

U.S. Army Center for Health Promotion
and Preventive Medicine

**Wildlife Toxicity Assessment for
Phenol**

JUNE 2008

**Prepared by
Health Effects Research Program
Environmental Health Risk Assessment Program**

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Wildlife Toxicity Assessment for Phenol

CAS No. 108-95-2

February 2008

1. INTRODUCTION

Phenol, C₆H₅OH, is a deliquescent crystalline solid found in petroleum products such as coal tar and creosote and is produced by the natural degradation of organic wastes such as benzene. Phenol is produced for industrial/commercial use through distillation of petroleum, oxidation of cumene or toluene, and by hydrolysis of chlorobenzene. Phenol is predominantly used in the production of other compounds including bisphenol-A and other phenolic resins, caprolactam (nylon), aniline (polyurethane), alkylphenols (detergents and plasticizers), and xylenols (pesticides and antioxidants). Because phenol is toxic to bacteria, fungi and viruses it is also used in a number of medicinal and cleaning agents. While the compound is present in a number of over-the-counter personal care products, such as mouthwashes, ointments, and antiseptic and antipruritic lotions, the corrosive nature of the substance militates against its excessive application. Additionally, the cell-killing properties of the substance are not confined to microorganisms, suggesting that a narrow dosimetric window may exist between the substance's therapeutic and toxicological thresholds. As specified in the Hazardous Substances Databank (HSDB), phenol should never be used on pregnant women or infants under 6 months of age (e.g., in products used for diaper rash) (HSDB 2002).

A substantial amount of information exists on the compound's potential threat to individuals who may become exposed to phenol in the workplace. The National Institute for Occupational Safety and Health and the Occupational Safety and Health Administration have established time-weighted average exposure limits of 5 ppm (19 mg/m³), with a 15-minute ceiling value of 15.6 ppm (60 mg/m³), and an immediately dangerous to life or health value of 250 ppm (950 mg/m³). The U.S. Environmental Protection Agency (U.S. EPA) has developed a reference dose (RfD) of 0.6 mg/kg-day from data on the developmental effects of the compound in laboratory rats (U.S. EPA 2002).

This Wildlife Toxicity Assessment summarizes available information on the likely effects of phenol on wildlife, stressing threshold doses for the onset of non-cancer effects, as described in reports of experimental studies of the compound. Surveying the threshold dosimetry of phenol may point to the establishment of toxicity reference values (TRVs) that could serve as protective exposure standards for all wildlife ranging in the vicinity of affected sites. The protocol for the performance of this assessment is

documented in the U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254, *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

2. TOXICITY PROFILE

2.1 Literature Review

Relevant biomedical, toxicological, and ecological databases were electronically searched June 3-4, 2002, and June 21, 2007, using DIALOG and TOXNET to identify primary reports of studies and reviews on the toxicology of phenol. Separate searches were carried out linking the compound to laboratory mammals, birds, reptiles and amphibians (combined), or wild mammals. In general, a two-tiered approach was used in which all citations were first evaluated as titles and “key words in context.” All available abstracts of those articles selected in Tier 1 as possibly relevant to TRV development were then evaluated for relevancy and retention in Tier 2. For phenol, 25 articles were marked for retrieval from 1,805 initial hits. Details of the search strategies and the results of each are documented in Appendix A. Secondary references and sources of information on phenol included the National Library of Medicine’s Hazardous Substances Databank (HSDB 2002), an Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for phenol (ATSDR 2006), and the U.S. EPA’s Integrated Risk Information System (IRIS) (U.S. EPA 2002).

2.2 Environmental Fate and Transport

There is a substantial body of information on the dispersion of phenol in the environment, with HSDB (2002) and ATSDR (2006) providing summaries of the salient facts. The compound may be released to the air through storage tank vents, during loading and unloading operations, during wood burning, through emissions of waste incinerators and coal-fired power plants, and in automobile exhaust and cigarette smoke. Releases to streams and rivers may occur via the waste water from chemical syntheses and manufacturing processes (e.g. resins, plastics, fibers, adhesives, rubber, etc.), from pulp mills and wood-treatment facilities, and during the use and discharge of phenol-containing commercial products (e.g., personal care items and disinfectants). Aquatic environments may also become contaminated with phenol through decomposition of organic wastes and phenol may be released in effluent from municipal sewage treatment facilities. Soil may become contaminated with phenol through spills at manufacturing sites and leaching from hazardous waste sites and landfills.

Transport and partitioning of phenol in environmental media is governed by its high solubility in water. Phenol released to the atmosphere may be washed out through rainfall and become deposited in soil and surface water bodies. However, only limited amounts of air-borne phenol will wash out in rainwater as the compound rapidly undergoes degradation by reaction with photochemically produced hydroxyl radicals (half-life 0.61 days). Owing to its high water solubility, phenol is also unlikely to sorb

to sediments, but will instead tend to leach to groundwater. However, this process is mitigated by the relatively rapid biodegradation of phenol in soil by a number of aerobic and anaerobic bacteria (half-life <5 days to 23 days). Phenol in sunlit surface waters will undergo photooxidation by hydroxyl and peroxy radicals, as well as biodegradation by some species of algae. Half-lives for biodegradation of phenol in water range from less than one day in fresh water to nine days in estuarine water. Phenol may also be taken up by higher plants; however, plants can readily metabolize the compound, limiting the potential for exposure via ingestion of plants grown in contaminated soils. Biodegradation of phenol may be hindered and phenol may persist in the air, water, and soil for extended periods if releases are continual and concentrations become toxic to microorganisms capable of degrading phenol.

The processes that would tend to remove phenol from the environment notwithstanding, the compound has been detected in all media. Phenol has been measured in air (0.03-44 ppb), sediment (>10 ppb), groundwater (1.9>10 ppb) and surface water (1.5>100 ppb) (ATSDR 2006). Additionally, phenol has been measured in effluents at concentrations as high as 53 ppm and has been detected in groundwater in ppm concentrations in the vicinity of facilities such as wood preservation plants and coal gasification installations.

Physical-chemical characteristics of phenol relevant to its environmental fate and transport are summarized in Table 1.

Table 1. Summary of Physical-chemical Properties of Phenol

CAS No.	108-95-2
Molecular weight	94.11
Color	Colorless to light pink
Physical state	Deliquescent crystals
Melting point	43 °C
Boiling point	181.8 °C
Odor	Acrid
Solubility in water	87 g/L, soluble in a number of organic solvents
Partition coefficients:	
Log K_{ow}	1.46
Log K_{oc}	1.21–1.96
Vapor pressure at 25 °C	0.35
Henry's Law constant at 25 °C	4.0×10^{-7} m ³ /mol
Conversion factors	1 ppm = 0.26 mg/m ³ 1 mg/m ³ = 3.92 ppm

Sources: HSDB (2002), ATSDR (2006)

2.3 Summary of Mammalian Toxicity

2.3.1 Mammalian Oral Toxicity

2.3.1.1 Mammalian Oral Toxicity - Acute

Oral median lethal doses (LD₅₀s) for phenol have been given in Lewis (1992), HSDB (2002), and Berman et al. (1995). Primarily, the values are clustered in the range 250–500 mg/kg, although the value reported in cats (80 mg/kg) is considerably lower (Lewis 1992, HSDB 2002). Lewis (1992) specifies values of 317 mg/kg for rats, 270 mg/kg for mice and 500 mg/kg for dogs. Berman et al. (1995) used the simplified up/down procedure to derive an oral LD₅₀ of 400 mg/kg in female F344 rats.

A number of groups have used a single dose of phenol to study toxicological endpoints other than lethality. For example, the Chemical Manufacturers Association (CMA) sponsored a study in which five F344 rats/sex/group received a single gavage dose of 0, 1.5, 15, or 150 mg/kg ¹⁴C-phenol (CMA 1994). The animals were kept in metabolic cages for 24 hours after dosing so that the amounts of radiolabel in urine, feces, and expired air could be monitored. Two additional test groups consisting of five male rats each were given a single dose of either 150 mg/kg (high dose) or 1.5 mg/kg (low dose) ¹⁴C-phenol. These male rats were cannulated in the jugular vein to permit the area under the curve of the blood activity time course to be monitored. Greater than 90 percent of the radioactivity was recovered in the urine, with few, if any, counts expired in the breath. Of the few counts that remained in the carcass, most were centered in the liver and kidney, suggesting no tissue-selective retention. Blood levels of free phenol were very low and peaked 1–3 minutes after dosing. Additionally, muscle twitching was observed in the 150 mg/kg dose group immediately following dosing, but disappeared within 45 minutes. Some radiolabeled glucuronides and sulfates of phenol and hydroquinone were identified, suggesting that the latter represent the primary conjugation products of orally administered phenol.

In one of a series of research reports wherein potential toxicants were tested using standard protocols, Moser et al. (1995) used two dosing regimens to examine the neurotoxicological characteristics of phenol in female Fischer rats (8 rats/dose). In the first report, animals received a single oral dose of phenol at 0, 12, 40, 120 or 224 mg/kg. In a "before-and-after" experimental design that permitted each animal to serve as its own control, a battery of neurological function tests were used to (1) determine the animal's autonomic, sensorimotor, neuromuscular, and physiological (body weight, body temperature, piloerection) responses to phenol, and (2) follow its level of activity and excitability, and document any related functional deficits. Two of the eight rats (25%) in the highest dose group died within four hours of dosing, and one of eight rats (13%) in the 120 mg/kg dose group died within 24 hours of dosing. Mild to severe whole-body tremors were observed in the 120 and 224 mg/kg dose groups within 1-2 minutes of dosing, but these rapidly disappeared. Decreased motor activity, crouched or flattened posture, decreased touch response, and body weight loss (7-8% within 24 hours) were also observed in the two highest dose

groups. Neuromuscular impairment (e.g., tiptoe gait) was observed in the highest dose group. The data suggested that 40 mg/kg would be a viable single-dose no observed adverse effects level (NOAEL), with a likely lowest observed adverse effects level (LOAEL) of 120 mg/kg.

2.3.1.2 Mammalian Oral Toxicity - Subacute

The reports of Berman et al. (1995) and Moser et al. (1995) describe experiments in female F344 rats that delineate the systemic and neurological toxicity of phenol when administered subacutely. In each case, aqueous phenol was administered to F344 rats at 0, 4, 12, 40, or 120 mg/kg for 14 days. All of the high-dose subjects died over the course of the study. Moser et al. (1995) also noted a 14% decrease in body weight in the high dose group. The principal systemic toxicity responses to phenol were necrosis of the renal tubules, formation of proteinaceous renal casts, and necrosis of the spleen and thymus (Berman et al. 1995). A 12 mg/kg-day NOAEL was suggested for systemic effects of phenol. Moser et al. (1995) noted neurological effects of phenol, including autonomic and activity deficits, with a subacute NOAEL of 12 mg/kg-day, similar to that reported for systemic effects, and a LOAEL of 40 mg/kg-day.

2.3.1.3 Mammalian Oral Toxicity – Subchronic

Only a single subchronic oral study was identified. CMA sponsored a 13-week neurotoxicity study in which 15 Sprague-Dawley rats/sex/group were exposed to 0, 200, 1000, or 5000 ppm phenol in drinking water (CMA 1998a). According to the authors, the doses equivalent to these drinking water concentrations were 0, 18.1, 83.1, and 308.2 mg/kg-day in males and 0, 24.6, 107, and 359.8 mg/kg-day in females. Clinical signs and drinking water intake were recorded daily; body weight and food intake were monitored weekly. Animals were subjected to a functional observational battery of qualitative and quantitative neurological tests at 4, 8, 13, and 17 weeks (the latter 4 weeks after cessation of dosing). All animals were necropsied at term, with five animals/sex in the control and 5000 ppm groups undergoing additional neuropathological evaluations. About 50 percent of the high-dose group became dehydrated, and their food and water consumption was reduced throughout the treatment phase. The decreased water consumption and resulting dehydration were attributed to the aversion to the taste of phenol rather than being a direct toxicological effect. Few, if any, compound-related responses were observed in the functional battery at any dose level. Although a sporadic reduction in motor activity in high- and mid-dose animals was observed, the effects were considered to be secondary to the reduction in food and water consumption. No effects of phenol on central or peripheral nervous tissue were observed during necropsy or histopathology. Based on these findings, the authors considered the high dose group (308 mg/kg-day in males and 360 mg/kg-day in females) to be the NOAEL for neurotoxicological effects of phenol in this experimental system.

2.3.1.4 Mammalian Oral Toxicity – Chronic

A single study documents the toxic effects of phenol in experimental animals under a chronic dosing regimen. As described in U.S. EPA's IRIS record (U.S. EPA 2002), a chronic drinking water study was conducted by the National Cancer Institute (NCI) in which 50 F344 rats and 50 B6C3F1 mice per sex per group were dosed with 0, 2500, or 5000 ppm phenol in drinking water for 103 weeks (NCI 1980). The drinking water concentrations correspond to estimated doses of 0, 260, 585 mg/kg-day for male rats, 0, 280, 630 mg/kg-day for female rats, and 0, 450, 660 mg/kg-day for male and female mice (U.S. EPA 2002). No toxicological effects could be unequivocally attributed to the compound. Although high-dose animals showed a reduction in body-weight gain this response may have resulted from the marked reduction in water consumption in these groups, a response almost certainly related to taste aversion. In the absence of compound-related effects on mortality, behavior, morphology, or histopathology, this study identified LOAELs of 585 mg/kg-day and 660 mg/kg-day and NOAELs of 260 mg/kg-day and 450 mg/kg-day for rats and mice, respectively, based on body weight depression. As the reduction in body weight was attributed to taste aversion and not a direct adverse effect of phenol, the LOAELs established based on this response may not be appropriate.

2.3.1.5 Mammalian Oral Toxicity – Other

Several studies of reproductive effects of oral phenol exposure in mammals were identified. These are described below.

The Research Triangle Institute (RTI) carried out a teratological evaluation of phenol in CD-rats on behalf of the National Institute of Environmental Health Sciences (RTI 1983a). The study was used by the IRIS compilers as the principal study for developing a human health RfD for the compound (U.S. EPA 2002). Pregnant female CD-rats (20-22 per group) were gavaged on gestation days (GDs) 6–15 with 0, 20, 60, or 120 mg phenol/kg-day in a volume of 5 ml/kg body weight. Dams were sacrificed on GD 20 and their uteri examined for implantation losses, fetal number, and viability. Each live fetus was weighed and examined for external, visceral, or skeletal abnormalities. The doses used in the experiment were chosen as a result of a preliminary range-finding exercise that extended into the lethal range. In the range finding study, seven of ten rats given 125 mg/kg-day in a volume of 1 ml/kg died whereas only one of six rats given 160 mg/kg-day in a volume of 5 ml/kg died. The reduced toxicity observed at the higher dose was attributed to the larger dose volume resulting in a decreased absorption rate. No maternal toxicity was evident in the sub-lethal phase of the study. The number of implantation sites and live fetuses did not differ among the groups; however, the proportion of litters with resorption sites was significantly increased in the low- and mid-dose groups, but not the high-dose group. Fetal body weight demonstrated a dose-related decrease, with the high dose fetuses weighing significantly less than the controls. Based on

this finding, the compound was determined to have developmental toxicity effects, with a NOAEL of 60 mg/kg-day and a LOAEL of 120 mg/kg-day.

Proctor & Gamble (P&G) sponsored two reproductive/developmental studies in Sprague-Dawley rats (P&G 1993, 1997). In the initial range-finding exercise, 10 pregnant female Sprague-Dawley rats/group were gavaged on GDs 6–15 with 0, 60, 120, or 180 mg/kg-day. Animals were sacrificed on GD 15 and the uteri were examined for organ weight, fetal viability, early and late resorptions, number of corpora lutea and total implants. The weights of major organs such as the liver, kidney, and stomach were recorded. Reduced food consumption and body-weight gain were evident in groups receiving phenol at the 120 and 180 mg/kg-day dose levels, but there were no other signs of maternal, reproductive, or developmental toxicity (P&G 1993).

In the follow-up study, 25 pregnant female Sprague-Dawley rats/group received 0, 20, 40, or 120 mg aqueous phenol/kg-day, three times/day by gavage (dose volume of 10 ml/kg) on GDs 6–15 (P&G 1997). This resulted in overall dose levels of 0, 60, 120, and 360 mg/kg-day. During the study, clinical signs and body weights were monitored daily and food consumption was measured on GDs 0, 6, 9, 12, 16, and 20. All dams were sacrificed on GD 20. A standard necropsy was supplemented by monitoring reproductive and developmental parameters such as the number of corpora lutea, the number and distribution of implantations, fetal viability, early and late resorptions, fetal weights, gross external fetal alterations, and soft tissue or skeletal alterations. In general, the effects of treatment were unremarkable. One high-dose dam died on GD 11, and several dams displayed clinical signs such as excess salivation and tachypnea. Maternal body-weight gain was reduced in dams receiving 120 mg/kg-day (11%) and 360 mg/kg-day (38%). Reduced maternal body-weight gain was associated with significant reductions in food consumption in the 120 mg/kg-day (11%) and 360 mg/kg-day (16%) groups. A NOAEL of 60 mg/kg-day and a LOAEL of 120 mg/kg-day were assigned for maternal effects. Fetal weights were reduced by five to seven percent in the high-dose group. The effect on fetal weight, along with a reduction in the number of ossification sites for metatarsals, justified assigning 120 mg/kg-day as a NOAEL and 360 mg/kg-day as a LOAEL for developmental effects.

Narotsky and Kavlock (1995) carried out a reproductive and developmental toxicity study on phenol in which approximately 20 pregnant female F344 rats/group were gavaged at doses of 0, 40, or 53.3 mg/kg-day on GDs 6-19. The dams were allowed to deliver their litters that were then evaluated for reproductive and developmental toxicity parameters. Non-significant reductions in body weight gain were observed in females, as was altered respiration in both dose groups. Additionally, one low dose (7%) and two high dose (13%) litters were fully resorbed, resulting in a significant reduction in litter size (number of live pups) and an increase in prenatal loss in the high dose group. It should also be noted that these three females suffered severe respiratory signs. There were few other changes in treated groups compared to control, although pups delivered by high-dose dams weighed significantly less than those

born to controls. The authors considered the difference, although significant, to have been unduly influenced by the progeny of a single dam, and, therefore, not necessarily indicative of a compound-related effect. The occurrence of kinked tails in progeny from the high dose group may be used to assign a teratological NOAEL of 40 mg/kg-day. Based on the significant reduction in number of live pups, 40 mg/kg-day could also be considered a reproductive NOAEL, with a corresponding LOAEL of 53.3 mg/kg-day.

B.F. Goodrich and CMA reported a two-generation reproductive study in which phenol was added to the drinking water of 30 pairs of Sprague-Dawley rats (CMA 1999). The experiment was subsequently published in the open literature by Ryan et al. (2001). The concentrations employed were 0, 200, 1000, and 5000 ppm, equivalent to daily doses in the F₀ generation of 0, 14.7, 70.9, and 301 (males), and 0, 20, 93, and 320.5 mg/kg-day (females) and doses in the F₁ generation of 0, 13.5, 69.8, and 319.1 (males) and 0, 20.9, 93.8, and 379.5 mg/kg-day (females). Exposure was for an initial 10-week period prior to mating, through a 2-week mating period, and through gestation and lactation until weaning. Randomly chosen F₁ animals were then exposed for 11 weeks prior to mating, and then through mating, gestation, delivery and weaning. A full slate of systemic, reproductive, and developmental toxicological parameters was evaluated in both generations, but the authors noted few obvious compound-related changes in any of the treated groups. Although significant reductions in water and food consumption, and corollary reductions in body weight and weight gain, were noted in the high dose group, these effects were attributed to taste aversion to phenol in the drinking water. Mating performance, fertility, vaginal cytology, and male reproductive function were similar to controls in all dose groups. Prostate and uterus weights were reduced in the F₁ generation in all dose groups; however, in the absence of underlying pathology or functional deficit in reproductive performance, these effects were not considered to be adverse. Litter survival was reduced in the 5000 ppm group of both generations, suggesting a developmental NOAEL of 1000 ppm which was equivalent to approximately 70 mg/kg-day for males and 93 mg/kg-day for females.

The Research Triangle Institute (RTI) carried out a teratological evaluation of phenol in CD-1 mice on behalf of the National Institute of Environmental Health Sciences (RTI 1983b). Pregnant female CD-1 mice (22-29 per group) were gavaged on GDs 6–15 with 0, 70, 140, or 280 mg phenol/kg-day in a volume of 10 ml/kg body weight. Dams were sacrificed on GD 17 and their uteri weighed and examined for implantation sites and fetuses. Live fetuses were weighed and examined for external, visceral, or skeletal abnormalities. The high dose group exhibited signs of maternal toxicity, including reduced body weight and weight gain, increased mortality (11%), tremors and ataxia. Prenatal viability (incidences of resorptions and dead fetuses) and fetal deformities were not significantly different among treatment groups. Uterine weight and fetal body weight demonstrated a dose-related decrease, with the high dose groups weighing significantly less than the controls for both measures. Based on this finding, the

compound was determined to have developmental toxicity effects with a NOAEL of 140 mg/kg-day and a LOAEL of 280 mg/kg-day.

2.3.1.6 Studies Relevant for Mammalian TRV Development for Ingestion Exposures

Several subacute, subchronic, chronic, and reproductive/ developmental studies were identified as appropriate for the development of Toxicity Reference Values (TRVs) for mammals. However, only one Order (Rodentia) and two families (Cricetidae and Muridae) are represented in the relevant studies.

Orally administered phenol is readily absorbed and is widely distributed throughout the body, with elevated tissue concentrations occurring in the liver and kidneys. The adverse effects observed following ingestion of phenol are consistent with its generalized toxic effects for which there is no target organ specificity. This was evidenced in the wide-spread effects (e.g., necrosis of the kidney, spleen, and thymus and neurological deficits) observed in subacute (gavage) studies by Berman et al. (1995) and Moser et al. (1995). Subchronic and chronic studies (all drinking water) did not demonstrate similar systemic toxicity effects (NCI 1980 and CMA 1998a). Although decreased body weight was observed in these studies, this effect was apparently secondary to decreased water consumption owing to the poor palatability and aversion to phenol in drinking water.

The developmental and reproductive effects of exposure to phenol, as discussed in Section 2.3.1.5, were similar among studies, however, the magnitude of the effect and the dose at which the effects were observed varied among studies utilizing different dosing regimes. A contrast is evident in the toxic effects of phenol when administered as a bolus compared to similar doses administered throughout the day. For example, Ryan et al. (2001) administered phenol in the drinking water and observed reproductive effects (e.g., reduced survival of F₁ pups) at the highest dose level, a dose about six times greater than the dose which produced similar effects in a gavage study (Narotsky and Kavlock 1995). The difference in effects between administration methods may be a result of the phenol serum levels not being linearly related to dose. At low doses, the rapid uptake, metabolism, and clearance of the compound results in almost all of the phenol being excreted without entering the bloodstream (CMA 1994). Administration of the compound as a bolus may saturate these mechanisms, at least temporarily, allowing phenol to appear in the bloodstream and its toxic impacts to become apparent.

The systemic toxicity of phenol, as indicated by “phenol twitching behavior (PTW)”, appears to be more closely related to peak blood levels than total dose as PTW coincided with peak blood concentrations following gavage dosing, but was not observed in drinking water exposure groups despite the total dose being higher than the high gavage dose (CMA 1994). Additionally, as a result of the more rapid absorption of the compound, the effects of phenol are increased when smaller dosing volumes are used (RTI 1983, P&G 1993).

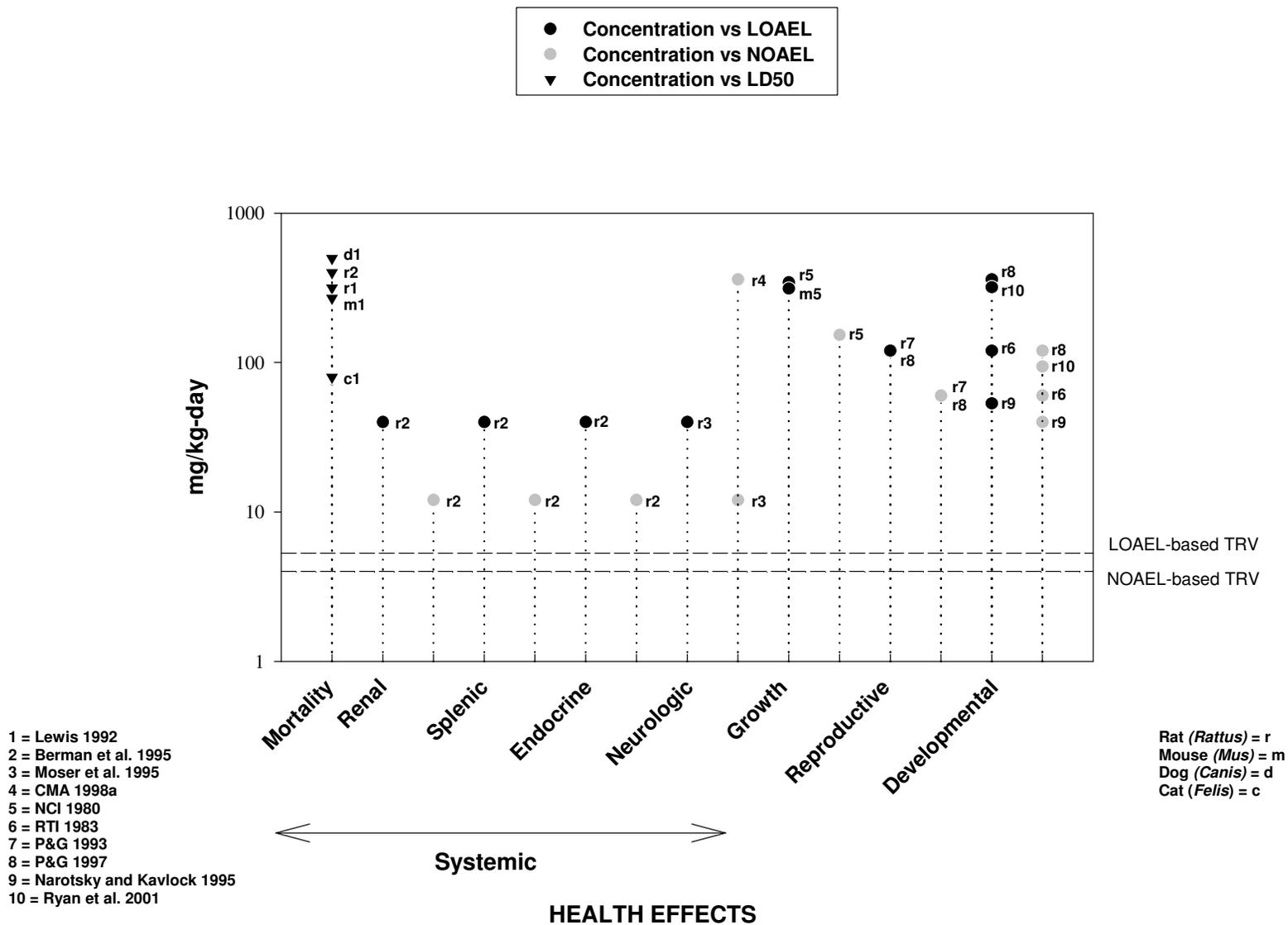
In light of the effect of dosing regime on phenol toxicity and given that drinking water dosing may be more ecologically relevant than gavage dosing, development of a TRV based on drinking water studies may be appropriate. However, the effects of phenol observed in drinking water studies can largely be attributed to taste aversion and decreased water consumption rather than toxicity. Additionally, precise determination of administered dose is difficult in drinking water studies as spillage can occur. As such, the P&G (1997) study, which decreases the impact of gavage dosing and approximates the toxicokinetic profile of drinking water studies by dividing the dose into three administrations per day, may be the most appropriate study for TRV development. As P&G (1997) is the only study conducted using a divided-dosing regime, support for a TRV based on this study may be drawn from other studies. The NCI (1980), Narotsky and Kavlock (1995), and Ryan (2001) studies are particularly valuable as they include chronic, reproductive, and developmental studies that evaluate numerous relevant endpoints. The LOAELs and NOAELs for studies relevant to TRV derivation are listed in Table 2 and displayed graphically in Figure 1.

Table 2. Summary of Relevant Mammalian Data for TRV Derivation

Study	Test Organism	Test Duration	Test Results		
			NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Effects Observed at the LOAEL
Berman et al. 1995	Rats (F344)	14 d	12	40	Necrosis of the kidney, spleen and thymus
Moser et al. 1995	Rats (F344)	14 d	12	40	Neurological deficits
CMA 1998a	Rats (Sprague-Dawley)	13 wk	360	-	None
NCI 1980	Rats (F344)	103 wk	260	585	Body weight depression
NCI 1980	Mice (B6C3F1)	103 wk	450	660	Body weight depression
RTI 1983a	Rats (CD)	GD 6-15	60	120	Reduced fetal body weight
RTI 1983b	Mice (CD-1)	GD 6-15	140	280	Reduced fetal body weight and gravid uterine weight, maternal toxicity
P&G 1993	Rats (Sprague-Dawley)	GD 6-15	60	120	Reduced maternal body weight gain and food consumption
P&G 1997	Rats (Sprague-Dawley)	GD 6-15	60	120	Reduced maternal body weight gain and food consumption
			120	360	Reduced fetal body weights; reduced number of ossification sites for metatarsals
Narotsky and Kavlock 1995	Rats (F344)	GD 6-19	40	53.3	Reduced number of live pups (reproductive effects); kinked tails (teratogenic effect), reduced maternal body weight
Ryan et al. (2001)	Rats (Sprague-Dawley)	10 or 11 wk prior to mating through weaning	70-94	319-380	Reduced survival of F ₁ pups

Figure 1

PHENOL: HEALTH EFFECTS TO MAMMALS



2.3.2 Mammalian Inhalation Toxicity

One mammalian inhalation toxicity study was located. CMA sponsored a 10-day inhalation toxicity experiment in which 20 F344 rats/sex/group were exposed 6 hours/day, 5 days/week for 2 weeks to phenol (nose only) at 0, 0.5, 5, or 25 ppm (CMA 1998b). Half of animals at each dose were permitted a 2-week recovery period. All animals were monitored for clinical signs, food consumption, and body-weight changes. At term, hematological and clinical chemistry parameters were measured, and a full necropsy was carried out to evaluate any morphological changes that might have occurred in response to treatment. Pieces of liver, kidney, spleen, and respiratory tract, as well as any gross lesions, were fixed and mounted for histopathological examination. The authors reported almost uniformly negative results for toxicological impacts of inhaled phenol in this experiment. Clinical signs such as chromodacryorrhea (i.e., red tears) and nasal discharge were evident in some of the animals in the study; however, these responses were reported in the published version of the study (Hoffman et al. 2001) to be sporadic and not treatment related, whereas in the CMA (1998b) version of the study these effects were reported to be concentration-related in males during the second week of exposure to 5 and 25 ppm. In the absence of abnormal nasal histopathology, these effects were not deemed to be adverse effects. Due to the equivocal nature of the responses, an appropriate NOAEL could not be determined.

2.3.3 Mammalian Dermal Toxicity

In the single mammalian dermal toxicity study located, phenol was one of a number of compounds applied to the ears of 8–11 female ICR mice/group to measure swelling as an index of irritation (Patrick et al. 1985). Four dose groups (1.0, 1.25, 1.5, 1.75, and 2.0 mg) were evaluated. Because solvent alone (ethanol, in this case) was applied to the other ear, each animal was able to serve as its own control. Five microliters of the dose was applied to the dorsal and ventral surfaces of the ear. Phenol was highly effective in inducing ear swelling, with striking dose-dependent increases in the incidence (13 to 100 percent) and degree of swelling.

2.4 Summary of Avian Toxicology

No studies were identified that examined the toxic effects of phenol in birds.

2.5 Summary of Amphibian Toxicology

Four studies on the effects of phenol on amphibian development were located, one using a short-term embryo exposure and three using embryo and larval exposures.

2.5.1 Amphibian Toxicity -- Other

Bernardini et al. (1996) exposed *Xenopus* embryos (8 in each dose level) to phenol at 0, 25, 50, 100, 150, 200, and 250 mg/L from eight hours post fertilization (p.f.) through 120 hours p.f. Mortality was recorded over the course of the study, dead and euthanized embryos (i.e., embryos surviving to 120 hours)

were evaluated for malformations, and head-to-tail length was measured. A concentration-dependent increase in both mortality and malformation rates was observed, with both responses increasing dramatically after 100 mg/L. There was also a significant concentration-dependent reduction in the mean length of embryos. Because significant growth retardation occurred at all exposure concentrations, 25 mg/L is considered the lowest observed effect concentration (LOEC) for this endpoint. Values for median lethal concentration (LC50), median teratogenic concentration (TC50), median teratogenic index (TI50; equals LC50/TC50), ten percent lethal concentration (LC10), and ten percent teratogenic concentration (TC10) were developed in the study. The LC50, TC50, TI50, LC10, and TC10 values are 178, 141, 1.3, 32, and 42 mg/L, respectively.

Dumpert (1987) examined the toxicity of phenol in the African clawed frog, *Xenopus laevis*, using concentrations of 0, 0.1, 1, 5, 10, and 50 ppm in a physiological salt medium. Exposure occurred during embryogenesis and larval development. Although the exact duration was not given, a five week period of exposure was indicated prior to measurement of body length. All larvae exposed to the highest concentration of phenol (50 ppm) died within three weeks of exposure. Development of larvae exposed to the remaining exposure concentrations was similar to that of the controls and no teratogenic effects of the compound were evident in this experiment. Larvae exposed to 5 and 10 ppm phenol, however, were slightly shorter than the controls. Although this effect was not statistically significant, it does indicate a possible growth retardation effect that is consistent with that reported by Bernardinin et al. (1996). Therefore, 1 ppm is considered the no observed effects concentration (NOEC), and 5 ppm the LOEC.

Two companion studies conducted by the University of Kentucky Water Resources Research Institute (Birge et al. 1980 and Black et al. 1982) examined the toxicity of phenol in eight species of amphibians using a flow-through bioassay system. Birge et al. (1980) exposed 50-130 embryos of *Rana pipiens*, *Rana catesbeiana*, *Rana palustris*, *Bufo fowleri*, and *Bufo americanus* to at least five test concentrations of phenol per species which ranged from 0.0007 to 21.8 mg/L from 0.5-6 hours post fertilization through four days post hatching. Using the same flow-through embryo-larval test system, Black et al. (1982) exposed 50-125 embryos of *Ambystoma gracile*, *Rana temporaria*, and *Xenopus laevis* to phenol at concentrations of 0.002, 0.010, 0.12, 0.72, 1.45, 14.0, and 26.4 mg/L from 30 minutes post fertilization through four days post hatching.

Percent survival of normal organisms, expressed as the frequency in test organisms relative to controls, was determined at hatching and four days after hatching. Percent egg hatchability included all embryos which completed the hatching process, regardless of teratogenic status. Teratogenesis was expressed as the percent of survivors affected by gross, debilitating abnormalities at the time of hatching. Control-adjusted median lethal concentration (LC50) was determined for each species, while LC10 and LC1 values were determined for select species (*R. pipiens* and *R. catesbeiana*). These determinations were based on the combined frequencies for lethality and teratogenesis. The authors considered the LC1 as the

threshold for adverse effects and the LC10 concentration the level at which exposure begins to produce appreciable reproductive impairment (Birge et al. 1980).

Based on the LC50 values, the order of increasing tolerance for the eight species tested was *R. pipiens* (0.04), *R. catesbeiana* (0.23), *R. temporaria* (0.27), *A. gracile* (0.38), *B. americanus* (>0.89), *B. fowleri* (2.45), *X. laevis* (7.68), *R. palustris* (9.87). The LC1 for *R. catesbeiana* and *R. pipiens* were reported as 1.0 and 1.1 µg/L, while the LC10 values for these species were 8.5 and 5.2 µg/L, respectively. Although no statistical tests were conducted and no NOAEL and LOAEL were reported in these studies, teratogenesis above that reported in the control groups (typically <1%) was reported to occur at concentrations starting at 0.0047 mg/L for *R. pipiens*, 0.12 mg/L in *R. temporaria*, 0.22 mg/L for *B. americanus*, 0.53 mg/L for *R. catesbeiana*, 1.86 mg/L for *R. palustris*, 10.2 mg/L for *B. fowleri*, 14.0 mg/L in *X. laevis*. No teratogenic effects were observed in *A. gracile* at concentrations up to 26.4 mg/L.

2.5.2 Studies Relevant for Amphibian TRV Development for All Exposures

The four studies identified for amphibians are relevant for TRV development. All of the studies document phenol toxicity during the critical life stages of embryogenesis and larval development. The Bernardini et al. (1996) study, however, was of limited duration and did not extend throughout embryogenesis. Dumpert (1987) conducted a longer term (> five weeks) study of the effects of phenol on *Xenopus laevis*. Although the exact duration of the study is not reported, it occurs during a critical life stage (i.e., during embryogenesis and larval development) and thus may be considered a chronic study and is highly relevant for TRV development. The studies by Birge et al. (1980) and Black et al. (1982) are limited in that they are of short duration, constitute single replicates, and do not report on growth effects. However, these studies extend through embryogenesis and are the only studies which utilize amphibian species other than *Xenopus laevis*, and are therefore important for TRV development. Eight species representing two Orders and three families of amphibians, including Anura: Ranidae, Bufonidae, and Pipidae, and Urodela: Ambystomatidae are represented by these studies.

The effects from exposure are consistent, but vary in magnitude. Differences in the magnitude of effects observed in *X. laevis*, the only species utilized in multiple studies, may be attributed to differences in exposure protocols (static renewal vs. flow-through) and duration of exposure (portion of embryo stage vs. embryo and larval stages). Two studies (Bernardini et al. 1996 and Dumpert 1987) identified LOAELs for growth retardation (25 mg/L and 5 mg/L, respectively) for *X. laevis*. A NOAEL for growth of 1 mg/L was identified by Dumpert (1987), but no NOAEL for growth could be identified in the Bernardini et al. (1996) study. The differences in growth effects in these studies may be attributable to the exposure duration and the measurement of growth during the larval phase in the Dumpert (1987) study. Effects on amphibian growth are likely to be more substantial during the larval phase when rapid growth occurs.

Teratogenic effects of phenol, including generalized edema and intestinal and ocular malformations were observed by Birge et al. (1980), Black et al. (1982), and Bernardini et al. (1996), however, LOAELs and NOAELs were not reported by the authors. The concentration expected to produce teratogenic effects in 10 or 50% of exposed *X. laevis* (TC10 or TC50) were reported by Bernardini et al. (1996) as 42 mg/L and 141 mg/L, respectively. The concentration of phenol that produced malformations ranged from 0.0047 mg/L in *R. pipiens* to 14.0 mg/L in *X. laevis* in the Birge et al. (1980) and Black et al. (1982) studies, although these changes may not be statistically different from controls (82-92% effect rate in the controls). The study designs (i.e. single replicates) were not sufficient to allow for statistical tests. Differences in the teratogenic effect concentration, as well as LC50s, reported for *X. laevis* in these studies is likely reflective of the differences in exposure regime. Bernardini et al. (1996) used a static renewal system with daily test solution renewal, whereas Birge et al. (1980) and Black et al. (1982) used a flow-through system with a retention time of 2.5 hours. Due to the relatively short half-life of phenol in freshwater (~1 day), exposure concentrations in the Bernardini et al. (1996) study likely decreased substantially between renewals, resulting in exposure to lower than expected concentrations and potentially inflated effect concentrations. Both exposure scenarios may be ecologically relevant for amphibians. The data from studies relevant to TRV derivation are listed in Table 3 and displayed graphically in Figure 2.

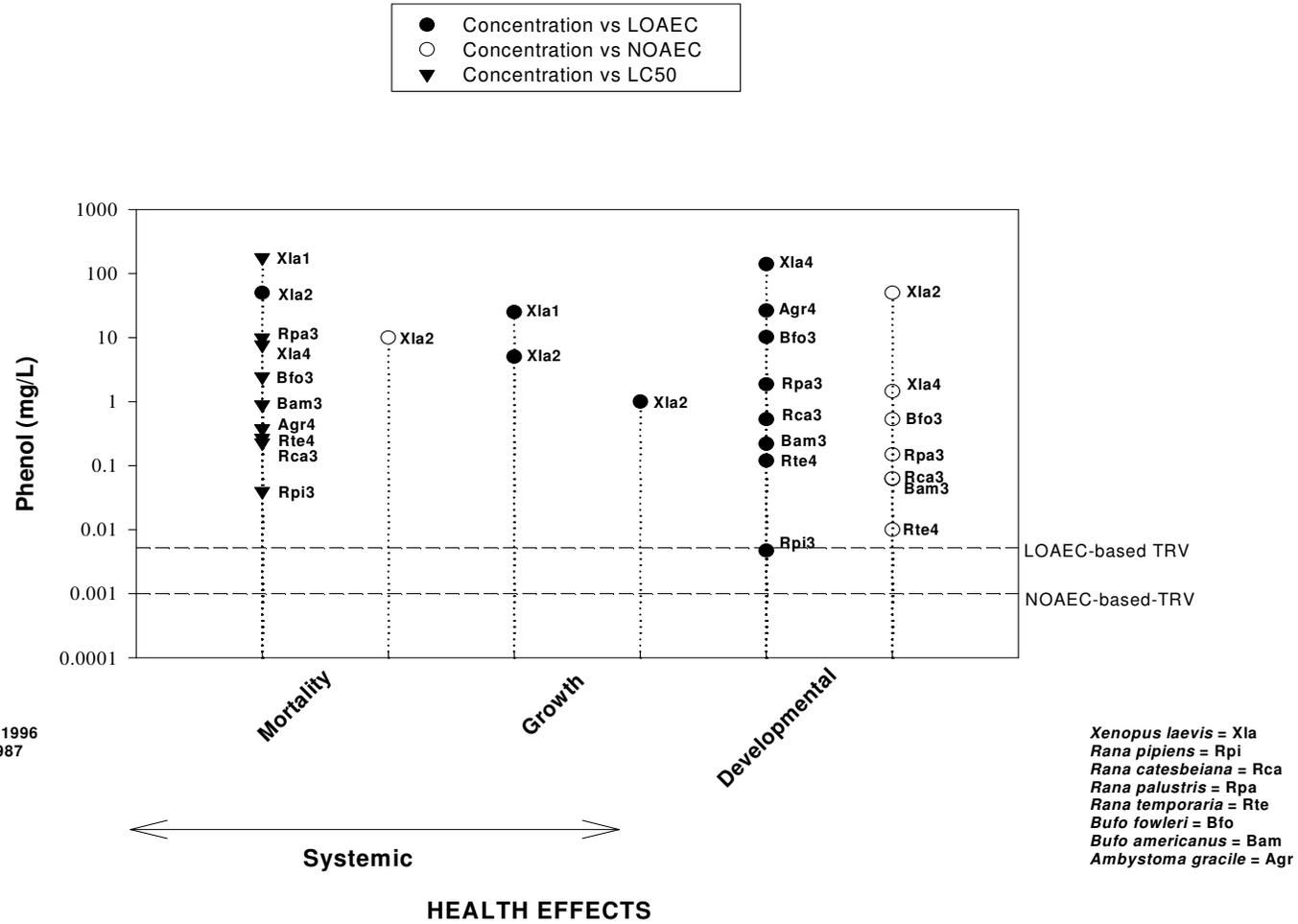
Table 3. Summary of Relevant Amphibian Data for TRV Derivation

Study	Test Organism	Test Duration	LC50 (mg/L)	Test Results		
				NOAEC (mg/L)	LOAEC (mg/L)	Effects Observed at the LOAEL
Bernardini et al. 1996	<i>Xenopus</i>	Hours 120 hrs p.f.	178	-	25	Reduced growth of larvae
Dumpert et al. 1987	<i>Xenopus laevis</i>	>5 wk	-	1	5	Reduced growth of larvae
	<i>Rana pipiens</i>	96 hrs p.f.	0.04	-	0.0047	Teratogenesis
	<i>Rana catesbeiana</i>	96 hrs p.f.	0.23	0.062	0.53	Teratogenesis
Birge et al. 1980*	<i>Rana palustris</i>	96 hrs p.f.	9.87	0.15	1.86	Teratogenesis
	<i>Bufo fowleri</i>	96 hrs p.f.	2.45	0.53	10.2	Teratogenesis
	<i>Bufo americanus</i>	96 hrs p.f.	>0.89	0.063	0.22	Teratogenesis
Black et. Al. 1982	<i>Ambystoma gracile</i>	96 hrs p.f.	0.38	-	>26.4	Teratogenesis
	<i>Rana temporaria</i>	96 hrs p.f.	0.27	0.010	0.12	Teratogenesis
	<i>Xenopus laevis</i>	96 hrs p.f.	7.68	1.45	140.0	Teratogenesis

p.f. = post fertilization

Figure 2

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1 = Bernardini et al. 1996
 2 = Dumpert et al. 1987
 3 = Birge et al. 1980
 4 = Black et al. 1982

2.6 Summary of Reptilian Toxicology

No data are available on the toxicity of phenol in reptiles.

3. RECOMMENDED TOXICITY REFERENCE VALUES

3.1 Toxicity Reference Values for Mammals

3.1.1 TRVs for Ingestion Exposures for the Class Mammalia

Studies relevant to the development of oral ingestion TRVs for mammals were discussed in Section 2.3.1.6 and presented in Table 2 and Figure 1. Subacute, subchronic, chronic, and reproductive/developmental studies were available; however, only the rat and mouse are represented. Based on the NCI (1980) study using similar methods and dosing regimes, rats and mice appear to be equally sensitive to phenol, with LOAELs for body weight depression of 585 and 660 mg/kg-day, respectively. This is supported by the acute data in which LD₅₀s for rats were 317 and 400 mg/kg compared to 270 mg/kg for mice (Lewis et al. 1992, Berman et al. 1995). Additionally, the reproductive/developmental studies conducted by Research Triangle Institute indicate that developing rats and mice have similar sensitivity to phenol, with LOAELs for fetal weight of 120 and 280 mg/kg-day, respectively (RTI 1983 a and b). The LD₅₀ data suggest that cats may be particularly sensitive to phenol (LD₅₀ = 80 mg/kg); however, no long term studies using cats were available.

Although organ necrosis (kidney, spleen, and thymus) was the most sensitive endpoint reported (Table 2, Figure 1), these effects were only observed in the two subacute studies (Berman et al. 1995, Moser et al. 1995) which administered the compound via gavage. As noted in Section 2.3.1.6, toxic responses to phenol may be mitigated by administration route. That is, dosing by gavage may have overwhelmed the processes that metabolize and excrete phenol from the body, resulting in more adverse effects. In contrast, studies in which phenol was administered in the drinking water had fewer toxic responses, particularly to body organs.

Similar reproductive and developmental effects were observed in studies dosing via gavage and drinking water, however, the dose at which the effects were observed were lower in studies that used gavage. For example, Narotsky and Kavlock (1995) used gavage methods and observed fewer live pups at a dose of 53.3 mg/kg-day, whereas Ryan et al. (2001) administered the doses in drinking water and observed reduced survival in pups at 319 mg/kg-day. The LOAEL (53.3 mg/kg-day) reported by Narotsky and Kavlock (1995) was the lowest reported in the five studies with reproductive (P&G 1993, P&G 1997) and developmental (RTI 1983a and b, P&G 1997, Narotsky and Kavlock 1995, and Ryan et al. 2001) effects. This LOAEL (53.3 mg/kg-day) is lower than developmental NOAELs identified in the

other studies (60 to 120 mg/kg-day), which may be a function of differing experimental designs (i.e., single dose gavage vs. divided dose gavage or drinking water) or dosing duration (i.e., during gestation days 6-19 vs. gestation days 6-15). Due to the differences in toxicity of phenol administered by gavage versus drinking water, the P&G (1997) study was identified as being an appropriate developmental study for TRV derivation (see Section 2.3.1.6). This study utilized a divided-dose gavage regime to decrease the impact of the bolus effect while avoiding the problems associated with drinking water studies (e.g. precise dosing, taste aversion). The LOAEL for developmental effects in the P&G (1997) study was 360 mg/kg-day and the NOAEL was 120 mg/kg-day.

Reduced fetal or pup survival may adversely impact the ecology or health of the population, and reduced fetal body weights (an indicator of effects on growth and/or energy efficiency) may have the potential to adversely affect future fitness. Therefore, these endpoints are considered to be ecologically relevant. The reproductive and developmental studies are considered chronic in nature because they evaluate the effects of phenol during a critical life stage (i.e., during gestation) (USACHPPM 2000). The rat and mouse studies by NCI (1980) are also considered chronic (duration of 103 weeks); however, the affected endpoint (depressed body weight in adults) appears to be less sensitive than developmental endpoints (Table 2, Figure 1) and may not be as ecologically relevant.

Because the minimum data set requirements as outlined in Section 2.2 (USACHPPM 2000) were not met (i.e., data that are representative of at least three species and two taxonomic orders were lacking), the approximation approach as described in USACHPPM (2000) was used to develop oral ingestion TRVs for mammals. Using the approximation method, an UF of 10 was applied to the NOAEL and LOAEL values reported by P&G (1997) to account for potential interspecies differences, resulting in a NOAEL-based TRV of 12.0 mg/kg-day and a LOAEL-based TRV of 36.0 mg/kg-day. The class-specific NOAEL and LOAEL are presented in Table 4. Developmental effects were generally consistent across studies; however, data were available for only two species and the data for mice were limited to a single study. Additionally, there is some uncertainty regarding the effect of dose administration methods on responses. Therefore, a low to medium degree of confidence was assigned to the TRVs.

Table 4. Selected Ingestion TRVs for the Class Mammalia

TRV	Dose	Confidence
NOAEL-based	12.0 mg/kg/d	Low-Medium
LOAEL-based	36.0 mg/kg/d	Low-Medium

3.1.2 TRVs for Ingestion Exposures for Mammalian Foraging Guilds

TRVs specific to particular guild associations (e.g., small herbivorous mammals) have not yet been derived. However, the class-specific TRVs shown in Table 3 may be considered to apply to herbivorous small mammals because rats are members of this guild. As with the class-specific TRVs, confidence in these TRVs, is low to medium because only one species is represented and there is some uncertainty related to the effect of dose administration methods on observed responses.

3.1.3 TRVs for Inhalation Exposures for the Class Mammalia

Although one 10-day inhalation study was available (CMA 1998b), the only effects observed were sporadic red tears (an indication of stress in rats) and nasal discharge. Because these data were inconsistent across dose levels, and the relevance to the health and ecology of the whole organism is uncertain, this study was considered insufficient for TRV development.

3.1.4 TRVs for Dermal Exposures for the Class Mammalia

Only one dermal exposure study for mammals (Patrick et al. 1985) was available. A clear dose-response relationship for ear swelling was observed; however, no systemic endpoints were evaluated. Ear swelling is a localized response that shows improvement with time and has uncertain, if any, ecological relevance. Therefore, these data were not considered suitable for TRV development.

3.2 Toxicity Reference Values for Birds

No data to derive values for birds were found.

3.3 Toxicity Reference Values for Amphibians

As indicated in Section 2.5.3, all four amphibian studies are relevant for TRV derivation. Growth was the most sensitive endpoint in the studies using *X. laevis* and may be a suitable endpoint for TRV development. Growth in larval amphibians is an ecologically relevant endpoint. Reduced larval growth can adversely affect adult fitness through impacts on developmental rate, timing of metamorphosis, survival to and size at maturity, and recruitment to the breeding population. An unbounded LOAEC for growth depression of 25 mg/L is indicated by the results presented in Bernardini et al. (1996), while a NOAEC of 1 mg/L and LOEC of 5 mg/L were identified for growth depression in the study by Dumpert (1987). Because the Dumpert (1987) study extends throughout the embryonic period into the larval period, and has a clearly identifiable NOAEC and LOAEC, it is more applicable to TRV development than the study by Bernardini et al. (1996). The studies by Birge et al. (1980) and Black et al. (1982), however, indicate that *X. laevis* is among the most tolerant of the eight species tested. TRVs based even on the most sensitive endpoint in this species may not be protective of other species. The most sensitive species in the Birge et al. (1980) and Black et al. (1982) studies was *R. pipiens*, with an LC50 of 0.04 mg/L. If LC1 values are considered thresholds for toxic effects (similar to LED10; see USACHPPM

2000), corresponding mean ED10s could be considered equivalent to the LC10 value or the level at which the authors suggest may cause appreciable reproductive impairment (Birge et al. 1980; *R. pipiens* – 0.0011, 0.0052; *R. catesbeiana* – 0.001, 0.0085 mg phenol/L for LC1 and LC10 values, respectively).

The relevant amphibian studies meet the minimum data set requirements of the Standard Practice, Section 2.2 (USACHPPM 2000); therefore, the NOAEC/LOAEC approach for TRV development is appropriate. The LOAEC for the most sensitive species and endpoint was the 0.0047 mg/L LOAEC for teratogenic effects in *R. pipiens* (Birge et al. 1980). However, given the lack of replicates involved, the dose at which a 1% response could be detected (LC1) that integrates the threshold for teratogenic effects was used for the NOAEC-based value and the 10% response level was used for the LOAEC-based value (LC10). Table 5 presents the selected TRVs. A low to medium level of confidence has been given to these TRVs because although four studies which examine a broad range of species are available, the endpoints examined are limited, and in some cases statistical comparisons were not possible. Additionally, the low level at which effects were reported for *R. pipiens* are not corroborated with other data. Moreover, the studies included only a small portion of the larval period and do not extend through metamorphosis, a period of heightened sensitivity

Table 5. Selected Aquatic TRVs for Amphibians

TRV	Dose	Confidence
NOAEC-based	0.001 mg/L	Low-Medium
LOAEC-based	0.005 mg/L	Low-Medium

3.4 Toxicity Reference Values for Reptiles

No data to derive values for reptiles were found.

4. IMPORTANT RESEARCH NEEDS

Although several studies were available and are consistent among reproductive and developmental effects, mammalian TRVs derived for phenol have a low to medium confidence level. This is due to uncertainty related to the dose administration methods (i.e., gavage vs. drinking water). Therefore, additional studies that would clarify the impact of differences between these methods on the magnitude and frequency of endpoint responses are needed. Evaluation of additional species and taxonomic orders is needed. In addition, toxicity studies that examine demographic factors such as birth, death, and recruitment would have much greater ecological significance. The additional data would increase

confidence in the mammalian TRVs and enable development of TRVs for specific foraging guilds. Inhalation and dermal studies on mammals were very limited for phenol and did not allow for TRV derivation. Amphibian toxicity data were available for eight species, however, sensitive endpoints were not included and statistical power was low, resulting in low to medium confidence in the TRVs. No data were available for birds and reptiles. Before reliable avian, amphibian, and reptilian TRVs can be derived, phenol toxicity in these wildlife classes needs to be adequately characterized. Appropriate acute, subacute, subchronic and especially chronic phenol toxicity data derived through biologically-relevant exposure routes are needed. Research studies should include experimental models of species genetically, biologically, and behaviorally similar to wildlife exhibiting the greatest propensity for toxicant exposure.

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APPENDIX A

LITERATURE REVIEW

The following files were searched in DIALOG:

File 155 MEDLINE; File 156, TOXLINE, File 5 BIOSIS, File 35 Dissertation Abstracts, File 76 Life Sciences Collection, and File 185 Zoological Record.

The search strategy for **Amphibians & Reptiles**:

- ◆ The expression phenol, its CAS number, and the synonym carbolic acid.
- ◆ AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)
- ◆ RD (reduce duplicates)
- ◆ AND (reproduc? or dietary or systemic or development or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))

The search strategy for **Birds**:

- ◆ The expression phenol, its CAS number, and the synonym carbolic acid.
- ◆ And chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus(domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl)
- ◆ AND (reproduc? or dietary or systemic or development or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD (reduce duplicates)

The search strategy for **Wild Mammals**:

- ◆ The expression phenol, its CAS number and the synonym carbolic acid.
- ◆ AND (didelphidae or opossum? or soricidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae)or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or mycocastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD (reduce duplicates)

The search strategy for **Laboratory Mammals**:

- ◆ The expression phenol, its CAS number, and the synonym carbolic acid.
- ◆ AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer? or phenol red)
- ◆ NOT (chromatog? or solvent()mixture or HPLC or TLC)
- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women or men or occupational)
- ◆ RD (reduce duplicates)

The strategy outlined above yielded 15 hits for phenol with reptiles/amphibians, 166 articles with birds, 67 with wild mammals and 1,557 articles with laboratory mammals.

All abstracts from the DIALOG search were reviewed and encoded in ProCite. When the search retrieved an appreciable number of hits, *keywords in context* were reviewed to minimize costs before any abstracts were downloaded (Tier 1). However, when only a limited number of studies were identified by the search, the abstracts were downloaded at the time of the search (Tier 2).

As noted above and in Section 2.1, 1,805 hits on phenol were obtained in the initial search, of which 25 were selected (Tier 2) as being relevant to this survey of the impacts of phenol in wildlife.