# Acute Exposure Guideline Levels for Selected Airborne Chemicals

## VOLUME 7

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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# Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the U.S. Department of Defense (DOD), the U.S. Department of Energy (DOE), the U.S. Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for approximately 200 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the seventh volume in the series

[2]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

*Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for acetone cyanohydrin, carbon disulfide, monochloroacetic acid, and phenol for scientific accuracy, completeness, and consistency with the NRC guideline reports.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the NAC authors of the documents. The committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

Two interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of two of the committtee's interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for monochloroacetic acid and phenol (*Thirteenth Interim Report of the Committee on Acute Exposure Guideline Levels*, 2005) and acetone cyanohydrin and carbon disulfide (*Fourteenth Interim Report of the Committee on Acute Exposure Guideline Levels*, 2006): Deepak K. Bhalla (Wayne State University), David W. Gaylor (Gaylor and Associates, LLC), and Sam Kacew (University of Ottawa).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of the interim report completed in 2005 was overseen by Sidney Green, Jr. (Howard University). The review of the interim report completed in 2006 was overseen by Robert A. Goyer, professor emeritus, University of Western Ontario. Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports were carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.). The committee acknowl-

edges James J. Reisa, director of the Board on Environmental Studies and Toxicology, and Susan Martel, senior program officer for toxicology, for their helpful guidance. Kulbir Bakshi, project director for his work in this project, and Raymond Wassel for bringing the report to completion. Other staff members who contributed to this effort are Ruth Crossgrove (senior editor), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Radiah Rose (editorial projects manager), Aida Neel (program associate), and Korin Thompson (project assistant). Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

# Contents

# Acute Exposure Guideline Levels for Selected Airborne Chemicals

**VOLUME 7**

# National Research Council Committee Review of Acute Exposure Guideline Levels for Selected Airborne Chemicals

This report is the seventh volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, or what steps to take in an emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States, the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the U.S. Department of Transportation, assist local emergency planning committees (LEPCs) by providing guidance for conducting health hazard assessments for the development of emergency response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values developed by the National Institute for Occupational Safety and Health in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for

exposures at high levels but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants , children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established by the federal government to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or $mg/m^3$ [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The NAC roster is shown on page 9.

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 adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

## SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These types include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans.

Such extrapolation requires experienced scientific judgment. The toxicity data for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points (including reproductive [in both genders], developmental, neurotoxic, respiratory, and other organ-related effects) are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 ($1 \times 10^{-4}$), 1 in 100,000 ($1 \times 10^{-5}$), and 1 in 1,000,000 ($1 \times 10^{-6}$) exposed persons are estimated.

## REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

The AEGL draft reports are initially prepared by ad hoc AEGL development teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Committee on Acute Exposure Guideline Levels for final evaluation.

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the NRC committee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee

relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared six reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b). This report is the seventh volume in that series. AEGL documents for acetone cyanohydrin, carbon disulfide, monochloroacetic acid, and phenol are each published as an appendix in this report. The NRC committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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# Appendixes

# 4

# Phenol[1]

# Acute Exposure Guideline Levels

## 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 (min) to 8 hours (h). AEGL-1, AEGL-2, and AEGL-3, as appropriate, will be developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) 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 parts per million [ppm] or milligrams per cubic meter [mg/m$^3$]) of a substance above which it is

[1]This document was prepared by the AEGL Development Team composed of Peter Griem (Forschungs- und Beratungsinstitut Gefahrstoffe GmbH) and Chemical Managers Robert Snyder and Bill Bress (National Advisory Committee [NAC] on Acute Exposure Guideline s for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline s. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory 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/m³) 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/m³) 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, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

## SUMMARY

Phenol is a colorless to pink, hygroscopic solid with a characteristic, sweet, tarlike 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 h. Likewise, Ogata et al. (191986) 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 phenol at more than 1 mg/liter (L) of contaminated drinking water for several weeks, gastrointestinal symptoms (diarrhea, nausea, and burning pain 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 a CEN (2003) comparable study.

No studies reporting $LC_{50}$ (concentrations with 50% lethality) 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 h resulted in ocular and nasal irritation, incoordination, and prostration in one of six rats (Flickinger 1976). After 4 h of exposure of phenol vapor at 211 or 156 ppm, a decrease of the number of white blood cells but no signs of toxicity were reported (Brondeau et al. 1990). After vapor exposure of rats at 0.5, 5, or 25 ppm for 6 h/d, 5 d/wk for 2 weeks, no clinical, hematologic, or histopathologic effects were found (Huntingdon Life Sciences 1998; published in Hoffman et al. 2001). Continuous exposure to phenol vapor at 5 ppm for 90 days caused no hematologic or histologic 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 5,000 ppm; the no-observed-adverse-effect level (NOAEL) was 1,000 ppm (equivalent to 70 mg/kg/d for males and 93 mg/kg/d for females). In an oral carcinogenicity study, $B6C3F_1$ mice and Fischer 344 rats received phenol at 2,500 or 5,000 mg/L of drinking water (corresponding to 281 and 412 mg/kg/d for mice and 270 and 480 mg/kg/d 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 high-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)" (IARC 1999, p.762). 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" (EPA 2002, p. 103). Therefore, carcinogenicity was not an end point in the derivation of AEGL values.

The AEGL-1 was based on a repeat inhalation study of phenol in rats (Huntingdon Life Sciences 1998; Hoffman et al. 2001), which found no clinical, hematologic or histopathologic effects after exposure to phenol at 25 ppm (highest concentration used) for 6 h/d, 5 d/wk for 2 weeks. An uncertainty factor of 1 was applied for interspecies variability: the toxicokinetic component of the un-

certainty 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. For 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 and the factor of 3 for the toxicodynamic component was retained, reflecting a possible variability of the target-tissue response in the human population. 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, because of the lack of suitable experimental data for deriving the concentration exponent. For the 10-min AEGL-1, the 30-min 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 to phenol at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination, and spasms of the muscle groups at 4 h into the exposure. After 8 h, additional symptoms (tremor, incoordination, and prostration) were observed in one of the six animals. No deaths occurred. Because the aerosol concentration was below the saturated vapor concentration at room temperature of about 530 ppm, it was assumed that much of the phenol had evaporated from the aerosol and a mixed aerosol and vapor exposure prevailed. This study is supported by the study of Brondeau et al. (1990), who reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. Although both studies had shortcomings—that is, 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 h. 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) who 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 database 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, because of the lack of suitable experimental data for deriving the concentration exponent. For the 10-min AEGL-2, the 30-min 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 Table 4-1.

**TABLE 4-1** Summary of AEGL Values for Phenol[a]

| Classification | 10 min | 30 min | 1 h | 4 h | 8 h | End Point (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 (Huntingdon Life Sciences 1998; Hoffman et al. 2001) |
| 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) | 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 because of insufficient data.

## 1. INTRODUCTION

Phenol is a colorless to pink, hygroscopic solid with a characteristic, sweet, tarlike 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 to be 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 the European Union (ECB 2002) and about 1,500,000 metric tons for 1994 in the United States (HSDB 2003).

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 2008) lists 649 sites in the United States where production and use of phenol causes emissions to the air. Chemical and physical data are provided in Table 4-2.

## 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 nineteenth 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, information about the absorbed dose is often not reported (WHO 1994). Lethality data in humans are summarized in Table 4-3.

#### 2.1.1. Case Studies

Heuschkel and Felscher (1983) reported on the 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 h.

**TABLE 4-2** Chemical and Physical Data for Phenol

| Parameter | Data | 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<br>A solution with approx. 10% water (phenolum liquefactum) is liquid at room temperature | ACGIH 1996<br>WHO 1994 |
| Color | Colorless<br>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<br>0.357 mm Hg at 20°C<br>1 mm Hg at 40.1°C<br>3.5 hPa at 25°C<br>2.48 mm Hg at 50°C<br>10 mm Hg at 73.8°C<br>18.39 hPa at 80.1°C<br>40 mm Hg at 100.1°C<br>100 mm Hg at 121.4°C | IUCLID 1996<br>WHO 1994<br>Weast 1984<br>IUCLID 1996<br>WHO 1994<br>Weast 1984<br>IUCLID 1996<br>Weast 1984<br>Weast 1984 |
| Density | 1.0719 g/cm³ | 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<br>WHO 1994 |
| Odor | Sweet, tarlike odor<br>Sweet and acrid | ACGIH 1996<br>IARC 1999 |
| Explosive limits in air | 1.7% (lower), 8.6% (upper) | ACGIH 1996 |
| Conversion factors | 1 ppm = 3.84 mg/m³<br>1 mg/m³ = 0.26 ppm | WHO 1994 |

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 h of exposure. It showed a gray-pale skin color, edema on the head and legs, and tachypnea and died on the fifth day from pro-

**TABLE 4-3** Summary of Data on Lethal Effects in Humans

| Subject Information | Exposure Route | Exposure Information | Estimated Dose | Effect | Reference |
|---|---|---|---|---|---|
| 1-d 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-y-old female | Oral | 70 mL of 42-52% phenol solution | 490-606 mg/kg<br>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-y-old male | Oral | Approx. 60 mL of an 88% phenol emulsion | 754 mg/kg<br>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. 1950 |
| 19-y-old female | Oral | 15 mL liquefied phenol | 250 mg/kg<br>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. 1950 |
| Adult female | Oral | 10-20 g phenol | 166-333 mg/kg<br>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 |
| 27-y-old male | Oral (+ dermal) | Unknown | 106-874 mg/kg,<br>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-d-old newborn | Dermal | 2% phenol solution in umbilical bandage | 125-202 mg/kg<br>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 |

gressive respiratory insufficiency. On experimental reconstitution of the exposure conditions, phenol at about 20 mg/m³ (5.2 ppm) and formaldehyde at about 30 mg/m³ (24.9 ppm) were measured in the incubator after 2 h (lower concentrations of phenol and formaldehyde after 5 h not reported) when disinfection solution was present in the evaporation container, and phenol at about 5 mg/m³ (1.3 ppm), formaldehyde at 50 mg/m³ (41.5 ppm), and methanol at 350 mg/m³ (267 ppm) 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.

A 65-year-old Japanese woman ingested 70 mL of 42-52% phenol in a suicide attempt. Upon hospital admission and about 1 h 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 on two suicide cases. The first case 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 that 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 h 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 of 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 h 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 that did not react to light. Almost 1 h after the ingestion, her heart and respiration stopped and, in spite of repeated attempts at resuscitation for 2 h, she died. Autopsy revealed marked hyperemia of the tracheal and bronchial mucous membranes. Histologic examination revealed pulmonary and liver edema as well as hyperemia of the intestine.

Tanaka et al. (1998) reported on 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, and 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 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 were swollen and reddish and looked like partial skin thickness burn wounds. Blood gas analysis revealed that oxygen saturation dropped from 99% on admission to 72% 6 h after exposure. During this period, cardiac arrhythmia and bradycardia were noted. Serum levels of phenol were 11.4 mg/L at 1 h, 17.4 mg/L at 4 h, 6.0 mg/L at 8 h, 0.37 mg/L at 22 h, and 0.07 mg/L at 28 h post-exposure. The man survived and his skin healed completely within 12 days.

Bentur et al. (1998) reported on 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 h 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 h.

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 h after application of an umbilical bandage that was accidentally soaked with 2% phenol instead of saline. After 6 h, the baby developed severe cyanosis and died at 11 h from central respiratory depression. Autopsy revealed edematous swelling of all parenchymal organs. Phenol concentrations of 125 mg/kg in blood, 144 mg/kg in liver and 202 mg/kg in kidney were measured. Another infant, 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 on 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 min 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 h; cardiac activity normalized after 8 h. 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.

### 2.2. Nonlethal Toxicity

Although 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 (seven men ages 25-42 and one woman age 30) were exposed by face mask to phenol concentrations between 5 and 25 mg/m³ (1.3-6.5 ppm) for 8 h, with two breaks of 0.5 h, each after 2.5 and 5.5 h. The author did not report any complaints concerning adverse effects of phenol exposure on the subjects, nor did the report explicitly state the absence of any effects.

Don (1986) reported an odor detection threshold of 0.010 ppm for phenol in a study considered equivalent to a CEN (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 five concentrations of phenol were tested. The individual concentrations were not reported. An odor recognition threshold of phenol at 0.047 ppm was determined for all four subjects.

Mukhitov (1964) determined the odor perception threshold in 14 subjects. Each subject was tested from 33 to 43 times over a period of 2-3 days. The odor perception threshold concentration ranged from 0.022 to 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 the 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 on a 5-year retrospective review of all exposures to a high-concentration phenol disinfectant (26% phenol) that were reported to a regional poison control center. 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 less than 5 years. There were 60 oral-only exposures, 7 dermal-only exposures, 12 oral and dermal exposures and 1 inhalation exposure; 52 cases were evaluated in a hospital. Eleven patients (all oral exposures) experienced some form of central-nervous-system (CNS) depression. Nine patients experienced lethargy (the time to onset was 15 min to 1 h, with a mean time of 20 min); lethargy progressed to unresponsiveness within 1 h. 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 and black was noted in five patients with oral exposure; oliguria or anuria was not seen. Recovery was complete in all cases. By history, the oral dose of exposure ranged from 2 to 90 mL of disinfectant (520 mg to 23.4 g of phenol). The largest ingested dose without effect was 30 mL (7.8 g of phenol), and the smallest dose with any effect was 5 mL (1.3 g of 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 L 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 and having at least one water test that revealed phenol at more than 0.1 mg/L in drinking water. Group 2 (61 persons, mean age 26.7 years) was composed of families living adjacent to group 1, that is, 210-670 m from the spill who had phenol at 0.1-0.001 mg/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, five individuals of group 2, and two of 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. The rashes 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 2 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 more than 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) was two subjects at 1.22 ± 0.52 ppm, five at 1.95 ± 0.47 ppm, five at 2.52 ± 0.49 ppm, two at 2.73 ± 0.45 ppm, two at 3.81 ± 0.26 ppm, and four at 4.95 ± 0.23 ppm. The authors did not 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 from the administrative departments located far away from any exposure to phenol. Transaminases, total protein, prothrom-

bin 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 of creatinine in controls (group III), 54 ± 27 mg/g of creatinine in group II, and 69 ± 47 mg/g of 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 magnesium (Mg), manganese (Mn), and calcium (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 platelet count, prothrombin time, eosinophils, cobalt, and iron were affected by combined exposure but were not affected after exposure to phenol only.

### 2.3. Reproductive and Developmental 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 3,805 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, two were rejected due to a false preliminary diagnosis of cancer and one 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 res-

piratory tumors with or without the adjustment for smoking years, respectively. When the duration of phenol exposure was considered, both exposures of less than 5 years and more than 5 years resulted in a statistically significant OR of 5.86 or 4.03, respectively (that is, 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 coexposure 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 exposure at about 5.2 ppm phenol and 24.9 ppm formaldehyde (concentrations after 2 h) with a decline in chamber phenol concentrations over 5-6 h followed by about 1.3 ppm phenol and 41.5 ppm formaldehyde (measured after 1 h, with decrease over time) for 14-15 h 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. 1950; 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 phenol at 5.4 ppm (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 h. 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 phenol at more than 1 mg/L of contaminated drinking water for several weeks (the authors' estimate of an intake of phenol at 10-240 mg/d), gastrointestinal symptoms (diarrhea, nausea, and burning pain and sores in the mouth) and skin rashes occurred (Baker et al. 1978). Odor thresholds for phenol were reported at 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 or developmental toxic effects in humans were available. In vitro, phenol induced signs of genotoxicity in human cells (Morimoto and Wolff 1980; Yager et al. 1990). Two epidemiologic 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 the 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 4-4.

#### 3.1.1. Rabbits

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 phenol at 0.252, 0.500, 1.00 or 2.00 g/kg to the intact skin of male albino rabbits (four animals/group). The observation period was 14 days. Death was observed in zero of four, zero of four, three of four, and

**TABLE 4-4** 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 | $LD_{50}$ | Kostovetskii and Zholdakova 1971 |

four of four 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 killed animals. The authors calculated an $LD_{50}$ of 0.85 g/kg (95% confidence interval [C.I.] 0.60-1.20 g/kg).

### 3.1.2. Rats

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 of 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) exposed groups of five male albino rats to phenol by gavage at 0.200, 0.398, 0.795, or 1.58 g/kg. The observation period was 14 days. Death was observed in zero of five, zero of five, four of five, and five of five rats (all deaths occurred at the day of dosing), respectively. All rats that died revealed hyperemia and distention of the stomach and intestines. None of the surviving rats exhibited any gross lesions. The authors calculated an $LD_{50}$ 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 h/d, 5 d/wk for 4 weeks. After three to five 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 1 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 for phenol at 282 mg/kg (Horikawa and Okada 1975), 300 mg/kg (Von Oettingen and Sharples 1946), and 427 mg/kg (Kostovetskii and Zholdakova 1971) have been reported.

## 3.2. Nonlethal Toxicity

Studies with single and repeated inhalation exposure are available for monkey, rabbit, rat, and mouse. However, several protocols used concentrations that failed to produce any adverse effects (Table 4-5).

**TABLE 4-5** Summary of Nonlethal 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, histologic degeneration in heart, liver and kidney | Deichmann et al. 1944 |
| Rat | 900 mg/m$^3$ 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. 1990 |
| 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, hematologic or histopathologic effects | Huntingdon Life Sciences 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 | Mukhitov 1964 |
| Rat | 5 | 24 h/d, 90 d | No hematologic or histopathologic 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 hematologic or histopathologic effects | Sandage 1961 |
| Mouse | 166 | 5 min | $RD_{50}$ | De Ceaurriz et al. 1981 |

### 3.2.1. Monkeys

Sandage (1961) exposed groups of 10 male rhesus monkeys to phenol at 0 or 5 ppm 24 h/d for 90 days. The exposure chambers were aluminium-insulated rooms of 10 × 8 × 7 feet. Monkeys were exposed in individual cages of 2 × 2 × 2 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 six of seven 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

Deichmann et al. (1944) exposed sixrabbits to phenol vapor concentrations of 100-200 mg/m³ (26-52 ppm) for 7 h/d, 5 d/wk 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 six female Harlan-Wistar rats whole body for 8 h to a phenol aerosol at 900 mg/m³. The aerosol was generated using aqueous phenol and a D18 Dautrebande aerosol generator operated at 30 pounds per square inch (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 post-exposure observation period was 14 days. The exposure to an aerosol containing phenol at 900 mg/m³ caused no deaths, but ocular and nasal irritation was observed, as well as slight loss of co-

ordination with skeletal muscle spasms within 4 h. Tremors and prostration developed in one of six rats within 8 h. 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. Because 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 to phenol at 0, 111, 156, or 211 ppm for 4 h. 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 that for five other chemicals also causing leukopenia this effect did not occur in adrenalectomized rats.

Huntingdon Life Sciences (1998; published in 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 h/d, 5 d/wk for 2 weeks. High-performance liquid chromatography (HPLC) measurement of exposure concentrations determined mean (±SD) analytic 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 of each sex in each group were killed and the remaining animals held for a recovery period of 2 weeks, after which these animals were killed. Food consumption was recorded 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, 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 2 weeks of exposure. However, the au-

thors 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 of 20, 0 of 20, 3 of 20, and 4 of 20 males and 0 of 20, 0 of 20, 1 of 20, and 0 of 20 females in the first week and 0 of 20, 0 of 20, 7 of 20, and 10 of 20 males and 0 of 20, 1 of 20, 3 of 20, and 0 of 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 to phenol vapor at 100 mg/m³ (26 ppm) 24 h/d 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 CNS, and the phenol-exposed rats showed a significantly reduced sliding angle than before exposure or compared with control.

Mukhitov (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 h/d for 61 days. Analytic concentrations were obtained once or twice daily using a colorimetric assay. Analytic 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). Although 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 five 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 h/d for 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 histopathologic examinations.

Deichmann et al. (1944) exposed 15 rats whole body to phenol vapor concentrations of 100-200 mg/m³ (26-52 ppm) for 7 h/d, 5 d/wk 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.

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 of 10 animals (see section 3.1.1). Hepatocellular necrosis was observed after a single dose of 40 mg/kg in one of seven animals and at 120 mg/kg in two of six but not after repeated exposure at 40 mg/kg. Renal tubular necrosis, protein casts, and papillary hemorrhage developed in four of six animals exposed at 224 mg/kg (single) and in three of eight animals exposed at 40 mg/kg (repeated). Necrosis or atrophy of spleen or thymus was found in one of eight animals exposed at 12 mg/kg (single and repeated), two of eight animals at 40 mg/kg (repeated), one of seven animals at 120 mg/kg, and four of six animals at 224 mg/kg.

#### 3.2.4. Mice

Sandage (1961) exposed groups of 100 male "general purpose albino mice" to phenol at 0 or 5 ppm 24 h/d 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 histopathologic 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 OF1 mice. Analytic 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 four concentrations and six 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 min, 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 min. The phenol vapor $RD_{50}$ for mice was calculated as 166 ppm.

### 3.3. Reproductive and Developmental Toxicity

#### 3.3.1. Rats

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 after being killed (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 morphologic 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 with 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/d was a NOAEL for developmental toxicity and the high dose of 120 mg/kg/d was an equivocal lowest-observed-adverse-effect level (LOAEL). The high dose was a maternal NOAEL.

In a screening-test validation study, Narotsky and Kavlock (1995) exposed groups of 15-20 pregnant Fischer 344 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 one litter in the low- and two 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 end points, such as sperm count and motility, developmental landmarks, histologic 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 of each sex in each group in the drinking water at concentrations of 0, 200, 1,000, or 5,000 ppm corresponding to daily intake of phenol of 0, 14, 70, and 310 mg/kg/d for males and 0, 20, 93, and 350 mg/kg/d for females. Parental (P1) animals were treated for 10 weeks prior to mating, during mating, gestation, lactation, and until they were killed. The F1 generation (P1 offspring) was treated using a similar regimen, while the F2 generation was not treated. After mating, 10 P1 males per 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 5,000-ppm group in both generations; corollary reductions in body weight and 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 5,000-ppm group and were considered to be secondary to the reduction in F1 body weight. Litter survival of both generations was reduced in the 5,000-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 5,000-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 tox-

icity of phenol administered in drinking water to rats is 1,000 ppm (equivalent to 70 mg/kg/d for males and 93 mg/kg/d for females).

### 3.3.2. Mice

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 of 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/d 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/d.

## 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,b; 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), 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 $B6C3F_1$ mice and Fischer 344 rats received phenol at 0, 2,500, or 5,000 mg/L of drinking water, leading to estimated doses of 281 or 412 mg/kg/d for mice and 270 or 480 mg/kg/d 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 of benzene, 2 times/wk 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)" (IARC 1999, p. 762). 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 in 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."(EPA 2002, p. 103) Therefore, carcinogenicity was not an end point 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 to phenol at 26-52 ppm for 7 h/d, 5 d/wk (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 histologic 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 (Von Oettingen and Sharples 1946; Kostovetskii and Zholdakova 1971; Horikawa and Okada 1975) have been reported.

In 10 rhesus monkeys, exposed 24 h/d for 90 days to phenol at 5 ppm 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 h developed ocular and nasal irritation, incoordination, and prostration (Flickinger 1976). A reduction of the number of circulating leucocytes was observed in rats after 4-h of exposure at 211 or 156 ppm; no effect was seen for 111 ppm (Brondeau et al. 1990). After exposure of rats at 0.5, 5, or 25 ppm for 6 h/d, 5 d/wk for 2 weeks, no clinical, hematologic, or histopathologic effects were found (Huntingdon Life Sciences 1998; Hoffman et al. 2001). Continuous exposure to phenol at 5 ppm for 90 days caused no hematologic or histologic 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,b). 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 5,000 ppm; the NOAEL was 1,000 ppm (equivalent to 70 mg/kg/d for males and 93 mg/kg/d 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 and 55 mg/L. Dugan

(1972) stated that humans eliminate 0.2-6.6 mg/kg/d in urine and up to 3 mg/kg/d in feces. Piotrowski (1971) reported 8.7 ± 2.0 mg/d 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 eight subjects by face mask to phenol concentrations between 5 and 25 mg/m³ (1.3-6.5 ppm) for 8 h, with two breaks of 0.5 h, each after 2.5 and 5.5 h. 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 h. The steady-state systemic uptake and absorption was 60-88%. Urinary recovery of absorbed phenol was 99% within 24 h 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 h (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-h 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 (seven men ages 25-42 and one woman age 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 h; 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, that is, 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 that clearance of airborne phenol through the lungs was 0.6 m³/h and concluded that percutaneous absorption was half the pulmonary uptake over the concentration range of 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 (ages 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-min 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 h amounted to about 80% of the absorbed dose. Increasing the phenol solution temperature from 20°C to 35°C led to a 1.67-fold increase in skin absorption (Baranowska-Dutkiewicz 1981).

Seventy-two 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 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 P-450 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 P-450 isoenzymes, such as 2F2, may also be involved in phenol oxidation (Powley and Carlson 2001). In vivo conjugation occurs mainly in the liver, lung and gastrointestinal tract (Cassidy and Houston 1984).

Because the sulfate conjugation pathway is saturable at lower doses than the glucuronic acid conjugation, the ratio of sulfate to 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 7-fold higher amounts of total hydroquinone than rats (Capel et al. 1972). Kenyon et al. (1995) administered 14C-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 2-fold 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 h excreted 99 ± 8% of the retained dose in the urine within 24 h after start of exposure (Piotrowski 1971). After oral exposure of humans to radiolabeled phenol, the mean 24-h 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 h 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 have occurred (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 irrita-

tion 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 (Deichmann and Witherup 1944; Bennett et al. 1950; Stajduhar-Caric 1968; Schaper 1981 Kamijo et al. 1999). Phenol blocks the cardiac sodium channel subtype, with little effect on sodium channels in skeletal muscle (Zamponi and French 1994). Following ingestion, typical signs in humans and animals include agitation, muscle tremors, confusion, incoordination, seizures, coma, and respiratory arrest (Deichmann and Witherup 1944; Schaper 1981; Kamijo et al. 1999). 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 CNS and that the resultant reduction in brain acetylcholine levels indirectly suppresses the tremor.

Because 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. Exposure of male $B6C3F_1$ mice with intraperitoneal doses of phenol as high as 150 mg/kg twice daily or for 12 days caused no suppression of bone marrow cellularity. Only minimal suppression was observed in mice exposed to hydroquinone at up to 100 mg/kg. By contrast, significant dose-related suppression was seen in mice exposed to phenol at 75 mg/kg and hydroquinone at 75 mg/kg 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 hydroquinone and benzoquinone.

It has been hypothesized that the genotoxicity of phenol on bone marrow results from 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; this can then 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 and substituted phenols and benzenediols, cresols, or chlorophenols have been published. Al-

though 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: 5 of 12 guinea pigs died after 20 exposures to phenol at 26-52 ppm for 7 h/d, 5 d/wk; under the same conditions, rabbits exposed for 88 days showed no signs of overt poisoning but some histologic degeneration in target tissues, and rats exposed for 74 days to the same concentrations developed neither clinical signs nor histologic 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 4-3) and were 420 mg/kg for rabbits, 400-650 mg/kg for rats (Deichmann and Witherup 1944) and 282-427 mg/kg for mice (Von Oettingen and Sharples 1946; Kostovetskii and Zholdakova 1971; Horikawa and Okada 1975).

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, and 30% of 5-week-old rats and 60% of adult rats died. After dermal application of 3,000 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 phenol at 5.2 ppm for 5-6 h and 1.3 ppm for another 14-15 h (Heuschkel and Felscher 1983) could not be attributed to a particular susceptibility because the newborn had a congenital pulmonary disorder. Moreover, the newborn was also exposed to formaldehyde (24.9 ppm [measured at 2 h] for 5-6 h and 41.5 ppm [highest concentration, with decrease over time] for another 14-15 h). The formaldehyde may have contributed to death. For example, rat exposure to formaldehyde at 40 ppm for 6 h/d, 5 d/wk 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 with adults (Brashear et al. 1988; Renwick 1998). Generally, cytochrome P-450

activity, which reduces the potential of toxic effects caused by oxidation and protein binding of quinone metabolites, is reduced in newborns and young infants. 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, although the available data do not point to a large intraspecies variability, they are not considered sufficient to use as the basis for reducing 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 eight volunteers by face mask to phenol at 5-25 mg/m³ (1.3-6.5 ppm) for 8 h, with two breaks of 0.5 h, each after 2.5 and 5.5 h. The author did not 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 did not 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), 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 a CEN (2003) comparable study.

Ruth (1986) reported an irritation threshold of 182.4 mg/m³ (47 ppm) in humans. The author tabulated the 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 to phenol at 0.5, 5, or 25 ppm for 6 h/d, 5 d/wk for 2 weeks, no clinical, hematologic or histopathologic effects were found (Huntingdon Life Sciences 1998; Hoffman et al. 2001). The authors reported the following incidences of red nasal discharge (chromadacryorrhea) in the control group and 0.5-ppm, 5-ppm, and 25-ppm groups: 0 of 20, 0 of 20, 3 of 20, and 4 of 20 males and 0 of 20, 0 of 20, 1 of 20, and 0 of 20 females in the first week (observations for individual exposures were not provided). However, histopathologic 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 to phenol at 5 ppm 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 histologic examinations.

Mukhitov (1964) reported that continuous exposure of rats to phenol 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; 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 a 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 Huntingdon Life Sciences (1998; published in Hoffman et al. 2001) was the only study fulfilling the standing operating procedures (SOP) requirements for a key study and, therefore, was used for derivation of AEGL-1 values, although it was a repeated exposure study. After exposure of rats for 6 h/d, 5 d/wk for 2 weeks, no histopathologic 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 extrava-

sation of red blood cells visible as red nasal discharge is caused easily in the rat 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 h.

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 dataset, a default value for n of 3 was used in the exponential function for extrapolation from the experimental period (6 h) to shorter exposure periods and a default value for n of 1 was used for extrapolation to longer exposure times. For the 10-min AEGL-1 the 30-min 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. On the basis of 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, and the factor of 3 for the toxicodynamic component was retained, reflecting a possible variability of the target-tissue response in the human population.

The derived AEGL-1 values are supported by the Sandage (1961) results, in which continuous inhalation of phenol by rhesus monkeys at 5 ppm for 90 days failed to result in any sign of phenol toxicity. Other supporting studies are the pharmacokinetic study by Piotrowski (1971) who exposed subjects at up to 6.5 ppm, and the study by Ogata et al. (1986) who reported a workplace exposure of up to 4.95 ppm. The values are listed in Table 4-6.

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.

**TABLE 4-6** AEGL-1 Values for Phenol

| AEGL | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| 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) |

## 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 phenol at more than 1 mg/L of contaminated drinking water for several weeks (the authors estimated an intake of phenol of 10-240 mg/d), gastrointestinal symptoms (diarrhea, nausea, and burning pain and sores in the mouth), and skin rashes occurred (Baker et al. 1978).

Ruth (1986) reported an irritation threshold at 182.4 mg/m³ (47 ppm) in humans. The author tabulated the 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 six female Harlan-Wistar rats for 8 h to a nominal phenol aerosol at 900 mg/m³ caused no deaths but resulted in ocular and nasal irritation as well as slight loss of coordination with spasms of the muscle groups within 4 h and tremors and prostration (in one of six rats) within 8 h. Rats appeared normal the following day. Because the aerosol concentration was below the vapor pressure at room temperature, it is likely that the animals were actually exposed to phenol vapor (or a 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 to phenol at 211 or 156 ppm for 4 h, 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 to phenol at 26-52 ppm for 7 h/d, 5 d/wk. 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 histologic alterations. It should be noted that these 1940s 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 1 day after exposure, impaired balance, disordered walking, muscle twitches, and involuntary head movements during the third and fourth days. The symptoms disappeared 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 was used as the basis for derivation of AEGL-2 values. Aerosol exposure to phenol at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination, and spasms of the muscle groups at 4 h into the exposure; after 8 h, 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), who reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. Although both studies had shortcomings, that is, aerosol exposures, nominal concentrations, and no description of toxic signs in one study, taken together, they had consistent results. Because 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, that is, acute CNS depression, and has a high penetration of dermal and mucosal surfaces. Therefore, it was considered adequate to calculate and use the phenol vapor concentration corresponding to a 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 h.

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 dataset, a default value for n of 3 was used in the exponential function for extrapolation from the experimental period (8 h) to shorter exposure periods. For the 10-min AEGL-2, the 30-min 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) who 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 database 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 listed in Table 4-7.

Comparison of the AEGL-2 values with the $RD_{50}$ in mice of 166 ppm (De Ceaurriz et al. 1981) supports 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 4-3) (Bennett et al. 1950; Stajduhar-Caric 1968; Tanaka et al. 1998; Kamijo et al. 1999). 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 the death of a newborn baby after exposure to phenol at 5.2 ppm for 5-6 h and 1.3 ppm for another 14-15 h 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 at 24.9 ppm (measured at 2 h) for 5-6 h and at 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 to phenol at 26-52 ppm for 7 h/d, 5 d/wk; 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 histologic alterations. These experiments lacked control groups.

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

**TABLE 4-7** AEGL-2 Values for Phenol

| AEGL | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| 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) |

### 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 4-8).

## 8. SUMMARY OF AEGLs

### 8.1. AEGL Values and Toxicity End Points

The AEGL values for various levels of effects and various time periods are summarized in Table 4-9. They were derived using the following key studies and methods.

The AEGL-1 was based on a repeated inhalation exposure study in rats (Huntingdon Life Sciences 1998; Hoffman et al. 2001), which found no clinical, hematologic or histopathologic effects after exposure to phenol at 25 ppm (highest concentration used) for 6 h/d, 5 d/wk for 2 weeks. A total uncertainty factor of 3 was applied. The other exposure duration-specific values were derived by

**TABLE 4-8** AEGL-3 Values for Phenol[a]

| AEGL | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| AEGL-3 | N.R. [a] | N.R. | N.R. | N.R. | N.R. |

[a]Not recommended because of insufficient data.

**TABLE 4-9** Summary of AEGL Values for Phenol[a]

| Classification | 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|---|
| 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 because of insufficient data.

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-min AEGL-1, the 30-min value was applied.

The AEGL-2 was based on a combination of the Flickinger (1976) and Brondeau et al. (1990) studies. Aerosol exposure to phenol at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination, and spasms of the muscle groups at 4 h into the exposure; after 8 h, 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), who reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 h. 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-min AEGL-2, the 30-min 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.

All inhalation data are summarized in Figure 4-1. 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,” and “some lethality” (animals that did not die at an experimental lethal concentration at which other animals died). 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.

### 8.2. Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures are listed in Table 4-10. In addition, biologic exposure values exist: the ACGIH BEI (Biological Exposure Index) is 250 mg of phenol per gram of creatinine in urine at the end of shift (ACGIH 1996), and the German BAT (Biologischer Arbeitsstoff-Toleranz-Wert; biologic tolerance value) is 300 mg of phenol per liter post-shift urine (Henschler und Lehnert 1990).

### 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

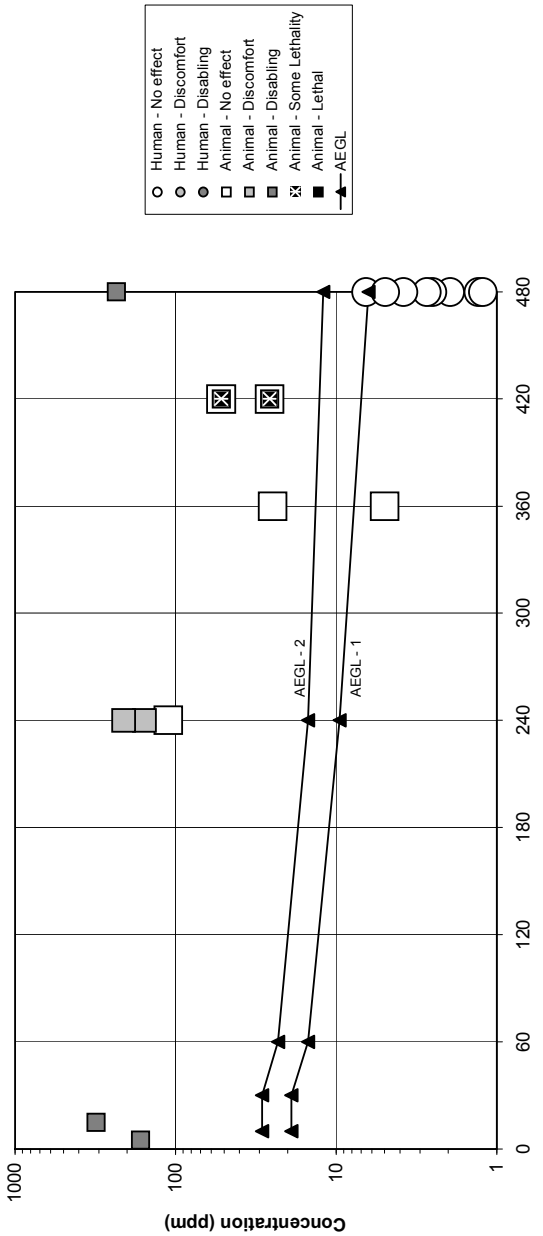


**FIGURE 4-1** Categorical representation of all phenol inhalation data.

**TABLE 4-10** Extant Standards and Guidelines for Phenol

| Guideline | Exposure Duration | | | | |
|---|---|---|---|---|---|
| | 10 min | 30 min | 1 h | 4 h | 8 h |
| 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 2007). The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h 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 h (Ruth 1986). Also monkeys, rats, and mice exposed at 5 ppm continuously for 90 days were not significantly affected (Sandage 1961). The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h 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-h 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 1 h 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 h resulted in ocular and nasal irritation, slight loss of coordination and muscular spasms, and no deaths (Flickinger 1976).

[b]OSHA PEL-TWA (Occupational Health and Safety Administration, permissible exposure limits–time-weighted average) (29 CFR 1910.1000 [1989]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/d, 40 h/wk.

[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 1996), 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-h workday and a 40-h 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 min, with no more than eight exposure periods per work shift; total exposure may not exceed 8-h MAK.
[h]MAC ([maximum workplace concentration], Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

laboratory animals, however, utilized accurate and reliable methods for characterizing exposure concentrations; however, exposure concentrations were often laboratory animals, however, utilized accurate and reliable methods for characterizing exposure concentrations; however, exposure concentrations were often 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, were 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 accurately assign an AEGL-1.

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# APPENDIX A

## TIME-SCALING CALCULATIONS FOR AEGLS

## AEGL-1 VALUES

| | |
|---|---|
| Key study: | Huntingdon Life Sciences 1998; Hoffman et al. 2001 |
| Toxicity end point: | Exposure of rats at 0.5, 5 or 25 ppm for 6 h/d, 5 d/wk for 2 weeks did not cause clinical, hematologic or histopathologic effects. A concentration of 25 ppm for 6 h was used as the basis for derivation of AEGL-1 values. |
| Scaling: | $C^3 \times t = k$ for extrapolation to 4 h, 1 h and 30 min<br>$k = 25^3$ ppm$^3 \times 6$ h = 93,750 ppm$^3$-h<br>$C^1 \times t = k$ for extrapolation to 8 h<br>$k = 25^1$ ppm $\times 6$ h = 150 ppm-h<br>The AEGL-1 for 10 min was set at the same concentration as the 30-min value. |
| Uncertainty factors: | Combined uncertainty factor of 3<br>1 for interspecies variability<br>3 for intraspecies variability |
| Calculations: | |
| 10-min AEGL-1 | 10-min AEGL-1 = 19 ppm (73 mg/m$^3$) |
| 30-min AEGL-1 | $C^3 \times 0.5$ h = 93,750 ppm$^3$-h<br>C = 57.24 ppm<br>30-min AEGL-1 = 57.24 ppm/3 = 19 ppm (73 mg/m$^3$) |
| 1-h AEGL-1 | $C^3 \times 1$ h = 93,750 ppm$^3$-h<br>C = 45.43 ppm<br>1-h AEGL-1 = 45.43 ppm/3 = 15 ppm (58 mg/m$^3$) |
| 4-h AEGL-1 | $C^3 \times 4$ h = 93,750 ppm$^3$-h<br>C = 28.62 ppm<br>4-h AEGL-1 = 28.62 ppm/3 = 9.5 ppm (37 mg/m$^3$) |
| 8-h AEGL-1 | $C^1 \times 8$ h = 150 ppm-h<br>C = 18.75 ppm<br>8-h AEGL-1 = 18.75 ppm/3 = 6.3 ppm (24 mg/m$^3$) |

## AEGL-2 VALUES

| | |
|---|---|
| Key study: | Flickinger 1976; Brondeau et al. 1990 |
| Toxicity end point: | Aerosol exposure to phenol at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination and spasms of the muscle groups at 4 h into the exposure, after 8 h 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 reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. The derivation of AEGL-2 values was based on an exposure concentration of 234 ppm for 8 h. |
| Scaling: | $C^3 \times t = k$ for extrapolation to 4 h, 1 h, and 30 min<br>$k = 234^3$ ppm × 8 h = $1.025 \times 10^8$ ppm³-h<br>The AEGL-2 for 10 min was set at the same concentration as the 30-min value. |
| Uncertainty/modifying factors: | Combined uncertainty factor: 10<br>3 for interspecies variability<br>3 for intraspecies variability<br>Modifying factor: 2 |
| Calculations: | |
| 10-min AEGL-2 | 10-min AEGL-2 = 29 ppm (110 mg/m³) |
| 30-min AEGL-2 | $C^3 \times 0.5$ h = $1.025 \times 10^8$ ppm³-h<br>C = 589.64 ppm<br>30-min AEGL-2 = 589.64 ppm/20 = 29 ppm (110 mg/m³) |
| 1-h AEGL-2 | $C^3 \times 1$ h = $1.025 \times 10^8$ ppm³-h<br>C = 468.00 ppm<br>1-h AEGL-2 = 468.00 ppm/20 = 23 ppm (90 mg/m³) |
| 4-h AEGL-2 | $C^3 \times 4$ h = $1.025 \times 10^8$ ppm³-h<br>C = 294.82 ppm<br>4-h AEGL-2 = 294.82 ppm/20 = 15 ppm (57 mg/m³) |
| 8-h AEGL-2 | 8-h AEGL-2 = 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, and 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 that is considered an equivalent to a CEN (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:

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

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

$3 = 2.33 \times \log (C/0.013) + 0.5$, which can be rearranged to
$\log (C/0.013) = (3\text{-}0.5)/2.33 = 1.07$ and results in
$C = (10^{1.07}) \times 0.016 = 11.8 \times 0.016 = 0.19$ 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.

$$LOA = C \times 1.33 = 0.19 \text{ ppm} \times 1.33 = 0.25 \text{ ppm}.$$

The LOA for phenol is 0.25 ppm.

# APPENDIX C

## ACUTE EXPOSURE GUIDELINES FOR PHENOL

### Derivation Summary for Phenol

**AEGL-1 VALUES**

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 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 Sciences Study No. 96-6107, CMA Reference No. PHL-4.0-Inhal-HLS. Chemical Manufacturers Association, Phenol Panel, Arlington, VA; Hoffman, 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 h/d, 5 d/wk 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 2 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 group and 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.

End Point/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 histopathologic 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).

*(Continued)*

**AEGL-1 VALUES** Continued

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 19 ppm | 19 ppm | 15 ppm | 9.5 ppm | 6.3 ppm |

The pharmacokinetic study in humans (Piotrowski 1971) was not used as a 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 Huntingdon Life Sciences 1998 (published as Hoffman 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 h/d, 5 d/wk for 2 weeks, no histopathologic 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 groups 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 extravasation of red blood cells visible as red nasal discharge is caused easily in the rat 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 h.

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 and the factor of 3 for the toxicodynamic component was retained, reflecting a possible variability of the target-tissue response in the human population.

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 dataset, a default value for n of 3 was used in the exponential function for extrapolation from the experimental period (6 h) to shorter exposure periods and a default value for n of 1 was used for extrapolation to longer exposure times. For the 10-min AEGL-1, the 30-min 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.

*(Continued)*

**AEGL-1 VALUES** Continued

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 19 ppm | 19 ppm | 15 ppm | 9.5 ppm | 6.3 ppm |

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 h (with 2 × 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.

**AEGL-2 VALUES**

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 29 ppm | 29 ppm | 23 ppm | 15 ppm | 12 ppm |

Reference: 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.

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:
Inhalation/900 mg phenol/m³ aerosol/8 h
Inhalation/111, 156 or 211 ppm/4 h

Effects: Ocular and nasal irritation were observed, as well as slight loss of coordination with spasms of the muscle groups within 4 h and tremors and prostration (in 1/6 rats) within 8 h. 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. 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.

End Point/Concentration/Rationale: Due to the lack of more adequate studies, a combination of the Flickinger (1976) and Brondeau et al. (1990) studies was used as the basis for derivation of AEGL-2 values. Aerosol exposure at 900 mg/m³ (equivalent to phenol vapor at 234 ppm) for 8 h resulted in ocular and nasal irritation, slight loss of coordination, and spasms of the muscle groups at 4 h into the exposure; after 8 h, additional symptoms (tremor, incoordination, and prostration) were observed in 1/6 animals. No deaths occurred. This study is supported by the study of Brondeau et al. (1990), who reported only slight effects after exposure to phenol vapor at 211 ppm for 4 h. Although both studies had shortcomings, that is, aerosol exposures, nominal concentrations, and no description of toxic signs in one study, taken together, they had

*(Continued)*

**AEGL-2 VALUES** Continued

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 29 ppm | 29 ppm | 23 ppm | 15 ppm | 12 ppm |

consistent results. It was considered adequate to calculate and use the phenol vapor concentration corresponding to a 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 h.

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) who 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 dataset, a default value of n of 3 was used in the exponential function for extrapolation from the experimental period (8 h) to shorter exposure periods. For the 10-min AEGL-2, the 30-min 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, that is, 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.

**AEGL-3 VALUES**

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| 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.

*(Continued)*

**AEGL-3 VALUES** Continued

| 10 min | 30 min | 1 h | 4 h | 8 h |
|---|---|---|---|---|
| N.R. | N.R. | N.R. | N.R. | N.R. |

End Point/Concentration/Rationale: The study by Deichmann et al. (1944) was not used as a key study because of 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.