±0.23 ppm. The authors neither reported any adverse effects of phenol exposure on the subjects nor did they explicitly state the absence of any effects.

Shamy et al. (1994) studied 82 male workers in an oil refining plant. Group I comprised workers (n=20; mean duration of exposure 13.2±6.6 years) exposed to phenol alone, during aromatic extraction from distillates containing aromatics, wax, oil and impurities. The time weighted average exposure was 5.4 ppm according to the factory. Group II (n=32; mean duration of exposure 14.3±6.1 years) represented those exposed to mixtures of phenol, benzene, toluene and methyl ethyl ketone (4.7, 0.7, 220 or 90 ppm, respectively). Group III (n=30) comprised employees not exposed to phenol from the administrative departments, located far away from any exposure. Transaminases, total protein, prothrombin time, clotting time, fasting blood sugar, serum creatinine and trace elements were determined in blood. The mean phenol concentrations measured in urine were 11.5 ±4.7 mg/g creatinine in controls (Group III), 54 ±27 mg/g creatinine in Group II and 69 ±47 mg/g creatinine in Group I. Groups I and II showed statistically significantly higher levels of serum alanine aminotransferase and serum aspartate aminotransferase, increased clotting time and lower levels of serum creatinine than subjects from the administrative departments. Groups I and II had statistically higher levels of hemoglobin, hematocrit, color index, mean corpuscular hemoglobin content, mean corpuscular volume, basophils and neutrophils and lower levels of monocytes than control subjects. Groups I and II had significantly higher levels of Mg, Mn and Ca. The effects of combined exposure did not differ from that of exposure to phenol alone for the majority of the tested parameters. Only the platelets count, prothrombin time, eosinophils, Co and Fe were affected by combined exposure, but not after exposure to phenol only.

2.3. Developmental/Reproductive Toxicity

No studies evaluating developmental or reproductive effects of phenol in humans were identified (ATSDR, 1998).

2.4. Genotoxicity

In tests using cultured human lymphocytes in vitro, phenol caused a weak increase in the frequency of micronuclei (Yager et al., 1990) and induced sister chromatid exchanges (Morimoto and Wolff, 1980). For more information on genotoxicity see Section 3.4.

2.5. Carcinogenicity

Kauppinen et al. (1986) reported a case-control study on respiratory cancers and chemical exposures in the wood industry. A cohort of 3805 Finnish men who worked in the particle board, plywood, sawmill, or formaldehyde glue industries for at least 1 year between 1944 and 1965 was followed until 1981. From the cohort, 60 cases of respiratory malignant tumors were identified. The tissue locations of these tumors included tongue (1), pharynx (1), larynx or epiglottis (4), and lung or trachea (54). No cases with tumor in the mouth, nose, or sinuses were identified. Among the 60 cases, 2 were rejected due to a false preliminary diagnosis of cancer and 1 was rejected as chronic lymphocytic leukemia. The final size of the group of cases was thus 57. The control group contained three subjects for each case, selected from the cohort and matched by birth year, for a total size of 171. Individual phenol exposures were determined qualitatively as "yes" or "no" and as a function of exposure time. Phenol exposure resulted in a statistically significant odds ratio (OR) of 3.98 or 4.94 for respiratory tumors with or without the adjustment for smoking years, respectively. When the duration of phenol exposure was considered, both exposures <5 years and >5 years resulted in a statistically significant OR of 5.86 or 4.03, respectively (i.e., no duration response). When a provision for a 10-year latency was introduced (excluding exposure during the 10 years immediately preceding the diagnosis of cases), phenol exposure resulted in a nonsignificant OR of 2.86 adjusted for smoking years but a significant or of 3.98 without smoking adjustment. An exclusion of workers exposed to both phenol and pesticides resulted in a change of the OR from a significant 4.9 to a nonsignificant 2.6. Thus, a confounding effect due to exposures to pesticides was very possible.

In an occupational epidemiology study, Dosemeci et al. (1991) evaluated mortality among 14,861 white male workers in five companies that used formaldehyde and phenol. Unfortunately, the phenol exposure was confounded by co-exposure to other compounds, such as formaldehyde, asbestos, urea, melamine, hexamethylenediamine, wood dust, plasticizers, carbon black, ammonia, and antioxidants. On the basis of phenol concentrations obtained from historical monitoring and industrial hygiene surveys, the investigators assigned each job/department/year combination to groups with no, low, medium, or high phenol exposure and then calculated cumulative exposure. Compared with the entire U.S. population, the entire cohort, had no significant increases in standardized mortality ratios (SMRs) for all causes of death or any diseases. The phenol-exposed workers as a group had slightly elevated SMRs for cancers of the esophagus (1.6), rectum (1.4), kidney (1.3), and Hodgkin's disease (1.7); however, none of these increases were statistically significant when compared with those in general population.

2.6. Summary

Fatalities after gross phenol exposures have been reported in the literature: one neonate died after about 5.2 ppm phenol and 24.9 ppm formaldehyde (concentrations after 2 hours) with a decline in chamber phenol concentrations over 5-6 hours followed by about 1.3 ppm phenol and 41.5 ppm formaldehyde (measured after 1 hour, with decrease over time) for 14-15 hours in an incubator

(Heuschkel and Felscher, 1983); a newborn died from dermal phenol exposure with resulting tissue concentrations of 125-202 mg/kg (Hinkel and Kintzel, 1968), lethal percutaneous exposures for which information on dose is lacking; the range of reported acute oral lethal dose in adults is 166-754 mg/kg (Kamijo et al., 1999; Bennett et al., 1959; Stajduhar-Caric, 1968).

Very few studies report the consequences in humans after inhaling phenol. One study reported slight increased serum transaminase activity, increased hemoglobin concentration, increased numbers of basophils and neutrophils and lower levels of monocytes after repeat occupational exposure to a mean time-weighted average concentration of 5.4 ppm phenol (Shamy et al., 1994). Piotrowski (1971) did not report any complaints or adverse effects in volunteers exposed to controlled concentrations of phenol at 6.5 ppm for 8 hours. Likewise, the field study of Ogata et al. (1986) did not mention the health status of workers exposed to mean workshift concentrations of 1.22-4.99 ppm. Baker et al. (1978) described an incidence in which residents drank contaminated well water for several weeks following an accidental spill of phenol. Among persons exposed to >1 mg/l phenol in contaminated drinking water for several weeks (the authors estimated an intake of phenol of 10 - 240 mg/d), gastrointestinal symptoms (diarrhea, nausea, burning pain in the mouth and sores in the mouth) and skin rashes occurred (Baker et al., 1978). Odor thresholds for phenol were reported as 0.010 ppm (Don, 1986), 0.047 ppm (Leonardos et al., 1969) and 0.060 ppm (mean of evaluated values from the literature) (AIHA, 1989).

No studies investigating reproductive/developmental toxic effects in humans were available. In vitro, phenol induced signs of genotoxicity in human cells (Yager et al., 1990; Morimoto and Wolff, 1980). Two epidemiological studies (Kauppinen et al., 1986; Dosemeci et al., 1991) evaluating carcinogenic effects in phenol-exposed workers did not show a clear correlation between phenol exposure and increased tumor incidences, but a very weak carcinogenic effect cannot be excluded on basis of the available data.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

No studies reporting death after a single inhalation exposure were available. One study evaluated repeated inhalation exposure in guinea pigs. For oral exposure, several studies are summarized in Table 3.

3.1.1. Rabbits

Studies with non-inhalation exposure

Deichmann and Witherup (1944) administered phenol at different concentrations by oral gavage to albino rabbits. The first muscle twitching occurred in the extrinsic eye muscles and those of the eyelids and ears, then spread to isolated bundles of muscles all over the body; the extremities were affected last. Pulse and respiration were increased in rate at first, but later became slow, irregular and weak. The pupils were contracted in the early stages of intoxication, being dilated later. There was some salivation and dyspnea was marked. Lethargy, coma and asphyxial convulsions occurred shortly before death. Death always followed an oral dose of 0.62 g/kg, some deaths were seen after a dose of 0.42 g/kg, but were not observed at a dose of 0.28 g/kg.

Flickinger (1976) applied 0.252, 0.500, 1.00 or 2.00 g/kg phenol to the intact skin of male albino rabbits (4 animals/group). The observation period was 14 days. Death was observed in 0/4, 0/4, 3/4 and 4/4 rats (all deaths occurred at the day of dosing), respectively. Necrosis of the skin was observed in all exposed rabbits. No internal gross lesions were observed upon autopsy of the sacrificed animals. The authors calculated a LD_{50} of 0.85 g/kg (95 % C.I. 0.60-1.20 g/kg).

3.1.2. Rats

Studies with non-inhalation exposure

Berman et al. (1995) reported an oral LD_{50} of 400 mg/kg (95 % C.I. 297-539 mg/kg) in female Fischer 344 rats. In a repeat gavage study (14 exposures; see Section 3.2.3), a dose of 120 mg/kg killed 8/10 animals (animals died between days 1 and 11). No deaths occurred at 40 mg/kg.

Deichmann and Witherup (1944) administered 2, 5, 10 or 20 % aqueous phenol by oral gavage to Wistar rats. The first muscle twitching occurred in the extrinsic eye muscles and those of the eyelids and ears, then spread to isolated bundles of muscles all over the body; the extremities were affected last. Pulse and respiration were increased in rate at first, but later became slow, irregular and weak. The pupils were contracted in the early stages of intoxication, being dilated later. There was some salivation and dyspnea was marked. Uncoordinated movements of the legs occurred shortly before death. The LD_{50} values for the different phenol concentrations were 0.53, 0.53, 0.54 and 0.34 g/kg, respectively.

Flickinger (1976) dosed groups of 5 male albino rats by gavage at 0.200, 0.398, 0.795 or 1.58 g/kg phenol. The observation period was 14 days. Death was observed in 0/5, 0/5, 4/5 and 5/5 rats (all deaths occurred at the day of dosing), respectively. All rats which died revealed hyperemia and distention of the stomach and intestines. None of the surviving rats exhibited any gross lesions. The authors calculated a LD_{50} of 0.65 g/kg (95 % C.I. 0.49-0.86 g/kg).

Conning and Hayes (1970) reported a dermal LD_{50} of 0.625 ml/kg in Alderley Park rats using molten phenol (40 °C).

3.1.3. Guinea pigs

Deichmann et al. (1944) exposed 12 guinea pigs to phenol vapor at 100-200 mg/m³ (26-52 ppm), 7 hours/day, 5 days/week for 4 weeks. After 3-5 exposures, the animals became lethargic during exposure. Body weight either decreased or remained stationary. After about 20 exposures over a period of 28 days, some of the animals began to show respiratory difficulties and signs of paralysis affecting primarily the hind quarters. Five animals died on day 28 and the other animals were killed one day later. Autopsy revealed extensive coagulation necrosis of the myocardium with extensive inflammation, lobular pneumonia with occasional abscesses and vascular damage in the lungs, centrolobular degeneration and necrosis in the liver and degenerative lesions in the kidneys.

3.1.4. Mice

For mice, oral LD_{50} values of 282 mg/kg (Horikawa and Okada, 1975), 300 mg/kg (Von Oettingen and Sharples, 1946) and 427 mg/kg (Kostoveckii and Zholdakova, 1971) have been reported.

TABLE 3: SUMMARY OF ACUTE ORAL LETHAL DATA IN ANIMALS

Species	Dose (mg/kg)	Remarks on administration	Total number of animals used	Datum	Reference
rabbit	420	solutions with different phenol concentrations were used	35	lowest dose that resulted in death	Deichmann and Witherup (1944)
rat	400	gavage	not stated	LD_{50}	Berman et al. (1995)
rat	530	gavage, 2 % solution	45	LD_{50}	Deichmann and Witherup (1944)
rat	530	gavage, 5 % solution	45	LD_{50}	Deichmann and Witherup (1944)
rat	540	gavage, 10% solution	40	LD_{50}	Deichmann and Witherup (1944)
rat	340	gavage, 20 % solution	45	LD_{50}	Deichmann and Witherup (1944)
rat	650	gavage	20	LD_{50}	Flickinger (1976)
mouse	282	not stated	not stated	LD_{50}	Horikawa and Okada, 1975
mouse	300	not stated	not stated	LD_{50}	Von Oettingen and Sharples, 1946
mouse	427	not stated	not stated	LD_{50}	Kostoveckii and Zholdakova, 1971

3.2. Nonlethal Toxicity

Studies with single and repeated inhalation exposure are available for monkey, rabbit, rat and mouse. However, several protocols employed concentrations which failed to produce any adverse effects (Table 4).

3.2.1 Monkeys

Studies with repeated inhalation exposure

Sandage (1961) exposed groups of 10 male rhesus monkeys at 0 or 5 ppm phenol 24 hours/day for 90 days. The exposure chambers were aluminium-insulated rooms of 10x8x7 feet. Monkeys were exposed in individual cages of 2x2x2 feet. Exposure concentrations were determined by a colorimetric assay [The reliability of the method could not be determined from the study]. An average phenol concentration of 4.72 ppm was measured (according to the authors the allowed range of 4.5-5.5 ppm was not exceeded). No significant effects were found in tests assessing hematology, urine parameters, blood chemistry and renal function. In discussion the authors stated that "pathology ... was essentially negative". Liver and kidney pathology was observed in 30% and 20%, respectively, of the monkeys (compared with 0% of the controls). However, the authors did not consider these changes to be significant, and they noted that 6/7 reports of pathology in monkeys were considered "minimal or doubtful." Although the authors concluded that there was no evidence that phenol exposure resulted in significant damage, there is some indication of liver, kidney, and lung pathology in this study, but the inadequate reporting precludes the determination of whether there was a treatment-related effect.

3.2.2. Rabbits

Studies with repeated inhalation exposure

Deichmann et al. (1944) exposed 6 rabbits to phenol vapor concentrations of 100-200 mg/m³ (26-52 ppm) for 7 hours/day, 5 days/week for a total of 63 exposures over a period of 88 days. Rabbits did not show any signs of illness or discomfort. Gross and microscopic examinations revealed widespread confluent lobular pneumonia in the lungs, myocardial degeneration with necrosis of muscle bundles and interstitial fibrosis, centrolobular degeneration and necrosis in the liver, cloudy swelling and edema of convoluted tubules, scattered tubular degeneration, atrophy and dilatation as well as glomerular degeneration in the kidney.

3.2.3. Rats

Flickinger (1976) exposed a group of 6 female Harlan-Wistar rats whole-body for 8 hours to a phenol aerosol at 900 mg phenol/m³. The aerosol was generated using aqueous phenol and a D_{18} Dautrebande aerosol generator operated at 30 psi. The author stated that at this operating pressure, the generator delivers droplet diameters of ≤ 1 µm. Nominal exposure concentrations were determined by measurement of the volume loss of solution following aerosolization. The weight of the chemical present in that volume was then calculated and related to the total volume of air used in generating the aerosol to obtain the chamber concentration. The postexposure observation period was 14 days. The exposure to an aerosol containing 900 mg phenol/m³ caused no deaths, but ocular and nasal irritation was observed, as well as slight loss of coordination with skeletal muscle spasms within 4 hours. Tremors and prostration developed in 1/6 rats within 8 hours. Rats appeared normal the following day and continued to gain body

weight normally over the next 14 days. No lesions attributable to inhalation of the aerosol were seen at gross autopsy. Since the aerosol concentration used was below the vapor pressure at room temperature, it was considered adequate to convert the aerosol concentration of 900 mg/m³ to an equivalent vapor concentration of 234 ppm for calculations and comparison with other studies.

Brondeau et al. (1990) exposed Sprague-Dawley rats whole-body at 0, 111, 156 or 211 ppm phenol for 4 hours. At conclusion of exposure, rats were killed and cellular components of the blood were analyzed. No effect on erythrocyte and leukocyte differential counts could be discerned. The total white blood cell count was significantly reduced after exposure at 156 or 211 ppm. Other signs of toxicity were not evaluated. The authors interpreted this finding as a result of increased secretion of corticosteroids as a response to sensory irritation. The authors showed for five other chemicals also causing leukopenia, that this effect did not occur in adrenalectomized rats.

Studies with repeated inhalation exposure

CMA (1998) (published as Hoffman et al., 2001) exposed groups of 20 male and 20 female Fischer 344 rats via flow-past nose-only inhalation protocol to phenol vapor at 0, 0.5, 5 or 25 ppm for 6 hours/day, 5 days/week for 2 weeks. HPLC measurement of exposure concentrations determined mean (± SD) analytical concentrations of 0.0±0.0, 0.52±0.078, 4.9±0.57 and 25±2.2 ppm, respectively; nominal concentrations for the three phenol-treated groups were 0.67±0.051, 6.6±0.21 and 29±1.3 ppm, respectively. Physical observations were performed once during each exposure for all animals and twice daily, in-cage, for viability (prior to and 30 min after exposure). Detailed physical examinations were conducted on all animals twice pretest and weekly thereafter. Body weight measurements were recorded twice pretest and weekly thereafter, as well as prior to the first exposure. Following 10 exposures, 10 animals/sex/group were sacrificed and the remaining animals held for a recovery period of 2 weeks, after which these animals were sacrificed. Food consumption was recorded conducted during the week prior to exposure initiation and weekly thereafter. Hematology and clinical chemistry parameters were collected at termination (10 animals/sex/group) or during recovery (10 animals/sex/group). Complete gross evaluations were conducted on all animals. Microscopic evaluations were conducted on the liver, kidney, nasopharyngeal tissues, larynx, trachea and lungs and gross lesions for animals in the control and high-exposure groups, at termination or during recovery. For histopathology of nasopharyngeal tissues, the skull, after decalcification, was serially sectioned transversely at approximately 3-µm intervals and routinely, four sections were examined per animal.

No differences between control and phenol-exposed animals for clinical observations, body weights, food consumption and clinical pathology were found. The authors stated that "scattered observations of chromodacryorrhea and nasal discharge" were noted during the two weeks of exposure. However, the authors found these changes did not appear treatment-related and mostly abated during the 2 week recovery period." While this was true for chromodacryorrhea, the summary tables of in-life physical observations reported the following incidences of red nasal discharge in the control, 0.5-ppm, 5-ppm and 25-ppm groups: 0/20, 0/20, 3/20 and 4/20 males and 0/20, 0/20, 1/20 and 0/20 females in the first week and 0/20, 0/20, 7/20 and 10/20 males and 0/20, 1/20, 3/20 and 0/20 females in the second week. No differences between control and phenol-exposed animals for organ weights and macroscopic and microscopic postmortem examinations were reported. The authors concluded that no adverse effects were seen at phenol concentrations up to 25 ppm.

Dalin and Kristoffersson (1974) exposed rats (males and females, two experiments with 7 phenol-exposed and 12 control animals each; rat strain not stated) whole-body at 100 mg/m³ (26 ppm) phenol vapor 24 hours/day for 15 days (the authors did not state whether the exposure concentration was checked analytically). One day after initiation of exposure the physical activity of the phenol-exposed rats was increased. During the third and fourth days, the animals showed impaired balance and abnormal gait. Involuntary skeletal muscle twitches were observed. The authors stated that these twitches were relatively mild and the external appearance of the animals indicated that they were in relatively good condition. These signs disappeared by day 5 and were replaced by sluggish behavior until the end of the exposure. At termination of phenol exposure, the tilting plane method was used to measure effects on the central nervous system and the phenol-exposed rats showed a significantly reduced sliding angle than before exposure or compared to control.

Mukhito (1964) exposed groups of 15 male "white rats" whole body to phenol at 0, 0.01, 0.1 or 5 mg/m³ (0.0026, 0.026 or 1.3 ppm) for 24 hours/day 61 days. Analytical concentrations were obtained once or twice daily using a colorimetric assay. Analytical concentrations were 0.0112±0.0014 mg/m³ (0.0029±0.00036 ppm), 0.106±0.0324 mg/m³ (0.028±0.0084 ppm) and 5.23±0.44 mg/m³ (1.36±0.11 ppm). While behavior of the rats at the two lower exposure concentrations was not different from controls, animals were "somewhat sluggish and sleepy" in the highest exposure group. Right hind leg muscle antagonists motor chronaxy was measured once every 10 days in 5 rats of each exposure group. A statistically significant motor chronaxy (mostly seen as shortened extensor chronaxy) was observed in rats exposed at 0.1 or 5 mg/m³, starting after 30 days of exposure.

Sandage (1961) exposed groups of 50 male Sprague-Dawley rats whole body at 0 or 5 ppm phenol vapor for 24 hours/day 90 days. Concentrations were determined by a colorimetric assay. An average phenol concentration of 4.72 ppm was measured (the allowed range of 4.5-5.5 ppm was not exceeded according to the authors). No significant effects were found in tests assessing hematology and urine parameters as well as in histopathological examinations.

Deichmann et al. (1944) exposed 15 rats whole body to phenol vapor concentrations of 100-200 mg/m³ (26-52 ppm) for 7 hours/day, 5 days/week for a total of 53 exposures over 74 days. These animals failed to show any signs of illness. No macroscopic or microscopic lesions were observed.

Studies with non-inhalation exposure

Berman et al. (1995) gave groups of 10 female Fischer 344 rats single oral gavage doses of 0, 12, 40, 120 or 224 mg/kg or daily doses of 0, 4, 12, 40 or 120 mg/kg for 2 weeks (14 total gavage doses) phenol in corn oil. Repeated exposure to 120 mg/kg killed 8/10 animals (see Section 3.1.1). Hepatocellular necrosis was observed after a single dose of 40 mg/kg in 1/7 animals and at 120 mg/kg in 2/6, but not after repeated exposure to 40 mg/kg. Renal tubular necrosis, protein casts and papillary hemorrhage developed in 4/6 animals given 224 mg/kg (single) and in 3/8 animals at 40 mg/kg (repeated). Necrosis or atrophy of spleen or thymus were found in 1/8 animals at 12 mg/kg (single and repeated), 2/8 animals at 40 mg/kg (repeated), 1/7 animals at 120 mg/kg and 4/6 animals at 224 mg/kg.

3.2.4. Mice

Studies with repeated inhalation exposure

Sandage (1961) exposed groups of 100 male "general purpose albino mice" at 0 or 5 ppm phenol 24 hours/day for 90 days. Exposure concentrations were determined by a colorimetric assay. An average phenol concentration of 4.72 ppm was measured (the allowed range of 4.5-5.5 ppm was not exceeded according to the authors). No significant effects were found in tests assessing hematology and urine parameters as well as in histopathological examinations.

De Ceaurriz et al. (1981) determined the phenol vapor concentration associated with a 50 % reduction in the respiratory rate (RD_{50}) in male Swiss OF_1 mice. Analytical exposure concentration measurements were performed by pumping a defined volume of air from the exposure chamber through a glass tube packed with silica gel as a solid sorbent and analyzing the amount of phenol by gas chromatography. The authors used at least 4 different concentrations and 6 mice at each concentration. For measurement of respiration rate, mice were secured in individual body plethysmographs. During phenol exposure, the plethysmographs were inserted through the wall of the exposure chamber; the head of each animal was extended into the inhalation chamber. During 10 minutes, a control level was established, during which time the mice were exposed to room air. The mice were then rapidly placed in the stabilized cell with a predetermined concentration of phenol and were exposed for about 5 minutes. The phenol vapor RD_{50} for mice was calculated as 166 ppm.

TABLE 4: SUMMARY OF NON-LETHAL EFFECTS IN ANIMALS AFTER INHALATION EXPOSURE

Species	Concentration (ppm)	Exposure duration	Comments	Reference
monkey	5	24 h/d, 90 d	no or minimal hepatic histologic change	Sandage (1961)
rabbit	26-52	7 h/d, 5 d/w, 88 d	pneumonia, histological degeneration in heart, liver and kidney	Deichmann et al. (1944)
rat	900 mg/m³ as aerosol (equivalent to 234 ppm)	8 h	ocular and nasal irritation, incoordination, prostration	Flickinger (1976)
rat	111, 156 or 211	4 h	reduced leucocyte counts after 211 or 56 ppm; no effects after 111 ppm	Brondeau et al. (1989)
rat	26	24 h/d, 15 d	after one day increased activity; during third and fourth day impaired balance, disordered gait and muscle twitchings; sluggish	Dalin and Kristofferson, 1974
rat	0.5, 5 or 25	6 h/d, 5 d/w, 2 w	no clinical, hematological or histopathological effects	CMA, 1998; Hoffman et al., 2001
rat	0.0026, 0.026 or 1.3	24 h/d, 61 d	significant motor chronaxy starting at 30 d in the two highest exposure groups	Mukhito (1964)
rat	5	24 h/d, 90 d	no hematological or histopathological effects	Sandage (1961)
rat	26-52	7 h/d, 5 d/w, 74 d	no signs of gross or histopathologic change	Deichmann et al. (1944)
mouse	5	24 h/d, 90 d	no hematological or histopathological effects	Sandage (1961)
mouse	166	5 min	RD_{50}	De Ceaurriz et al. (1981)

3.3. Developmental/Reproductive Toxicity

3.3.1 Rats

Studies with repeated non-inhalation exposure

Jones-Price et al. (1983a) exposed groups of 20-22 pregnant CD rats by gavage to phenol at 0, 30, 60 or 120 mg/kg on gestational days 6 to 15. The dams were evaluated at sacrifice (day 20) for body weight, liver weight, gravid uterine weight, and status of uterine implantation sites. Live fetuses were weighed, sexed, and examined for gross morphological abnormalities and malformations in the viscera

and skeleton. No dose-related signs of maternal toxicity were observed. Although the number of resorptions was increased in all treated groups compared to the control group, this increase was not dose-dependent and was not observed in a previous range-finding study. In the group given 120 mg/kg, fetal body weights were significantly reduced. No other signs of developmental toxicity were observed. Thus, on the basis of decreased fetal body weight, the mid dose in this study of 60 mg/kg/day was a NOAEL for developmental toxicity and the high dose of 120 mg/kg/day was an equivocal LOAEL. The high dose was a maternal NOAEL.

In a screening-test validation study, Narotsky and Kavlock (1995) exposed groups of 15-20 pregnant F344 rats by gavage to doses of 0, 40 or 53.3 mg/kg on gestational days 6 to 19. In both treated groups, dams showed dyspnea and rales in the lungs. Complete resorptions were found in 1 litter in the low and 2 litters in the high exposure group.

Ryan et al. (2001) evaluated the potential reproductive toxicity of phenol in a rat two-generation reproduction study, which included additional study endpoints, such as sperm count and motility, developmental landmarks, histological evaluation of suspect target organs (liver, kidneys, spleen, and thymus), weanling reproductive organ weights, and an immunotoxicity screening plaque assay. Phenol was administered to 30 Sprague-Dawley rats/sex/group in the drinking water at concentrations of 0, 200, 1000, or 5000 ppm corresponding to daily intake of phenol of 0,14, 70, and 310 mg/kg/day for males and 0, 20, 93, and 350 mg/kg/day for females. Parental (P1) animals were treated for 10 weeks prior to mating, during mating, gestation, lactation, and until sacrifice. The F1 generation (P1 offspring) was treated using a similar regimen, while the F2 generation was not treated. After mating, 10 P1 males/group were evaluated using standard clinical pathology parameters and an immunotoxicity screening plaque assay. Significant reductions in water and food consumption were observed in the 5000-ppm group in both generations; corollary reductions in body weight/body weight gain were also observed. Mating performance and fertility in both generations were similar to controls, and no adverse effects on vaginal cytology or male reproductive function were observed. Vaginal opening and preputial separation were delayed in the 5000-ppm group, and were considered to be secondary to the reduction in F1 body weight. Litter survival of both generations was reduced in the 5000-ppm group. Absolute uterus and prostate weights were decreased in the F1 generation at all dose levels; however, no underlying pathology was observed and there was no functional deficit in reproductive performance. Therefore, these findings were not considered to be adverse. No evidence of immunotoxicity was noted in the 5000-ppm group. The effects noted at the high concentration were presumed to be associated with flavor aversion to phenol in the drinking water. Based on a comprehensive examination of all parameters, the NOAEL for reproductive toxicity of phenol administered in drinking water to rats is 1000 ppm (equivalent to 70 mg/kg/day for males and 93 mg/kg/day for females).

3.3.2 Mice

Studies with repeated non-inhalation exposure

Jones-Price et al. (1983b) exposed groups of 22-29 pregnant CD-1 mice in a teratogenicity study by gavage to phenol doses of 0, 70, 140 or 280 mg/kg on gestational days 6 to 15. Maternally toxic effects, such as tremor, ataxia, reduced body weight development and death of 4/36 dams were observed at 280 mg/kg. At 140 mg/kg slight tremor was observed after the first three exposures. Reduced fetal weights were observed in the highest exposure group. An increased incidence of cleft palate was also reported at the highest dose level, although the incidence was not significantly different from that of the

other groups and there was no statistically significant increase in the incidence of litters with malformations. There was no other evidence of altered prenatal viability or structural development. Thus, the high dose of 280 mg/kg/day was a maternal frank effect level and also a developmental LOAEL based on decreased fetal body weight (accompanied by a possible increase in the incidence of cleft palate) in the fetuses, an effect that was likely secondary to the severe toxicity in the dams. The study NOAEL for maternal and developmental toxicity was 140 mg/kg/day.

3.4. Genotoxicity

Genotoxicity studies have found that phenol tends not to be mutagenic in Salmonella typhimurium tester strains either with or without S9-mix (Haworth et al., 1983; Glatt et al., 1989), but positive or equivocal results have been obtained in gene mutation assays in mammalian cells (McGregor et al., 1988a, 1988b; Tsutsui et al., 1997). Increases were larger in the presence of S9 activation.

Phenol tended to induce micronuclei in mice when administered intraperitoneally (LOEL 90-160 mg/kg injected intraperitoneally daily for 2 or 3 days) (Shelby et al., 1993; Marrazzini et al., 1994; Chen and Eastmond,1995), but it produced negative (or positive only at very high doses) results when administered orally (see Greim, 1998; IARC, 1999; EPA, 2002 for review). This difference is likely due to the first-pass conjugation and inactivation of orally administered phenol in the liver.

Using cultured Syrian hamster embryo cells, phenol induced DNA synthesis (starting at 1 µmol/l), chromosomal aberrations (positive at 100 µmol/l) and sister chromatid exchanges (starting at 1000 µmol/l) and cell transformation (starting at 10 µmol/l) (Tsutsui et al., 1997).

Phenol was also positive in in vitro micronucleus tests with human lymphocytes (Yager et al., 1990) and CHO cells (Miller et al., 1995), and it caused chromosome aberrations in the presence of S9 activation in CHO cells (Ivett et al., 1989).

3.5. Carcinogenicity

No valid inhalation studies evaluating the potential carcinogenic activity were located (BUA, 1998; IARC, 1999; EPA, 2002).

In an oral bioassay (NCI, 1980), groups of 50 male and female B6C3F1 mice and F344 rats received 0, 2500 or 5000 mg/l phenol in drinking water, leading to estimated doses of 281 or 412 mg/kg/day for mice and 270 or 480 mg/kg/day for rats. Rats showed inflammation in the kidneys. No increased incidence of tumors was observed in mice or female rats. A significant incidence of tumors (pheochromocytomas of the adrenal gland, leukemia or lymphoma) occurred in male rats of the low exposure group, but there was no dose-response relationship.

Topical phenol has a tumor promoting activity and can induce skin tumors in mice after repeated dermal exposure (2.5 mg in 25 µl benzene, 2 times/week for 40 weeks). However, the promotion was evident only in the presence of skin lesions, which were observed during the first 6 weeks) (Boutwell and Bosch, 1959).

IARC (1999) evaluated the findings on carcinogenicity and concluded that there is inadequate evidence in both humans and experimental animals for the carcinogenicity of phenol. Consequently, phenol was found "not classifiable as to its carcinogenicity to humans (Group 3)". EPA (2002) concluded that, "the data regarding the carcinogenicity of phenol via the oral, inhalation, and dermal exposure routes are inadequate for an assessment of human carcinogenic potential. Phenol was negative in oral carcinogenicity studies in rats and mice, but questions remain regarding increased leukemia in male rats in the bioassay as well as the positive gene mutation data and the positive results in dermal initiation/promotion studies at doses at or above the maximum tolerated dose (MTD). No inhalation studies of an appropriate duration exist. Therefore, no quantitative assessment of carcinogenic potential via any route is possible." Therefore, carcinogenicity was not an endpoint in the derivation of AEGL values.

3.6. Summary

No studies reporting LC_{50} values for phenol are available. Five of 12 guinea pigs died after 20 exposures at 26-52 ppm phenol for 7 hours/day, 5 days/week (Deichmann et al., 1944). Under the same conditions, rabbits exposed for 88 days showed no clinical signs of overt poisoning, but developed pneumonia and degeneration in heart, liver and kidney. Rats exposed for 74 days showed neither clinical signs nor histological alterations (Deichmann et al., 1944). Oral lethal doses of 420 mg/kg for rabbits, 400-650 mg/kg for rats (Deichmann and Witherup, 1944) and 282-427 mg/kg for mice (Horikawa and Okada, 1975; Von Oettingen and Sharples, 1946; Kostoveckii and Zholdakova, 1971) have been reported.

In 10 rhesus monkeys, exposed 24 hours/day for 90 days at 5 ppm phenol by inhalation, no significant effects were found in hematology, urine parameters, blood chemistry or renal function or at autopsy or histologic examinations (Sandage, 1961).

Rats that inhaled a phenol aerosol at 900 mg/m³ (equivalent to 234 ppm) for 8 hours developed ocular and nasal irritation, incoordination and prostration (Flickinger, 1976). A reduction of the number of circulating leucocytes was observed in rats after 4-hour exposure at 211 or 156 ppm; no effect was seen for 111 ppm (Brondeau et al., 1989). After exposure of rats at 0.5, 5 or 25 ppm for 6 hours/day, 5 days/week for 2 weeks no clinical, hematological or histopathological effects were found (CMA, 1998; Hoffmann et al., 2001). Continuous exposure at 5 ppm phenol for 90 days caused no hematological or histological effects in rats and mice (Sandage, 1961). A concentration of 166 ppm (for 5 min) resulted in a 50 % decrease of respiration (RD_{50}) in mice (De Ceaurriz et al., 1981).

Reduced fetal body weights were found in studies using repeated oral gavage and doses of up to 120 mg/kg in CD rats (on gestational days 6-15) and 140 mg/kg in CD-1 mice (on gestational days 6-19) (Jones-Price et al., 1983a; 1983b). In a two-generation drinking water study in Sprague-Dawley rats, decreased pup survival linked to decreased maternal body weight was observed at the highest dose of 5000 ppm; the NOAEL was 1000 ppm (equivalent to 70 mg/kg/day for males and 93 mg/kg/day for females) (Ryan et al., 2001).

Phenol has weak clastogenic and genotoxic activity both in vitro and in vivo (Shelby et al., 1993; Marrazzini et al., 1994, Chen and Eastmond, 1995; Tsutsui et al., 1997). A lifetime oral bioassay of phenol in rats and mice, using exposure through drinking water, found increased numbers of male rats of the low exposure group with pheochromocytoma, leukemia or lymphoma, but not among male rats of the

high exposure group, female rats and mice (NCI, 1980). Phenol has tumor promoting and tumorigenic activity when applied dermally (Boutwell and Bosch, 1959). IARC (1999) evaluated the findings on carcinogenicity and concluded that there is inadequate evidence in both humans and experimental animals for the carcinogenicity of phenol. Consequently, phenol was found "not classifiable as to its carcinogenicity to humans (Group 3)". EPA (2002) concluded that, "the data regarding the carcinogenicity of phenol via the oral, inhalation, and dermal exposure routes are inadequate for an assessment of human carcinogenic potential".

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Phenol is a normal product of protein catabolism and it is taken up directly from cigarette smoke and food (especially smoked products). Sittig (1980) reported phenol concentrations in human urine between 5-55 mg/l. Dugan (1972) stated that humans eliminate 0.2-6.6 mg/kg/day in urine and up to 3 mg/kg/day in feces. Piotrowski (1971) reported 8.7±2.0 mg/day as the daily excretion rate of total phenol (free plus conjugates) in humans with no known exposure to phenol.

Inhaled phenol is absorbed readily into systemic circulation. Piotrowski (1971) exposed 8 subjects by face mask to phenol concentrations between 5 and 25 mg/m³ (1.3-6.5 ppm) for 8 hours, with two breaks of 0.5 hours each after 2.5 and 5.5 hours. The concentration of phenol in inhaled and exhaled air was determined and urine was analyzed for total phenol (phenol and conjugates). Steady state was achieved within 3 hours. The steady state systemic uptake/absorption was 60-88 %. Urinary recovery of absorbed phenol was 99 % within 24 hours after initial exposure.

After a single oral dose of 0.01 mg/kg radiolabeled phenol given to three male subjects (smoker status not reported), 85-98 % of the dose was excreted in the urine in 14 hours (Capel et al., 1972). These data demonstrate that very small concentrations of phenol are readily absorbed by the human gastrointestinal tract. In 18 other mammalian species, mean 24-hour recoveries ranged from 95 % in the rat to 31 % in the squirrel monkey (Capel et al., 1972).

Piotrowski (1971) also performed whole-body skin exposures in human subjects (7 men aged 25-42 and one woman aged 30, smoker status not reported). The subjects were exposed to phenol vapor concentrations of 5, 10 or 25 mg/m³ (1.3, 2.6 or 6.5 ppm) for 6 hours; fresh air was supplied through a face mask to preclude pulmonary absorption. The total amount of phenol excreted in urine during and after exposure was used as a measure of absorption. Percutaneous clearance was estimated to be 0.35 m³/h, i.e. the amount of phenol contained in 0.35 m³ was taken up per hour.

Assuming a ventilation rate of 0.8 m³/h and a pulmonary retention of 70 %, ATSDR (1998) calculated clearance of airborne phenol through the lungs was 0.6 m³/h and concluded percutaneous absorption to be half the pulmonary uptake over the concentration range between 5-25 mg/m³ (1.3-6.5 ppm).

Topical phenol is absorbed readily. After application of phenol solutions of 2.5-10.0 g/l on the forearm skin of 12 male and female subjects (aged 20-42 not having phenol contact or taking medicines, smoker status not reported), absorption rate increased with concentration (0.079 to 0.301 mg/cm²/h). After 30-minute immersion of a whole hand into the same phenol concentrations (with calculated absorbed doses between 15.2 and 62.4 mg), phenol excretion in urine within 24 hours amounted to about 80 % of the absorbed dose. Increasing the phenol solution temperature from 20 °C to 35 °C led to an 1.67fold increase in skin absorption (Baranowska-Dutkiewicz, 1981).

At 72 hours after intratracheal instillation of radiolabeled phenol, radioactivity (1-5 % of total dose) was found in rat lungs, skin, blood, muscle, adipose tissue and liver (Hughes and Hall, 1995). Seventy-two hours after oral exposure of rats, radioactivity was distributed mainly in muscle, skin,

adipose tissue, liver and blood (Hughes and Hall, 1995). Thirty minutes after oral exposure of rats, the highest concentrations of administered dose were found in liver (29-56 %); approximately 67-85 % was present in the plasma, of which 41-50 % was bound to proteins or other macromolecules (Liao and Oehme, 1981).

Three different enzymes participate in phenol metabolism: phenol sulfotransferases catalyze transfer of inorganic sulfate from 3'-phosphoadenosine-5'-phosphosulfate to the hydroxyl group of phenol to form the sulfate conjugate. Uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases) catalyze the transfer of a glucuronic acid moiety to the hydroxyl group of phenol to form an O-glucuronide conjugate. Cytochrome P450 2E1 catalyzes the hydroxylation of phenol to form hydroquinone and to a much lesser extent catechol, which are then conjugated mainly with sulfate and glucuronic acid (Capel et al., 1972; Cassidy and Houston, 1984). In addition, other cytochrome P450 isoenzymes, such as 2F2, may also be involved in phenol oxidation (Powley and Carlson, 2001). In vivo conjugation occurs mainly in liver, lung and gastrointestinal tract (Cassidy and Houston, 1984).

Since the sulfate conjugation pathway is saturable at lower doses than the glucuronic acid conjugation, the ratio of sulfate/glucuronide conjugates in rats decreased with increasing phenol dose (Koster et al., 1981). The ration of sulfate/glucuronide conjugates shows a species dependency (Capel et al., 1972). With respect to oxidation, at a dose of 25 mg/kg, mice excreted 7fold higher amounts of total hydroquinone than rats (Capel et al., 1972). Kenyon et al. (1995) administered ^{14}C-phenol to B6 mice of both sexes and observed that, males excreted a greater proportion of hydroquinone glucuronide than did females at all doses; the difference was roughly twofold at a dose of 40 µmol/kg.

Phenol, in both free and conjugated forms, is excreted rapidly in urine. Human volunteers, exposed to phenol concentrations between 5 and 25 mg/m³ (1.3-6.5 ppm) for 8 hours excreted 99 ± 8 % of the retained dose in the urine within 24 hours after start of exposure (Piotrowski, 1971). After oral exposure of humans to radiolabeled phenol, the mean 24-hour recovery of radioactivity in the urine was 90 % (range 85-90 %) (Capel et al., 1972). In rats, elimination of radioactivity in the urine was 95 % complete 24 hours after intratracheal or oral administration of radiolabeled phenol (Hughes and Hall, 1995).

The urinary level of total phenol (free phenol and conjugated phenol) increased linearly with phenol concentrations in air in exposed workers (Ohtsuji and Ikeda, 1972).

4.2. Mechanism of Toxicity

Phenol is an irritant of eyes and nose in rats (Brondeau et al., 1990; Flickinger, 1976). After acute ingestion of high doses by humans, burns, hyperemia and inflammation of mucous membranes and edema and inflammation of the lungs has been found (Bennett et al., 1950; Stajduhar-Caric, 1968; Tanaka et al., 1998). Burns and necrosis develop in humans after skin contact (Spiller et al., 1993; Schaper, 1981). From these findings it can be concluded that phenol causes local tissue damage at the sites of contact. The mechanism of acute irritation of skin and mucous membranes is not known. However, because phenol at higher concentrations precipitates proteins from solution (Lewin, 1992) and dissolves in both water and organic solvents, interference with normal protein, enzyme and membrane function seems likely. Direct toxicity on bone marrow cells in vivo was suggested by Tunek et al. (1981) at high exposure concentrations.

With regard to systemic it has been reported that phenol exposure results in hypotension and arrhythmias in humans and experimental animals (Bennett et al., 1950; Stajduhar-Caric, 1968; Schaper, 1981 Kamijo et al., 1999; Deichmann and Witherup, 1944). Phenol blocks the cardiac sodium channel subtype, with little effect on sodium channels in skeletal muscle (Zamponi et al., 1994). Following ingestion, typical signs in both humans and animals include agitation, muscle tremors, confusion, incoordination, seizures, coma and respiratory arrest (Kamijo et al., 1999; Schaper, 1981; Deichmann and Witherup, 1944). Kamijo et al. (1999) suggested that phenol causes tremors directly by inducing increased acetylcholine release both in the peripheral nervous system at motor nerve endings and within the central nervous system, and that the resultant reduction in brain acetylcholine levels indirectly suppresses the tremor.

Since phenol is rapidly metabolized, systemic toxicity may be due to the combined actions of the parent compound and its metabolites. Eastmond et al. (1987) investigated the role of phenol in benzene-induced myelotoxicity. Treatment of male B6C3F1 mice with intraperitoneal doses as high as 150 mg phenol/kg twice daily or for 12 days caused no suppression of bone marrow cellularity. Only minimal suppression was observed in mice dosed with up to 100 mg hydroquinone/kg . By contrast, significant, dose-related suppression was seen in mice treated with 75 mg/kg phenol and 75 mg/kg hydroquinone under the same conditions. In further in vitro studies, the authors showed that phenol stimulates the horseradish peroxidase-mediated metabolism of hydroquinone, and they hypothesized that similar stimulation of local myeloperoxidase occurs in the bone marrow. Corti and Snyder (1998) evaluated the effects of benzene metabolites on cultured mouse bone marrow cells by measuring colony forming units of erythroid progenitor cells and found that the cytotoxicity of phenol was much lower than that of other hydroquinone and benzoquinone.

It has been hypothesized that the genotoxicity of phenol on the bone marrow result form the following chain of events: phenol is conjugated in the liver to phenylsulfate, this metabolite reaches the bone marrow via the blood stream and is cleaved there by sulfatases yielding phenol again, which can than be oxidized to hydroquinone and benzoquinone, resulting in damage of cells by direct binding to macromolecules and by formation of oxygen radicals (Greim, 1998).

4.3. Structure-Activity Relationships

No clear structure-toxicity relationships between phenol, substituted phenols and benzenediols, cresols or chlorophenols have been published. While IDLH values were based on "an analogy to cresol" (NIOSH, 1996), Deichmann and Keplinger (1981) stressed the considerable differences in toxicity between phenol and other phenolic compounds including cresols.

4.4. Other Relevant Information

4.4.1. Interspecies Variability

Deichmann et al. (1944) found species differences after repeated inhalation exposure: five of 12 guinea pigs died after 20 exposures at 26-52 ppm phenol for 7 hours/day, 5 days/week, while under the same conditions, rabbits exposed for 88 days showed no signs of overt poisoning, but some histological degeneration in target tissues and rats exposed for 74 days to the same concentrations developed neither clinical signs nor histological alterations. No definitive information on the reasons for these species differences is available.

In contrast to the 1944 inhalation data, oral lethal doses differed little between species (see Table 3) and were 420 mg/kg for rabbits, 400-650 mg/kg for rats (Deichmann and Witherup, 1944) and 282-427 mg/kg for mice (Horikawa and Okada, 1975; Von Oettingen and Sharples, 1946; Kostoveckii and Zholdakova, 1971).

Overall the available data are not considered a sufficient basis in itself to reduce the default interspecies uncertainty factor.

4.4.2. Intraspecies Variability

Deichmann and Witherup (1944) found some differences in lethality following an oral dose of phenol between 10-day old and 5-week-old or adult rats. After oral gavage of 600 mg/kg of 5 % aqueous phenol, 90 % of 10-day-old rats died, while 30 % of 5-week-old rats and 60 % of adult rats died. After dermal application of 3000 mg/kg mortality was 65, 25 and 45 %, respectively.

There are no studies indicating that newborn babies and infants are more sensitive to phenol than adults. The death of a newborn after exposure to 5.2 ppm phenol for 5-6 hours and 1.3 ppm for another 14-15 hours (Heuschkel and Felscher, 1983) could not be attributed to a unique susceptibility because the newborn had a congenital pulmonary disorder. Moreover, the newborn was additionally exposed to formaldehyde (24.9 ppm (measured at 2 hours) for 5-6 hours and 41.5 ppm (highest concentration, with decrease over time) for another 14-15 hours). The formaldehyde may have contributed to death. For example, in rats exposure at 40 ppm formaldehyde for 6 hours/day, 5 days/week was lethal (Maronpot et al., 1986).

With respect to metabolism, both reduced and increased capacities for sulfate and glucuronic acid conjugation, depending on the chemical (no data available for phenol), have been described in newborn and young infants compared to adults (Brashear et al., 1988, Renwick, 1998). Generally cytochrome P450 activity is reduced in newborn and young infants, which reduces the potential of toxic effects caused by oxidation and protein binding of quinone metabolites. However, elimination via the kidney is reduced for many chemicals and drugs (low glomerular filtration rate during the first 8 months; Besunder et al., 1988; Renwick, 1998) and this could lead to an increased half-life of phenol. Nonetheless, no definitive data for phenol are available.

Overall, while the available data do not point at a large intraspecies variability, they are not considered a sufficient basis in itself to reduce the default intraspecies uncertainty factor.

4.4.3. Skin Irritation and Sensitization

Application of concentrated phenol to intact human skin resulted in inflammation and necrosis at the site of application (Spiller et al., 1993; Schaper, 1981). Increased skin rash, mouth sores and throat sores have been reported in 17 of 39 humans following repeated contact with phenol (>1 ppm) in drinking water (Baker et al., 1978).

Phenol showed no sensitizing capacity in a human maximization test using 24 subjects and a 2 % phenol solution (Kligman, 1966), a guinea pig maximization test (Itoh, 1982) and a mouse ear swelling test (Descotes, 1988).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Piotrowski (1971) exposed 8 volunteers by face mask to phenol at 5-25 mg/m³ (1.3-6.5 ppm) for 8 hours, with two breaks of 0.5 hours each after 2.5 and 5.5 hours. The author did neither report any complaints or adverse effects of phenol exposure nor did the report explicitly state the absence of any effects. In a toxicokinetic field study (Ogata et al., 1986), 20 workers were exposed to mean workshift concentrations of 1.22-4.95 ppm. The authors neither reported any health effects of phenol exposure on the subjects nor did they explicitly state the absence of any adverse effects.

Odor thresholds for phenol were reported as 0.0057-0.036 ppm (odor recognition threshold; Mukhitov, 1964) and 0.047 ppm (odor detection threshold; Leonardos et al., 1969) and 0.060 ppm (mean odor detection thresholds from the literature) (AIHA, 1989). Don (1986) reported an odor detection threshold of 0.010 ppm in an EN13725:2003-comparable study.

Ruth (1986) reported an irritation threshold of 182.4 mg/m³ (47 ppm) in humans. The author tabulated odor and irritation threshold for a large number of chemicals, but did not indicate the source for the values.

5.2. Animal Data Relevant to AEGL-1

After exposure of rats at 0.5, 5 or 25 ppm for 6 hours/day, 5 days/week for 2 weeks no clinical, hematological or histopathological effects were found (CMA, 1998; Hoffmann et al., 2001). The authors reported the following incidences of red nasal discharge (chromadacryorrhea) in the control, 0.5-ppm, 5-ppm and 25-ppm groups: 0/20, 0/20, 3/20 and 4/20 males and 0/20, 0/20, 1/20 and 0/20 females in the first week (observations for individual exposures were not provided). However, histopathological analyses revealed no alterations of the epithelium of the nasal turbinates or other respiratory tract tissues.

Sandage (1961) exposed groups of 10 male rhesus monkeys at 5 ppm phenol continuously for 90 days. Exposure concentrations were determined by a colorimetric assay. No adverse effects were found in tests assessing hematology, urine parameters, blood chemistry and kidney function as well as in histological examinations.

Mukhito (1964) reported that continuous exposure of rats at 0.026 or 1.3 ppm for 61 days resulted in significant motor chronaxy (mostly seen as shortened extensor chronaxy) starting after 30 days, while no effect was found at 0.0026 ppm. The authors described the rats of the highest exposure group as "somewhat sluggish and sleepy".

5.3. Derivation of AEGL-1

Phenol is not a potent irritant; contact with phenol causes local tissue damage in the respiratory tract (Deichmann et al., 1944). At concentrations higher than 150 ppm, phenol causes irritation in rats (Flickinger, 1976) and respiratory depression in mice (De Ceaurriz et al., 1981).

The pharmacokinetic study in humans (Piotrowski, 1971) was not used as key study because it did not report on health effects. The Sandage (1961) study in monkeys was not used because, apparently, exposure chambers did not allow observation of the animals during the exposure and histopathology was performed on the lungs, but not on the upper respiratory tract so that possible upper airway irritation was not adequately evaluated. Therefore, the study by CMA (1998) (published as Hoffmann et al., 2001) was the only study fulfilling the SOP requirements for a key study and was therefore used for derivation of AEGL-1 values although it was a repeated exposure study. After exposure of rats for 6 hours/day, 5 days/week for 2 weeks, no histopathological alterations of the epithelium of the nasal turbinates or other respiratory tract tissues were found. The observation of red nasal discharge in a few male rats of the 5-ppm and 25-ppm group was not considered a relevant effect, because no clear dose-response relationship was found and because predominately males, but not females, showed this effect. Moreover, red nasal discharge occurs at the plexus antebrachii, which is very prominent in the rat, and in the rat extravasation of red blood cells visible as red nasal discharge is caused easily not only by locally acting chemicals, but also by stress, dry air or upper respiratory tract infections. The derivation of AEGL-1 values was based on an exposure concentration of 25 ppm for 6 hours.

Time scaling using the equation $C^n \times t = k$ was carried out to derive exposure duration-specific values. Due to lack of a definitive data set, a default value for n of 3 was used in the exponential function for extrapolation from the experimental period (6 hours) to shorter exposure periods and a default value for n of 1 was used for extrapolation to longer exposure times. For the 10-minute AEGL-1 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship. The calculations of exposure concentrations scaled to AEGL-1 time periods are shown in Appendix A.

A total uncertainty factor of 3 was applied in derivation of the phenol AEGL-1. An uncertainty factor of 1 was applied for interspecies variability: the toxicokinetic component of the uncertainty factor was reduced to 1 because toxic effects are mostly caused by phenol itself without requirement for metabolism. Moreover, possible local irritation effects depend primarily on the phenol concentration in inhaled air with little influence of toxicokinetic differences between species. The starting point for AEGL derivation was a NOAEL from a repeated exposure study and, thus, the effect level was below that defined for AEGL-1. The human experimental and workplace studies (Piotrowski, 1971; Ogata et al., 1986) support the derived values. Based on these arguments, the interspecies factor was reduced to 1. An uncertainty factor of 3 was applied for intraspecies variability because for local effects, the toxicokinetic differences do not vary considerably within and between species. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 while the factor of 3 for the toxicodynamic component, reflecting a possible variability of the target-tissue response in the human population was retained.

The derived AEGL-1 values are supported by the Sandage (1961) results, in which continuous inhalation by rhesus monkeys of 5 ppm phenol for 90 days failed to result in any sign of phenol toxicity. Other supporting studies are the pharmacokinetic study by Piotrowski (1971) which exposed subjects at up to 6.5 ppm and the study by Ogata et al. (1986) that reported an workplace exposure to up to 4.95 ppm.

The values are listed in Table 5 below.

TABLE 5: AEGL-1 VALUES FOR PHENOL					
AEGL Level	**10 minutes**	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	19 ppm (73 mg/m³)	19 ppm (73 mg/m³)	15 ppm (58 mg/m³)	9.5 ppm (37 mg/m³)	6.3 ppm (24 mg/m³)

A level of distinct odor awareness (LOA) for phenol of 0.25 ppm was derived on the basis of the odor detection threshold from the study of Don (1986) (see Appendix B for LOA derivation). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Inhalation data relevant for the derivation of AEGL-2 values are lacking.

Baker et al. (1978) described an incidence in which residents drank contaminated well water for several weeks following an accidental spill of phenol. Among persons exposed to >1 mg/l phenol in contaminated drinking water for several weeks (the authors estimated an intake of phenol of 10-240 mg/d), gastrointestinal symptoms (diarrhea, nausea, burning pain in the mouth and sores in the mouth) and skin rashes occurred (Baker et al., 1978).

Ruth (1986) reported an irritation threshold of 182.4 mg/m³ (47 ppm) in humans. The author tabulated odor and irritation threshold for a large number of chemicals, but did not indicate the source for the values.

6.2. Animal Data Relevant to AEGL-2

Flickinger (1976) reported that exposure of 6 female Harlan-Wistar rats for 8 hours at a nominal phenol aerosol at 900 mg phenol/m³ caused no deaths, but resulted in ocular and nasal irritation as well as in slight loss of coordination with spasms of the muscle groups within 4 hours and tremors and prostration (in 1/6 rats) within 8 hours. Rats appeared normal the following day. Since the aerosol concentration was below the vapor pressure at room temperature, it is likely that the animals were actually exposed to phenol vapor (or an vapor/aerosol mixture) and it is thus considered adequate to convert the aerosol concentration of 900 mg/m³ to an equivalent vapor concentration of 234 ppm.

After exposure of rats at 211 or 156 ppm phenol for 4 hours, a decreased white blood cell count was observed (Brondeau et al., 1990). The authors did not explicitly state the absence of other effects.

Deichmann et al. (1944) found that 5 of 12 guinea pigs died after 20 exposures at 26-52 ppm phenol for 7 hours/day, 5 days/week. Rabbits exposed under the same conditions for 88 days developed degeneration and necrosis in heart, liver and kidney. Rats exposed for 74 days showed neither clinical signs nor histological alterations. It should be noted that these 1940's experiments did not include concurrent control groups.

In the study of Dalin and Kristoffersson (1974), rats continuously exposed at 26 ppm showed increased activity about one day after exposure, impaired balance, disordered walking, muscle twitches and involuntary head movements during the third and fourth days. The symptoms passed off during the fifth day.

6.3. Derivation of AEGL-2

Due to the lack of more adequate studies, a combination of the Flickinger (1976) and Brondeau et al. (1990) studies were used as the basis for derivation of AEGL-2 values. Aerosol exposure at 900 mg/m³ phenol (equivalent to 234 ppm phenol vapor) for 8 hours resulted in ocular and nasal irritation, slight loss of coordination and spasms of the muscle groups at 4 hours into the exposure, after 8 hours additional

symptoms (tremor, incoordination and prostration) were observed in one of the six animals. No deaths occurred. This study is supported by the study of Brondeau et al. (1990), which did report only slight effects after exposure at 211 ppm phenol vapor for 4 hours. Although both studies had shortcomings, i.e., aerosol exposures, nominal concentrations, and no description of toxic signs in one study, taken together, they had consistent results. Since the aerosol concentration was below the saturated vapor concentration at room temperature of about 530 ppm, it can be assumed that much phenol had evaporated from the aerosol so that a mixed aerosol/vapor exposure can be assumed for the Flickinger (1976) study. A significant difference between vapor and aerosol inhalation toxicity was considered unlikely because phenol causes systemic effects, i.e., acute CNS depression, and has a high penetration of dermal and mucosal surfaces. It was therefore considered adequate to calculate and use the phenol vapor concentration corresponding to an phenol aerosol concentration of 900 mg/m³. The aerosol concentration of 900 mg/m³ is equivalent to a vapor concentration of 234 ppm. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 hours.

Time scaling using the equation $C^n \times t = k$ was carried out to derive exposure duration-specific values. Due to lack of a definitive data set, a default value for n of 3 was used in the exponential function for extrapolation from the experimental period (8 hours) to shorter exposure periods. For the 10-minute AEGL-2 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship. The calculations of exposure concentrations scaled to AEGL-2 time periods are shown in Appendix A.

A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies variability because oral lethal data did not indicate a high variability between species (cf. Section 4.4.1.) and because application of a higher uncertainty factor would have resulted in AEGL-2 values below levels that humans can stand without adverse effects (Piotrowski, 1971; Ogata et al., 1986). An uncertainty factor of 3 was applied for intraspecies variability because the study of Baker et al. (1978) that investigated health effects in members of 45 families (including children and elderly), that were exposed to phenol through contaminated drinking water for several weeks, did not indicate that symptom incidence or symptom severity was higher in any specific subpopulation. Moreover, newborns and infants were not considered more susceptible than adults because of their smaller metabolic capacity to form toxic phenol metabolites (cf. Section 4.4.2.). Based on the small data base and study shortcomings, a modifying factor of 2 was applied.

The calculations of AEGL-2 values are shown in Appendix A and the values are values are listed in Table 6 below.

TABLE 6: AEGL-2 VALUES FOR PHENOL

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-2	29 ppm (110 mg/m³)	29 ppm (110 mg/m³)	23 ppm (90 mg/m³)	15 ppm (57 mg/m³)	12 ppm (45 mg/m³)

Comparison of the AEGL-2 values with the RD_{50} in mice of 166 ppm (De Ceaurriz et al., 1981) support the derived values.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Case reports described lethal poisonings in adults after ingestion of doses of about 166-874 mg/kg (see Table 2) (Kamijo et al., 1999; Bennett et al., 1959; Stajduhar-Caric, 1968; Tanaka et al., 1998). In a newborn baby, tissue concentrations between 125 and 202 mg/kg were found after lethal dermal phenol exposure (Hinkel and Hintzel, 1968).

The study by Heuschkel and Felscher (1983) reporting death of a newborn baby after exposure to 5.2 ppm phenol for 5-6 hours and 1.3 ppm for another 14-15 hours will not be used for derivation of AEGL-3 values because 1) use of solid sorbent test tubes for measurement did not allow accurate determination of the exposure concentration, 2) the concomitant exposure to formaldehyde (24.9 ppm (measured at 2 hours) for 5-6 hours and 41.5 ppm (highest concentration, with decrease over time; also measured using test tubes) has probably contributed to death and 3) the newborn had a congenital pulmonary adaptation disorder, which probably rendered it vulnerable to phenol (and formaldehyde) inhalation.

7.2. Animal Data Relevant to AEGL-3

Deichmann et al. (1944) found that 5 of 12 guinea pigs died after 20 exposures at 26-52 ppm phenol for 7 hours/day, 5 days/week, while under the same conditions rabbits exposed for 88 days showed no signs of poisoning, but developed degeneration and necrosis in heart, liver and kidney, and rats exposed for 74 days showed neither clinical signs nor histological alterations. These experiments lacked untreated control groups.

Oral lethal doses of 420 mg/kg for rabbits and 400-650 mg/kg for rats have been reported (Deichmann and Witherup, 1944).

7.3. Derivation of AEGL-3

The study by Deichmann et al. (1944) was not used as key study due to the uncertainties in the exposure concentration and because deaths were observed only after repeated exposure. Although phenol is a high-production-volume chemical, no acceptable vapor or aerosol LC_{50} studies in experimental animals or suitable reports on lethality after inhalation exposure in humans were available for the derivation of AEGL-3. Therefore, due to insufficient data and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended.

TABLE 7: AEGL-3 VALUES FOR PHENOL

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-3	N.R. [a]	N.R.	N.R.	N.R.	N.R.

[a] not recommended due to insufficient data

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for various levels of effects and various time periods are summarized in Table 8. They were derived using the following key studies and methods.

The AEGL-1 was based on a repeated inhalation exposure study in rats (CMA, 1998; Hoffmann et al., 2001), which found no clinical, hematological or histopathological effects after exposure at 25 ppm phenol (highest concentration used) for 6 hours/day, 5 days/week for 2 weeks. A total uncertainty factor of 3 was applied. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods. For the 10-minute AEGL-1 the 30-minute value was applied.

The AEGL-2 was based on a combination of the Flickinger (1976) and Brondeau et al. (1990) studies. Aerosol exposure at 900 mg/m³ phenol (equivalent to 234 ppm phenol vapor) for 8 hours resulted in ocular and nasal irritation, slight loss of coordination and spasms of the muscle groups at 4 hours into the exposure, after 8 hours additional symptoms (tremor, incoordination and prostration) were observed in one of the six animals. No deaths occurred. This study is supported by the study of Brondeau et al. (1990), which did report only slight effects after exposure at 211 ppm phenol vapor for 4 hours. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 hours. A total uncertainty factor of 10 was used. A modifying factor of 2 was applied. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods. For the 10-minute AEGL-1 the 30-minute value was applied.

No relevant studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data, AEGL-3 values were not recommended.

TABLE 8: SUMMARY/RELATIONSHIP OF AEGL VALUES FOR PHENOL [a]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	19 ppm (73 mg/m³)	19 ppm (73 mg/m³)	15 ppm (58 mg/m³)	9.5 ppm (37 mg/m³)	6.3 ppm (24 mg/m³)
AEGL-2 (Disabling)	29 ppm (110 mg/m³)	29 ppm (110 mg/m³)	23 ppm (90 mg/m³)	15 ppm (57 mg/m³)	12 ppm (45 mg/m³)
AEGL-3 (Lethal)	N.R. [b]	N.R.	N.R.	N.R.	N.R.

[a] Skin contact with molten phenol or concentrated phenol solutions should be avoided; dermal penetration is rapid and fatal intoxications have been observed when a small part of the body surface was involved.
[b] not recommended due to insufficient data

All inhalation data are summarized in Figure 1. Data were classified into severity categories consistent with the definitions of the AEGL health effects. The category severity definitions are "No

effect"; "Discomfort"; "Disabling"; "Lethal"; "Did not die at a lethal concentration" (at an experimental concentration in which some of the animals died and some did not, this label refers to the animals which did not die) and "AEGL". Note that the AEGL values are designated as triangles without an indication to their level. AEGL-3 values were not recommended. The AEGL-2 values are higher than the AEGL-1 values.

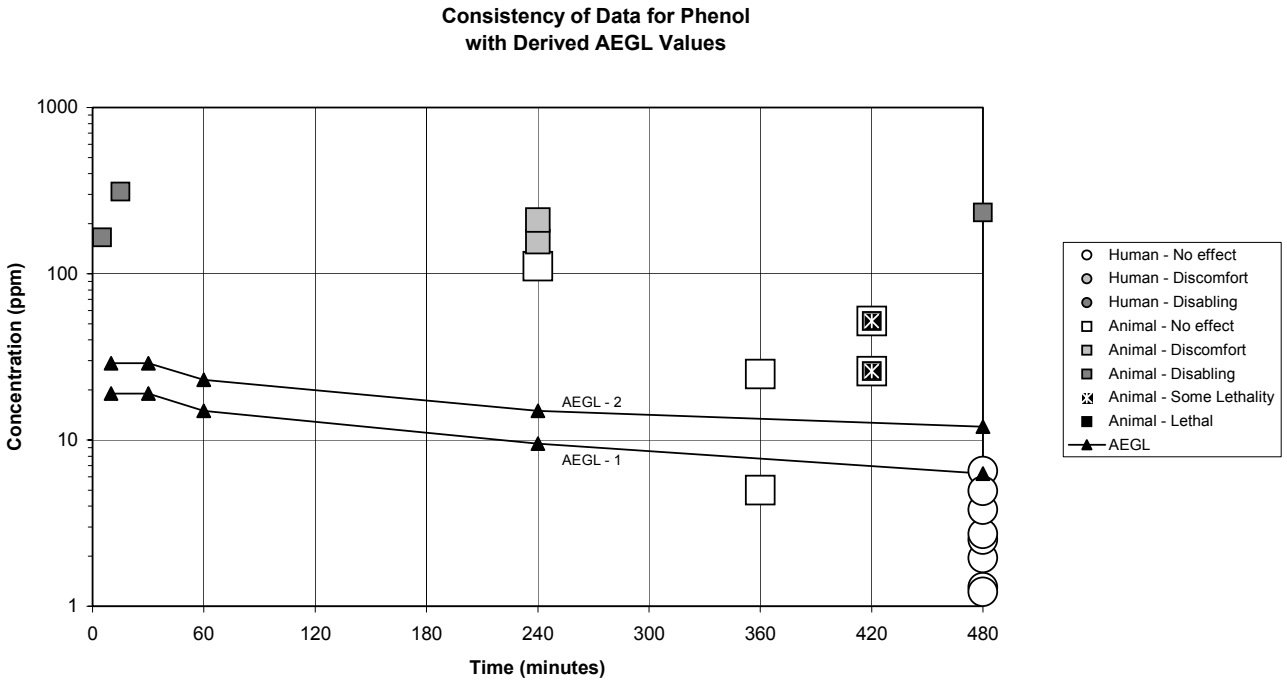

FIGURE 1: CATEGORICAL REPRESENTATION OF ALL PHENOL INHALATION DATA

8.2. Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures are listed in Table 9. In addition, biological exposure values exist: the ACGIH BEI (biological exposure index) is 250 mg phenol per g creatinine in urine at the end of shift (ACGIH, 1996). The German BAT (Biologischer Arbeitsstoff-Toleranz-Wert; biological tolerance value) is 300 mg phenol per liter post-shift urine (Henschler und Lehnert, 1990).

TABLE 9. EXTANT STANDARDS AND GUIDELINES FOR PHENOL

Guideline	Exposure Duration				
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	19 ppm	19 ppm	15 ppm	9.5 ppm	6.3 ppm
AEGL-2	29 ppm	29 ppm	23 ppm	15 ppm	12 ppm
AEGL-3	N.R.	N.R.	N.R.	N.R.	N.R.
ERPG-1 (AIHA)[a]			10 ppm		
ERPG-2 (AIHA)			50 ppm		
ERPG-3 (AIHA)			200 ppm		
PEL-TWA (OSHA)[b]					5 ppm
IDLH (NIOSH)[c]		250 ppm			
REL-TWA (NIOSH)[d]					5 ppm [ceiling 15.6 ppm)
TLV-TWA (ACGIH)[e]					5 ppm
MAK (Germany)[f]	The MAK value of 5 ppm and the peak limit of 10 ppm have been withdrawn due to the genotoxic effects of phenol				
MAK Spitzen-begrenzung (Germany)[g]					
MAC (The Netherlands)[h]					2 ppm

[a] **ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association)** (AIHA, 1991)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for phenol is based on human data in which no adverse effects were observed after exposure at 6.5 ppm for 8 hours (Ruth, 1986). Also monkeys, rats and mice exposed at 5 ppm continuously for 90 days were not significantly affected (Sandage, 1964).
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual‘s ability to take protective action. The ERPG-2 for phenol is based on the observation that a 1-hour exposure of rats at 312 ppm produced only signs of lacrimation (Flickinger, 1976) and on an occupational study that reported eye, nose and throat irritation after intermittent exposure at 48 ppm phenol and 8 ppm formaldehyde (ACGIH, 1996).
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects. The ERPG-3 for phenol is based on the observation that exposure of rats at 235 ppm for 4 hours resulted in ocular and nasal irritation, slight loss of coordination and muscular spasms, but no deaths (Flickinger, 1976).

[b] **OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA, 1989)
is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[c] **IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH, 1996), is based on acute inhalation toxicity data in animals (Flickinger et al., 1976) and an analogy to cresol, which has a revised IDLH of 250 ppm.

[d] **NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH, 1992), is defined analogous to the ACGIH-TLV-TWA.

[e] **ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH, 1996)
The time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[f] **MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungs-gemeinschaft [German Research Association], Germany)** (Greim, 1998)
is defined analogous to the ACGIH-TLV-TWA.

[g] **MAK Spitzenbegrenzung (Kategorie I) [Peak Limit Category I]** (Greim, 1998)
constitutes the maximum average concentration to which workers can be exposed for a period up to 5 minutes, with no more than 8 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

[h] **MAC ([Maximum Workplace Concentration], Dutch Expert Committee for Occupational Standards, The Netherlands)** (MSZW, 1999)
is defined analogous to the ACGIH-TLV-TWA.

8.3. Data Adequacy and Research Needs

Definitive studies assessing health effects of phenol in humans after a single inhalation exposure are not available. Air odor threshold determinations have been published. Older inhalation studies in animals were often compromised by uncertain quantitation of exposure concentrations. Recent studies in laboratory animals, however, utilized accurate and reliable methods for characterizing exposure concentrations, however often exposure concentrations were used that did not lead to any adverse effects. Therefore, AEGL-1 values were based on a repeated exposure study in rats, in which no effects were found at the highest exposure concentration tested. AEGL-2 values were derived on the basis of two rat inhalation studies in which after a single exposure incoordination and prostration, but no death, was observed, although the number of animals used in the study was very small and data presentation was incomplete. For derivation of AEGL-3 values, studies reporting LC_{50} values in animals were lacking. Therefore, no AEGL-3 values were recommended.

Single inhalation exposure studies that measure duration and concentration dependent lethality in animals would allow for derivation of an AEGL-3. Quantitative data on the ocular and upper respiratory tract irritant potential of phenol in air for humans are necessary to more carefully assign an AEGL-1.

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APPENDIX A

Time Scaling Calculations for AEGLs

AEGL-1

Key study:	CMA, (1998); Hoffmann et al. (2001)
Toxicity endpoint:	Exposure of rats at 0.5, 5 or 25 ppm for 6 hours/day, 5 days/week for 2 weeks did not cause clinical, hematological or histopathological effects. A concentration of 25 ppm for 6 hours was used as the basis for derivation of AEGL-3 values.
Scaling:	$C^3 \times t = k$ for extrapolation to 4 hours, 1 hours and 30 minutes $k = 25^3$ ppm^3 x 6 h = 93750 ppm^3 h $C^1 \times t = k$ for extrapolation to 8 hours $k = 25^1$ ppm x 6 h = 150 ppm h The AEGL-2 for 10 minutes was set at the same concentration as the 30-minute value.
Uncertainty factors:	Combined uncertainty factor of 3 1 for interspecies variability 3 for intraspecies variability
Calculations:	
10-minute AEGL-1	10-min AEGL-1 = 19 ppm (73 mg/m^3)
30-minute AEGL-1	$C^3 \times 0.5$ h = 93750 ppm^3 h C = 57.24 ppm 30-min AEGL-1 = 57.24 ppm/3 = 19 ppm (73 mg/m^3)
1-hour AEGL-1	$C^3 \times 1$ h = 93750 ppm^3 h C = 45.43 ppm 1-hour AEGL-1 = 45.43 ppm/3 = 15 ppm (58 mg/m^3)
4-hour AEGL-1	$C^3 \times 4$ h = 93750 ppm^3 h C = 28.62 ppm 4-hour AEGL-1 = 28.62 ppm/3 = 9.5 ppm (37 mg/m^3)
8-hour AEGL-1	$C^1 \times 8$ h = 150 ppm h C = 18.75 ppm 8-hour AEGL-1 = 18.75 ppm/3 = 6.3 ppm (24 mg/m^3)

AEGL-2

Key study:	Flickinger (1976) and Brondeau et al. (1990)
Toxicity endpoint:	Aerosol exposure at 900 mg/m³ phenol (equivalent to 234 ppm phenol vapor) for 8 hours resulted in ocular and nasal irritation, slight loss of coordination and spasms of the muscle groups at 4 hours into the exposure, after 8 hours additional symptoms (tremor, incoordination and prostration) were observed in one of the six animals. No deaths occurred. This study is supported by the study of Brondeau et al. (1990), which did report only slight effects after exposure at 211 ppm phenol vapor for 4 hours. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 hours
Scaling:	$C^3 \times t = k$ for extrapolation to 4 hours, 1 hours and 30 minutes $k = 234^3$ ppm x 8 h = 1.025×10^8 ppm³ h The AEGL-3 for 10 minutes was set at the same concentration as the 30-minute value.
Uncertainty/ modifying factors:	Combined uncertainty factor: 10 3 for interspecies variability 3 for intraspecies variability Modifying factor: 2
Calculations:	
10-minute AEGL-3	10-min AEGL-3 = 29 ppm (110 mg/m³)
30-minute AEGL-3	$C^3 \times 0.5$ h = 1.025×10^8 ppm³ h C = 589.64 ppm 30-min AEGL-3 = 589.64 ppm/20 = 29 ppm (110 mg/m³)
1-hour AEGL-3	$C^3 \times 1$ h = 1.025×10^8 ppm³ h C = 468.00 ppm 1-hour AEGL-3 = 468.00 ppm/20 = 23 ppm (90 mg/m³)
4-hour AEGL-3	$C^3 \times 4$ h = 1.025×10^8 ppm³ h C = 294.82 ppm 4-hour AEGL-3 = 294.82 ppm/20 = 15 ppm (57 mg/m³)
8-hour AEGL-3	8-hour AEGL-3 = 234 ppm/20 = 12 ppm (45 mg/m³)

APPENDIX B

Level of Distinct Odor Awareness

Derivation of the Level of Distinct Odor Awareness (LOA)

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

For derivation of the odor detection threshold (OT_{50}), a study (Don, 1986) is available which is considered to be equivalent to an EN13725:2003-compliant study. The study methodology has been described in TNO (1985). In this study, the odor threshold for the reference chemical n-butanol (odor detection threshold 0.04 ppm) has also been determined:

Don (1986):
odor detection threshold for phenol: 0.0102 ppm
odor detection threshold for n-butanol: 0.026 ppm
corrected odor detection threshold (OT_{50}) for phenol: 0.0102 ppm * 0.04 ppm / 0.026 ppm = 0.016 ppm

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$I = k_w * \log (C / OT_{50}) + 0.5$

For the Fechner coefficient, the default of $k_w = 2.33$ will be used due to the lack of chemical-specific data:

$3 = 2.33 * \log (C / 0.013) + 0.5$ which can be rearranged to

$\log (C / 0.013) = (3-0.5) / 2.33 = 1.07$ and results in

$C = (10^{1.07}) * 0.016 = 11.8 * 0.016 = 0.19$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life factors, such as sex, age, sleep, smoking, upper airway infections and allergy as well as distraction, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4 / 3 = 1.33

$LOA = C * 1.33 = 0.19$ ppm $* 1.33 = 0.25$ ppm

The LOA for phenol is 0.25 ppm.

APPENDIX C

Derivation Summary for Phenol AEGLs

ACUTE EXPOSURE GUIDELINES FOR PHENOL
(CAS NO. 108-95-2)

AEGL-1 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
19 ppm	19 ppm	15 ppm	9.5 ppm	6.3 ppm

Reference: CMA, Chemical Manufacturers Association, 1998. Two-week (ten day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. Huntingdon Life Scienes Study No. 96-6107, CMA Reference No. PHL-4.0-Inhal-HLS. Chemical Manufacturers Association, Phenol Panel, Arlington, VA 22209, USA; Hoffmann, G.M., B.J. Dunn, C.R. Morris, J.H. Butala, S.S. Dimond, R. Gingell and J.M. Waechter, Jr., 2001. Two-week (ten-day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. *International Journal of Toxicology* 20, 45-52.

Test Species/Strain/Number: Rats / Fischer 344 / 20/sex/group

Exposure Route/Concentrations/Durations: Inhalation / 0, 0.5, 5 or 25 ppm / 6 hours/day, 5 days/week for 2 weeks (half of the animals were killed for analysis at the end of the exposure period and the other half after a 2-week recovery period)

Effects:
No differences between controls and phenol-exposed animals for clinical observations, body weights, food consumption and clinical pathology were found. The authors stated that "scattered observations of chromodacryorrhea and nasal discharge were noted during the two weeks of exposure. However, they did not appear in a clearly treatment-related pattern and mostly abated during the 2 week recovery period." While this was true for chromodacryorrhea, the summary tables of in-life physical observations reported the following incidences of red nasal discharge in the control, 0.5-ppm, 5-ppm and 25-ppm groups: 0/20, 0/20, 3/20 and 4/20 males and 0/20, 0/20, 1/20 and 0/20 females in the first week and 0/20, 0/20, 7/20 and 10/20 males and 0/20, 1/20, 3/20 and 0/20 females in the second week. No differences between controls and phenol-exposed animals for organ weights and macroscopic and microscopic postmortem examinations were reported. Complete macroscopic evaluations were conducted on all animals. Microscopic evaluations were conducted on the liver, kidney, respiratory tract tissues (examined organs were nasopharyngeal tissues, larynx, trachea and lungs) and gross lesions for animals in the control and high-exposure groups, at termination and recovery. For histopathology of nasopharyngeal tissues, the skull, after decalcification, was serially sectioned transversely at approximately 3-µm intervals and routinely, four sections were examined per animal.

Endpoint/Concentration/Rationale: Although phenol does not seem to be a strong irritant, it causes local tissue damage in the respiratory tract as evidenced by the histopathological findings after repeated exposure described by Deichmann et al. (1944) for guinea pigs and rabbits. At higher concentrations, phenol causes irritation in rats (Flickinger, 1976) and respiratory depression in mice (De Ceaurriz et al., 1981). The pharmacokinetic study in humans (Piotrowski, 1971) was not used as key study because it did not report on health effects. The Sandage (1961) study was not used because, apparently, exposure chambers did not allow observation of monkeys during the exposure and histopathology was performed on the lungs, but not on the upper respiratory tract so that possible upper airway irritation was not adequately evaluated. Therefore, the study by CMA (1998) (published as Hoffmann et al., 2001) was the only study fulfilling the SOP requirements for a key study and was therefore used for derivation of AEGL-1 values although it was a repeated exposure study. After exposure of rats for 6 hours/day, 5 days/week for 2 weeks, no histopathological alterations of the epithelium of the nasal turbinates or other respiratory tract tissues were found. The observation of red nasal discharge in a few male rats of the 5-ppm and 25-ppm group was not considered a relevant effect, because no clear dose-response relationship was found and because predominantly males, but not females, showed this effect. Moreover, red nasal discharge occurs at the plexus antebrachii, which is very prominent in the rat, and in the rat extravasation of red blood cells visible as red nasal discharge is caused easily not only by locally acting chemicals, but also by stress, dry air or upper respiratory tract infections. The derivation of AEGL-1 values was based on an exposure concentration of 25 ppm for 6 hours.
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: 1 - the toxicokinetic component of the uncertainty factor was reduced to 1 because toxic effects are mostly caused by phenol itself without requirement for metabolism, moreover, possible local irritation effects depend primarily on the phenol concentration in inhaled air with little influence of toxicokinetic differences between species. The starting point for AEGL derivation was a NOAEL from a repeated exposure study and, thus, the effect level was below that defined for AEGL-1. The human experimental and workplace studies (Piotrowski, 1971; Ogata et al., 1986) support the derived values. Therefore, the interspecies factor was reduced to 1. Intraspecies: 3 - because for local effects, the toxicokinetic differences do not vary considerably within and between species. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 while the factor of 3 for the toxicodynamic component, reflecting a possible variability of the target-tissue response in the human population was retained
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: The equation $C^n \times t = k$ was used to derive exposure duration-specific values. Due to lack of a definitive data set, a default value for n of 3 was used in the exponential function for extrapolation from the experimental period (6 hours) to shorter exposure periods and a default value for n of 1 was used for extrapolation to longer exposure times. For the 10-minute AEGL-2 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.
Data Adequacy: No study assessing irritative effects in humans was available. However, in two toxicokinetic studies, no statement was made on the presence or absence of effects in humans exposed experimentally at up to 6.5 ppm for 8 hours (with 2 x 30 min breaks) (Piotrowski, 1971) or exposed at the workplace to a mean workshift concentration of up to 4.95 ppm (Ogata et al., 1986). The derived AEGL-1 values are supported by the study of Sandage (1961), in which continuous exposure of rhesus monkeys at 5 ppm phenol for 90 days did not result in any signs of toxicity.

ACUTE EXPOSURE GUIDELINES FOR PHENOL
(CAS NO. 108-95-2)

AEGL-2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
29 ppm	29 ppm	23 ppm	15 ppm	12 ppm

Reference: a) Flickinger, C.W., 1976. The benzenediols: catechol, resorcinol and hydroquinone - a review of the industrial toxicology and current industrial exposure limits. *American Industrial Hygiene Association Journal* 37, 596-606.
b) Brondeau, M.T., P. Bonnet, J.P. Guenier, P. Simon and J. de Ceaurriz, 1990. Adrenal-dependent leucopenia after short-term exposure to various airborne irritants in rats. *Journal of Applied Toxicology* 10, 83-86.

Test Species/Strain/Sex/Number: a) Rat / Wistar / 6 females
b) Rat / Sprague-Dawley / not stated

Exposure Route/Concentrations/Durations: a) Inhalation / 900 mg phenol/ m³ aerosol / 8 hours
b) Inhalation / 111, 156 or 211 ppm / 4 hours

Effects:
a) Ocular and nasal irritation were observed, as well as slight loss of coordination with spasms of the muscle groups within 4 hours and tremors and prostration (in 1/6 rats) within 8 hours. Rats appeared normal the following day and had normal 14-day weight gains. No deaths occurred. No lesions attributable to inhalation of the aerosol were seen at gross autopsy.
b) The total white blood cell count was significantly decreased after exposure to 156 or 211 ppm, no effect was observed at 111 ppm. Other signs of toxicity were not evaluated. The authors interpreted this finding as a result of increased secretion of corticosteroids as a response to sensory irritation.

Endpoint/Concentration/Rationale:
Due to the lack of more adequate studies, a combination of the Flickinger (1976) and Brondeau et al. (1990) studies were used as the basis for derivation of AEGL-2 values. Aerosol exposure at 900 mg/m³ phenol (equivalent to 234 ppm phenol vapor) for 8 hours resulted in ocular and nasal irritation, slight loss of coordination and spasms of the muscle groups at 4 hours into the exposure, after 8 hours additional symptoms (tremor, incoordination and prostration) were observed in one of the six animals. No deaths occurred. This study is supported by the study of Brondeau et al. (1990), which did report only slight effects after exposure at 211 ppm phenol vapor for 4 hours. Although both studies had shortcomings, i.e., aerosol exposures, nominal concentrations, and no description of toxic signs in one study, taken together, they had consistent results. It was considered adequate to calculate and use the phenol vapor concentration corresponding to an phenol aerosol concentration of 900 mg/m³. The aerosol concentration of 900 mg/m³ is equivalent to a vapor concentration of 234 ppm. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 hours.

Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3 - because oral lethal data did not indicate a high variability between species (cf. Section 4.4.1.) and because application of a higher uncertainty factor would have resulted in AEGL-2 values below levels that humans can stand without adverse effects (Piotrowski, 1971; Ogata et al., 1986). Intraspecies: 3 - because the study of Baker et al. (1978) that investigated health effects in members of 45 families (including children and elderly), that were exposed to phenol through contaminated drinking water for several weeks, did not indicate that symptom incidence or symptom severity was higher in any specific subpopulation. Moreover, newborns and infants were not considered more susceptible than adults because of their smaller metabolic capacity to form toxic phenol metabolites (cf. Section 4.4.2.).
Modifying Factor: 2 - because of the small data base and study shortcomings
Animal to Human Dosimetric Adjustment: Not applicable, local irritative effect
Time Scaling: The equation $C^n \times t = k$ was used to derive exposure duration-specific values. Due to lack of a definitive data set, a default value of n of 3 was used in the exponential function for extrapolation from the experimental period (8 hours) to shorter exposure periods. For the 10-minute AEGL-2 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.
Data Adequacy: Both studies used for the AEGL-2 derivation had shortcomings, i.e., aerosol exposures, nominal concentrations, and no description of toxic signs in one study. Nevertheless, the studies had consistent results and the derived values are supported by the overall toxicity profile of phenol.

ACUTE EXPOSURE GUIDELINES FOR PHENOL
(CAS NO. 108-95-2)

AEGL-3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
N.R.	N.R.	N.R.	N.R.	N.R.

Reference: Not applicable

Test Species/Strain/Sex/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale:
The study by Deichmann et al. (1944) was not used as key study due to the uncertainties in the exposure concentration and because deaths were observed only after repeated exposure. No acceptable vapor or aerosol LC_{50} studies in experimental animals or suitable reports on lethality after inhalation exposure in humans were available for the derivation of AEGL-3. Therefore, due to insufficient data and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended.

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: Not applicable

Data Adequacy:
Adequate animal data relevant for the derivation of AEGL-3 values are not available.