Phenol; CASRN 108-95-2

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Phenol

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/2002
Inhalation RfC (I.B.)	qualitative discussion	09/30/2002
Carcinogenicity Assessment (II.)	yes	09/30/2002

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Phenol
CASRN — 108-95-2
Last Revised — 09/30/2002

The oral RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

This RfD replaces the previous RfD of 0.6 mg/kg-day entered on IRIS 6/1/89, which was based on a developmental toxicity study in rats (NTP, 1983a), with a NOAEL of 60 mg/kg-day. New studies published since the previous RfD include a new two-generation study (Ryan et al., 2001; available in unpublished form as IIT Research Institute, 1999), a new developmental toxicity study using divided gavage dosing (Argus Research Laboratories, 1997), and a 13-week drinking water neurotoxicity study (ClinTrials BioResearch, 1998). Although these new studies result in a stronger database, another new study (Hsieh et al., 1992) raises questions as to whether the critical effect has been appropriately identified, or whether immunotoxicity is the critical effect. A database uncertainty factor of 3 was added to account for this uncertainty. The new developmental toxicity study (Argus Research Laboratories, 1997) is the new principal study, with a NOAEL of 60 mg/kg-day and a BMDL of 93 mg/kg-day. The RfD is based on the BMDL because, unlike the NOAEL, the BMDL is not limited to one of the experimental doses. The NTP (1983a) study was not considered appropriate as a co-principal study due to the equivocal nature of the identified LOAEL and because the effect observed was not supported in the more recent study in rats using a more environmentally relevant dosing protocol (divided gavage dosing rather than a single bolus dose).

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased maternal weight gain **Rat developmental study** **Argus Research Laboratories, 1997**	BMDL: 93 mg/kg-day BMD: 157 mg/kg-day	300	1	3E-1 mg/kg-day

*Conversion Factors and Assumptions — This RfD is applied to ingested phenol only and is in addition to phenol formed endogenously in the gut by bacterial metabolism of protein. BMDL = 95% lower confidence limit on the maximum likelihood estimate of the dose

corresponding to a one standard deviation change in the mean
BMD = Maximum likelihood estimate of the dose corresponding to a one standard deviation change in the mean

I.A.2. Principal and Supporting Studies (Oral RfD)

Argus Research Laboratories. (1997) Oral (gavage) developmental toxicity study of phenol in rats. Horsham, PA. Protocol number: 916-011.

In an unpublished developmental toxicity study conducted according to GLP guidelines (Argus Research Laboratories, 1997), pregnant Crl:CDRBR VAF/Plus Sprague-Dawley rats (25/group) received phenol by oral gavage on gestation days (GDs) 6 through 15. Dosing was three times daily with 0, 20, 40, or 120 mg phenol/kg/dosage, using a dosing volume of 10 mL/kg. The corresponding daily doses were 0, 60, 120, and 360 mg/kg-day. The exposed dams were observed twice a day for viability and daily for clinical signs, abortions, and premature deliveries. In addition, the maternal body weights were recorded every day, and food consumption was also recorded periodically. The rats were sacrificed on GD 20 and gross necropsy was performed and the number of corpora lutea in each ovary was recorded. The uterus of each rat was excised and examined for number and distribution of implantations, live and dead fetuses, and early and late resorptions. Each fetus was weighed, sexed, and examined for gross external alterations. One half of the fetuses were examined for soft tissue alterations and the rest were examined for skeletal alterations.

One high-dose dam died on GD 11. The study authors attributed this death to phenol treatment, because it occurred only at the high dose, although there were no adverse clinical observations and no abnormal necropsy findings in this animal. Other high-dose animals exhibited excess salivation and tachypnea (rapid breathing). There were no other treatment-related clinical observations and no treatment-related necropsy findings. Dose-dependent decreases in body weight of the exposed animals as compared with the controls were observed. Statistically significant decreases in both maternal body weight (8%) and body weight gain (38% for GDs 6-16) were observed at the high dose; although a statistically significant decrease in body weight gain (11%) was observed at the mid dose, the decrease at the mid dose (relative to controls) in absolute maternal weight at the end of dosing (3%) was not statistically significant. Dose-dependent decreases in food consumption were also observed during the dosing period.

Fetal body weights in the high-dose group were significantly lower than those of controls-by 5-7%. The high-dose group had a statistically significant decrease in ossification sites on the hindlimb metatarsals, but it is unlikely that this small change is biologically significant. The incidence of litters with incompletely ossified or unossified sternal centra was 0/23, 0/25, 3/23,

and 3/24; this increase was not statistically significant. There were small, dose-related increases in the number of litters with fetuses with "any alteration" and with "any variation" at 120 mg/kg/day and higher. However, neither of these changes was statistically significant, and the response was not clearly dose-related. In addition, an increase in total variations is of questionable significance in the absence of any increase in individual variations. No other treatment-related effects were observed in uterine contents, malformations, or variations.

The maternal NOAEL was 60 mg/kg-day, based on small decreases in maternal body weight gain at 120 mg/kg-day, and the developmental NOAEL was 120 mg/kg-day, based on decreased fetal body weight and delayed ossification at 360 mg/kg-day. Benchmark dose (BMD) modeling was also conducted for the decreased maternal weight. Defining the benchmark response as a one-standard-deviation decrease in maternal body weight gain, the 95% lower confidence limit on the BMD (i.e., the BMDL) was 93 mg/kg-day. This BMDL was calculated using the polynomial model, which gave slightly better fit than the power and Hill models, using BMDS Version 1.3.

No human studies that addressed the developmental toxicity of phenol were identified. In a well-designed developmental toxicity study (NTP, 1983a), timed-mated CD rats were administered phenol by gavage at 0, 30, 60, or 120 mg/kg-day in 5 mL/kg distilled water on GD 6 to 15 and sacrificed on GD 20. Females were weighed on GDs 0, 6 through 15 (prior to daily dosing), and 20 (immediately following sacrifice), and they were also observed during treatment for clinical signs of toxicity. A total of 20-22 females per group were confirmed to be pregnant at sacrifice on GD 20. The dams were evaluated at sacrifice for body weight, liver weight, gravid uterine weight, and status of uterine implantation sites. Live fetuses were weighed, sexed, and examined for gross morphological abnormalities and malformations in the viscera and skeleton. Results of this study did not show any dose-related signs of maternal toxicity or any clinical symptoms of toxicity related to phenol treatment. The number of implantation sites was slightly higher in the dosed groups, but this change could not be treatment-related, because implantations in this strain take place prior to GD 6 (prior to dosing).

Significant increases in the litters with nonlive (dead plus resorbed) were observed in the low- and mid-dose groups but not in the high-dose group, but this effect was not considered treatment related, because this response was not dose dependent, and the response in the high-dose group was comparable with that of the control. In addition, there was no effect on the more appropriate measure of nonlive per litter. There was also no effect on live fetuses, sex ratio, malformations, or variations. However, a clear dose-related downward trend in fetal body weight was observed, although the changes at the two lower doses were small and the effect was statistically significant only at the high dose. Fetal body weights in the high-dose group were 93% of the average in the control group; fetal body weights were not reported

separately for males and females. Historical control data from the supplier report the average fetal body weight in this strain as being well below the weight in the high-dose group (Charles River Laboratories, 1988). (Concurrent control weight was 4.14 g, high-dose weight was 3.84 g, and historical control weight was 3.39 g.)

The litter size in the high-dose group was also somewhat higher (but not statistically significant) than in the controls, possibly contributing to the smaller fetal weight at the high dose. The total pup burden (total fetal weight) and the gravid uterine weight were highest in the low-dose group, and then in the high-dose group; both of these values were higher than those in the control group. In addition, the treatment-period maternal weight gain was very similar in the control and high-dose groups (but higher in the low-dose group), but the absolute maternal weight gain (i.e., adjusted for the gravid uterine weight) was much lower in the high-dose group than in the controls. The results from the low-dose group suggest that the dams could have borne a somewhat higher burden of the total in utero package. However, the results also suggest that the dams were near the limit of what they could carry, based on the lower absolute weight gain but unaffected treatment-period weight gain in the high-dose group. No dose-related signs of maternal toxicity and no clinical symptoms of toxicity related to phenol treatment were observed in this study. On the basis of these considerations and the potential for the decreased fetal weight to reflect primarily the larger litter size, the decreased fetal weight in this study could be considered an equivocal LOAEL. Thus, on the basis of decreased fetal body weight, the mid dose in this study of 60 mg/kg-day was a NOAEL for developmental toxicity and the high dose of 120 mg/kg-day was an equivocal LOAEL. The high dose (120 mg/kg-day) was a maternal NOAEL. BMD modeling could not be done for the decreased fetal weight, because NTP did not have information on the fetal weight by sex, either in the report or in its archives. Data on fetal weight by sex is needed for meaningful modeling, because the average weight of males and females is different and the number of males per group varied.

Although the same NOAEL of 60 mg/kg-day was identified for this study as in the principal study (Argus Research Laboratories, 1997), this study was not considered adequate to be a co-principal study in light of the equivocal nature of the LOAEL and the absence of an effect on fetal weight in another gavage developmental study in rats (Argus Research Laboratories, 1997) at a maternally toxic dose in that study of 120 mg/kg-day.

In a standard mouse developmental toxicity study (NTP, 1983b), phenol was administered by gavage in water at 0, 70, 140, or 280 mg/kg-day on GDs 6 to 15 to groups of 31-36 plug-positive female CD-1 mice. The pregnancy rate in the controls was only 83%; the pregnancy rate in dosed animals ranged from approximately 83% in the low- and mid-dose groups to 71% at the high dose. In addition, 4/36 high-dose mice died; no deaths occurred in any other groups. The average maternal body weight gain during treatment was statistically significantly

reduced at the high dose, as was the maternal body weight at terminal sacrifice on GD 17 (by 10%, compared with the control group). In addition, tremors were observed at the high dose throughout the dosing period. As in the rat study, a highly statistically significant decrease in fetal body weight per litter (18%) was observed at the high dose. An increased incidence of cleft palate was also reported at the highest dose level, although the incidence was not significantly different from that of the other groups, and there was no statistically significant increase in the incidence of litters with malformations. There was no other evidence of altered prenatal viability or structural development.

Thus, the high dose of 280 mg/kg-day was a maternal frank effect level based on the observed deaths; tremors and decreased body weight also occurred at this dose. The high dose was also a developmental LOAEL based on decreased fetal body weight (accompanied by a possible increase in the incidence of cleft palate) in the fetuses, an effect that was likely secondary to the severe toxicity in the dams. The study NOAEL for maternal and developmental toxicity was 140 mg/kg-day.

Hsieh et al. (1992) investigated the effects of phenol exposure on hematological, immune, and neurochemical endpoints in a study of 6-week-old male CD-1 mice (5 per dose) administered actual concentrations of 0, 4.7, 19.5, or 95.2 ppm in drinking water for 28 days. On the basis of measured concentrations and water intake, the authors reported that the corresponding daily doses were 0, 1.8, 6.3, and 33.6 mg/kg-day. After 28 days, the mice were sacrificed by decapitation, gross pathological examinations were performed, and the liver, spleen, thymus, and kidney were weighed. Blood was taken at sacrifice for analysis. Splenocytes were prepared for analysis of antibody production response, mitogen-stimulated lymphocyte proliferation, mixed lymphocyte response, and cell-mediated cytolysis response.

During the 28-day exposure, no mortality and no overt clinical signs occurred in exposed mice. Phenol treatment had no effects on food or water consumption or on body weight gain. Exposed mice had no gross lesions in the liver, kidney, spleen, thymus, lung, heart, and brain, and no effect on organ weights for the liver, kidney, spleen, and thymus was seen. A dose-related decrease in erythrocyte counts was statistically significant at all doses. The hematocrit was decreased only at the high dose. A decreased erythrocyte count in the absence of an effect on hematocrit may have been due to macrocytosis (enlarged erythrocytes), but insufficient data were provided to evaluate this possibility. The erythrocyte counts in all dosed groups were markedly lower than the historical control values provided by the animal distributor (Charles River Laboratories, 1986), although the hematocrit concentration in all groups was above the historical control mean. There was no effect on total or differential leukocyte counts.

A decreased antibody response to sheep red blood cells was observed, as indicated by both the plaque-forming cell (PFC) assay (expressed as PFC/million spleen cells and PFC/spleen) and the antibody titer using an enzyme-linked immunosorbent assay (ELISA). Two of these measures were statistically significantly decreased at the mid dose, and PFC/spleen was significantly decreased only at the high dose. These decreases reached 40% (a value often used by immunotoxicologists as a rule of thumb for clinically relevant decreases) at the high dose. Decreases in the absolute splenocyte lymphoproliferative responses to mitogens and the mixed lymphocyte response (the proliferative ability of splenic lymphocytes in response to alloantigens) were also observed at the high dose; there was no effect on the cytolytic response to tumor cells at any dose.

Although these assays were conducted according to the methods of the day, the latter two do not conform to modern protocols, and there is little biological significance to the results of the mitogen response assay. Identification of a NOAEL in this study is somewhat problematic, because immunotoxicity risk assessment guidelines have not been developed. The determination of what degree of decrease is adverse is also problematic, because the clinical relevance of a decrement in immune function will depend on the magnitude and type of immune challenge, with a sufficiently large challenge resulting in illness even for unimpaired individuals. In a report on the use of immunotoxicity data for risk assessment, Selgrade (1999) recommended that any statistically significant and consistent change be considered a risk for the purposes of hazard identification, but the degree of change considered adverse for the purposes of dose-response assessment was not addressed.

On the basis of the magnitude of the decreases in antibody response observed in three related assays, supported by decreased hematocrit and red blood cells, the high dose (33.6 mg/kg-day) can be considered the study LOAEL, and the mid dose (6.2 mg/kg-day) can be considered the study NOAEL. There is, however, considerable uncertainty regarding the reliability of these values due to issues of study interpretation and because the study used only 5 animals per group as compared with the recommended 8 per group (U.S. EPA, 1998).

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 300

A factor of 10 is used to protect sensitive human subpopulations (intraspecies variability). The data on the within-human variability in the toxicokinetics and toxicodynamics of ingested phenol are insufficient to adjust the default uncertainty factor for intraspecies variability. In a sample of liver fractions from 10 people, Seaton et al. (1995) found that the kinetics of phenol sulfation and hydroquinone conjugation varied by up to approximately threefold. Much larger variability is observed in CYP2E1 (the cytochrome P450 enzyme that oxidizes phenol to

potentially toxic metabolites), particularly between neonates and adults (Vieira et al., 1996). These data on inter-individual variability in enzymatic metabolism are not adequate to move from the default UF_H of 10 because they do not reflect potential variability in portal-of-entry metabolism of phenol or uncertainty regarding the identity of the toxic moiety.

A factor of 10 is used to extrapolate from animals to humans (UF_A). The absorption, distribution, and metabolism of ingested phenol in rats and humans appear to be generally qualitatively similar, although the data are insufficient for a quantitative comparison. Comparison of laboratory animal and human phenol toxicokinetics is also limited by the lack of knowledge regarding the identity of the toxic moiety. It is not possible to quantitatively use the toxicokinetic data to adjust the default 10-fold factor for interspecies variability, and the default UFA of 10 is judged to be appropriate. It may be possible to reduce this default value of 10 following review and evaluation of data comparing the toxicokinetics of phenol and its metabolites in rats and humans (perhaps supplemented by a physiologically based pharmacokinetic model), if such data become available.

The BMDL was based on an effect of minimal severity (decreased maternal weight *gain*), and a higher BMDL and NOAEL were obtained for the related endpoint of effects on maternal weight. The BMDL is also within 50% of the NOAEL identified for the decreased maternal weight endpoint. Therefore, no uncertainty factor is required for extrapolation from a NOAEL to a LOAEL. No uncertainty factor for extrapolation across duration is needed, because this developmental study is supported by chronic bioassays in two species in which toxicity was observed only at higher doses. An additional uncertainty factor for sensitive populations such as infants and children is not needed for phenol because sufficient studies of reproductive and developmental toxicity have been performed, with the observation of decreased fetal body weight (in the absence of other indications of fetal toxicity or teratogenicity) only at doses equal to or higher than the LOAEL for the endpoint used for developing the oral RfD.

The toxicity database for phenol by the oral route can be considered complete. It includes 2-year drinking water studies conducted in rats and mice (NCI, 1980), a two-generation drinking water study conducted in rats (Ryan et al., 2001; available in unpublished form as IIT Research Institute, 1999), and gavage developmental toxicity studies in rats (Argus Research Laboratories, 1997; NTP, 1983a; Narotsky and Kavlock, 1995) and mice (NTP, 1983b). However, the range of endpoints evaluated in the chronic toxicity studies was limited and did not include hematological or serum biochemistry evaluations. Immunological and hematological effects in mice were observed at low doses by Hsieh et al. (1992) in a 28-day drinking water study. These endpoints were evaluated, and no significant hematological or serum biochemistry effects were observed at doses of up to >300 mg/kg-day in the two-generation rat study (IIT Research Institute, 1999; Ryan et al., 2001). The difference in these results suggest species differences between mice and rats, but confirmation of the

immunological and hematological effects in an assay done according to modern test methods would be useful.

The results of a study of the effects of phenol on bone marrow cellularity in mice dosed intraperitoneally at up to 300 mg/kg-day (Eastmond et al., 1987) and an in vitro study with mouse bone marrow cells (Corti and Snyder, 1998) also do not indicate that mouse blood cells are highly susceptible to effects of phenol. However, these studies did not evaluate the same parameter measured by Hsieh et al. (1992), and significant interspecies differences in immunotoxicity are not unusual. It is of interest that the endpoints affected in the Hsieh et al. (1992) study (two measures of effects on antibody production, the PFC and ELISA) are the immune endpoints most highly predictive of effects on host resistance (Luster et al., 1992, 1993). Therefore, to account for the uncertainties regarding the immunological and hematological effects in mice, a database uncertainty factor of 3 is used. The database factor could be reconsidered with results of an immunotoxicity study in mice that is compliant with EPA immunotoxicity test guidelines (U.S. EPA, 1998).

An additional degree of public health protection may also be provided by the use of a gavage study rather than the more environmentally relevant route of drinking water. This is because gavage administration results in a higher peak blood level-presumably even using a divided dosing protocol-than does ingestion of the same daily dose in drinking water, and at least some effects of phenol are related to peak blood levels. Thus, a composite uncertainty factor of 300 was used, based on default factors of 10 each for interspecies extrapolation and intraspecies variability and a database factor of 3 to account for uncertainties regarding the immunotoxic potential of phenol.

MF = 1

No MF is applied because the existing uncertainties have been addressed with the standard uncertainty factors.

I.A.4. Additional Studies/Comments (Oral RfD)

Phenol is produced endogenously by bacteria in the gut at a rate estimated at 1 to 10 mg/day, corresponding to approximately 0.014-0.14 mg/kg-day (Bone et al., 1976; Lawrie and Renwick, 1987; Renwick et al., 1988), based on total phenol (free plus conjugated) levels in urine. Because endogenous phenol is formed in the gut, the toxicokinetics would be similar to that of ingested phenol. Both humans and laboratory animals efficiently conjugate and excrete phenol at low doses, resulting in only a small degree of systemic exposure to free phenol (or any of its oxidative metabolites) at these low levels. The phenol conjugation capacity of the liver is an important determinant of the ingested dose that would result in toxicity, but there is

no information on the degree of phenol conjugation by humans at doses in the range of the RfD.

Human variability exists in both the levels of endogenous phenol production and in the conjugative capacity of the liver. In the absence of more detailed information, it is reasonable to assume that humans have adapted by having adequate conjugation capacity for the range of endogenous phenol production. Therefore, the default total uncertainty factor of 10 for human variability in toxicokinetics and toxicodynamics described above is considered adequate. Determining whether oxidative metabolites are formed in people with high endogenous levels of phenol formation would enhance the confidence in the determination of the intraspecies uncertainty factor. The RfD is at least twice the endogenous rate of phenol formation in humans, meaning that endogenous production is approximately 5-50% of the RfD.

An extensive database for the effects of orally administered phenol in laboratory animals is available. Two-year drinking water studies have been conducted in groups of F344 rats and B6C3F1 mice (50 animals/sex/dose/species). The rats were exposed to 0, 2500, or 5000 ppm, corresponding to 0, 260, and 585 mg/kg-day for male rats and 0, 280, and 630 mg/kg-day for female rats. The mice were exposed to 0, 2500, or 5000 ppm in drinking water, corresponding to estimated doses of 0, 450, and 660 mg/kg-day for both sexes. These studies identified NOAELs of 260 mg/kg-day and 480 mg/kg-day for rats and mice, respectively, based on decreased body weight gain and decreased water consumption (NCI, 1980). A complete histopathology evaluation was included, but no increases in noncancer lesions were found. Hematology and serum biochemical evaluations were not included in those chronic studies, but they were included in a recent two-generation drinking water study conducted in Sprague-Dawley rats (Ryan et al., 2001; available in unpublished form as IIT Research Institute, 1999), as described below.

Toxicity in gavage studies with phenol is typically much higher than that in drinking water studies. NOAELs for systemic effects were 5- to10-fold lower in gavage studies (Berman et al., 1995; Moser et al., 1995; Dow Chemical Co., 1945) than those seen in drinking water studies. Many (but not all) of the effects in drinking water studies appeared to be due to decreased water consumption resulting from poor palatability. Effects observed in gavage studies included tremor and liver and kidney histopathology; effects in drinking water studies were less severe. As described in greater detail in the Toxicological Review, this difference between gavage and drinking water exposure is consistent with toxicokinetic data that suggest that toxicity is correlated with peak blood concentrations rather than being a measure of total dose, such as the area under the phenol blood concentration curve (AUC). Due to this marked difference in toxicity between gavage and drinking water, the RfD was not based on gavage studies of systemic effects, even though those effects occurred at lower doses.

Although the principal study for the development of the RfD (Argus Research Laboratories, 1997) used gavage dosing, it is not clear whether this difference in toxicity also applies to the endpoint of decreased maternal weight gain. In addition, Argus Research Laboratories (1997) used a divided dosing protocol, a significant enhancement that made the gavage dosing more closely resemble an environmentally relevant route of exposure.

In an unpublished 13-week neurotoxicity study conducted according to good laboratory practice (GLP) guidelines (ClinTrials BioResearch Ltd., 1998), groups of 15 male and 15 female Sprague-Dawley rats received phenol via drinking water at concentrations of 0, 200, 1000, or 5000 ppm for 13 weeks followed by a 4-week recovery period. The study authors calculated that the average doses were 0, 18.1, 83.1, and 308.2 mg/kg-day for males and 0, 24.6, 107.0, and 359.8 mg/kg-day for females. During the exposure period, clinical signs and water intake were recorded daily and body weight and food consumption were recorded weekly. In addition, a functional observational battery and a motor activity test were conducted pre-study and once each during weeks 4, 8, 13, and 17. At the end of the exposure and at the end of the recovery period, five rats/sex in the control and 5000 ppm groups underwent neuropathological evaluations (including a thorough evaluation of the brain and several nerves). The rest of the rats were sacrificed at the end of the 4-week recovery and were subjected to gross necropsy.

The primary clinical sign was dehydration, which was associated with marked decreases in water consumption at the high dose and smaller decreases at the mid-dose. Decreases in water consumption were more pronounced in females than in males and were most evident during the first week of dosing. Water consumption was decreased to approximately 90% of the control level in mid-dose males and females, to approximately 60% of control levels in high-dose males, and to approximately 55% (40% during the first week) of control levels in high-dose females. Water consumption rebounded to levels higher than those of controls during the recovery period. The decreased water consumption was likely due to the poor palatability of phenol at high concentrations rather than being a manifestation of an overt toxicological effect. In addition, the high-dose group had decreased body weights as compared with the controls (8% for males and 12% for females) and decreased food intake (approximately 10% for males and 10-20% for females). The only toxicologically significant neurological effect was decreased motor activity in females. A statistically significant reduction in total group mean motor activity counts was observed at week 4 in the 5000 ppm group. The authors reported that the rate of linear change of motor activity with time was also significantly decreased at weeks 8 and 13 in the 1000 ppm and 5000 ppm groups. The authors attributed the decreased activity to dehydration, noting that the control group mean total activity increased by >20% at week 4 as compared with prestudy levels, whereas activity of the dehydrated females in the 5000 ppm group at week 4 was decreased by 17% and activity of the females in this group that were not dehydrated increased by 2%. However, a detailed analysis of the

individual animal data, as discussed in the Toxicological Review, did not support the hypothesis that all of the decreased motor activity could be attributed to dehydration; phenol at least contributed to the decreased motor activity. On the basis of decreased motor activity, the study NOAEL in females was 1000 ppm phenol (107 mg/kg-day) and the LOAEL was 5000 ppm (360 mg/kg-day). No LOAEL was identified in males; the high dose of 308 mg/kg-day was a NOAEL. A BMDL of 219 mg/kg-day was calculated for decreased motor activity in females in week 4 in this study

In a two-generation reproductive toxicity study following modern GLP guidelines (Ryan et al., 2001; full unpublished study available as IIT Research Institute, 1999), 30 Sprague-Dawley rats/sex/group were exposed to 0, 200, 1000, or 5000 ppm phenol in drinking water. The authors calculated that the average daily phenol intake during week 10 was 0, 14.7, 70.9, and 301.0 mg/kg-day for P1 males and 0, 20.0, 93.0, and 320.5 mg/kg-day for P1 females. For the F1 generation, the average phenol intake during week 10 was 0, 13.5, 69.8, and 319.1 mg/kg-day for males and 0, 20.9, 93.8, and 379.5 mg/kg-day for females. Most of the treatment-related changes in P1 rats were observed in the high-dose groups.

The only significant observed clinical sign was redness around the nose fur, which occurred in the high-dose males and females of the F1 generation before mating and in P1 dams during lactation. This redness likely reflected a nonspecific stress response. A significant decrease in water consumption was observed throughout the study in both P1 and F1 animals of both sexes, which was attributed to poor palatability. The low water consumption at the high dose was accompanied by decreased body weights as compared with the controls.

Decreased absolute organ weights and increased relative organ weights were observed for a number of organs at the high dose in both the P1 and F1 generations. Most of these changes likely reflected the lower body weight and overall dehydration in these groups. F1 females had a statistically significant, dose-related decrease in absolute uterine weights at all doses, but P1 females were not affected. The decreased uterine weight was not considered adverse because there was no evidence of a dose-response relationship for relative uterine weight, no effect on reproductive function, and no histopathological changes in the uterus and the individual animal data showed that the uterine weight was below the control range for only a few rats in each dose group. No other organ weight changes in either the P1 or the F1 generation were considered adverse. The histopathological examinations showed no treatment-related lesions in the kidneys, spleen, liver, thymus, or reproductive organs.

An immunotoxicity screen in this study found no significant effects on spleen weight, cellularity, or antibody-forming cells for any test group as compared with the control group. Complete hematological evaluations and serum biochemical evaluations were conducted on P1 males prior to sacrifice, and no biologically significant changes were observed. No effect

on fecundity or fertility in either generation was observed. In addition, there was no effect on other indicators of reproductive toxicity, including the frequency of estrus, testicular sperm count, sperm motility and sperm morphology.

The survival of the high-dose F1 pups was significantly decreased on prenatal day 4 (pre-culling), although there was no effect on overall F1 pup survival. In the F2 generation, high-dose pup survival was significantly decreased throughout the lactation period. This decreased survival of both generations of pups was likely secondary to the decreased maternal water intake and associated decreases in milk production. In the F1 generation, delayed vaginal patency and delayed preputial separation were observed at the high dose. The delay was considered secondary to decreased fetal growth at the high dose and as resulting from decreased water consumption due to poor palatability and associated decreased food consumption.

Thus, all of the adverse systemic and reproductive effects of phenol in the Ryan et al. (2001) study occurred at the high dose, and they appear to be secondary to decreased water consumption due to poor palatability rather than a toxic effect of phenol. On the basis of decreased parental and pup body weight (compared with the controls) and decreased pup survival, the high dose is a LOAEL. The study NOAEL is 70.9 mg/kg-day (based on the NOAEL corresponding to the lowest LOAEL in this study, in P1 males). BMD modeling was not conducted for this study because the observed effects appeared to be secondary to decreased water consumption and not reflective of phenol toxicity.

Phenol is readily absorbed by the inhalation, oral, and dermal routes (Piotrowski, 1971; Capel et al., 1972; Dow Chemical Co., 1994). Portal-of-entry metabolism for the inhalation and oral routes appears to be extensive and involves sulfate and glucuronide conjugation and, to a lesser extent, oxidation, primarily by CYP2E1. The primary oxidative metabolites include hydroquinone and catechol, which are also substrates for conjugation. Secondary products of hydroquinone or catechol metabolism, including benzoquinone and trihydroxybenzene, can also be formed (Capel et al., 1972; Dow Chemical Co., 1994; Kenyon et al., 1995). Once absorbed, phenol is widely distributed in the body, although the levels in the lung, liver, and kidney are often reported as being higher than those in other tissues (on a per-gram-tissue basis) (Tanaka et al., 1998; Liao and Oehme, 1981; Dow Chemical Co., 1994). Elimination from the body is rapid, primarily as sulfate and glucuronide conjugates in the urine, regardless of route of administration; phenol does not appear to accumulate significantly in the body (Ohtsuji and Ikeda, 1972; Deichmann and Witherup, 1944; Dow Chemical Co., 1994).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium to high
RfD — Medium to high

The principal study (Argus Research Laboratories, 1997) used an adequate number of animals and evaluated an appropriate array of endpoints for a developmental toxicity study. Although gavage dosing was used, the divided-dosing protocol provided a significant enhancement that made the gavage dosing more closely resemble an environmentally relevant route of exposure. Although the use of gavage dosing lowers the confidence in the study, the dosing frequency in the divided-dose gavage study may be fairly similar to that in drinking water studies, in which rodents typically consume water in a few larger doses, often in association with food consumption.

Confidence in the supporting database is medium to high. Although the oral toxicity database meets the minimal criteria for a high-confidence database (chronic studies in two species, developmental toxicity studies in two species, and a multigeneration reproduction study), the chronic studies did not evaluate a sufficient array of endpoints. In particular, the chronic mouse study (NCI, 1980) did not evaluate hematological and immunological effects, making interpretation of the results of the Hsieh et al. (1992) study difficult. Considering the above issues results in medium to high confidence in the RfD.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 2002

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in the finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — Summary Review of the Health Effects Associated with Phenol: Health Issue Assessment. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. U.S. EPA. 1986.

Agency Consensus Date — 08/28/2002

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for phenol conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (email address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Phenol
CASRN -108-95-2
Last Revised — 09/30/2002

The inhalation RfC is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for the respiratory system (portal of entry) and effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/m^3. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to *Interim Methods for Development of Inhalation Reference Doses* (EPA/600/8-88/066F August 1989) and, subsequently, according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Not applicable. No adequate inhalation exposure studies exist from which an inhalation RfC may be derived. A route-to-route extrapolation is not appropriate, because phenol can be a direct contact irritant, and so portal-of-entry effects are a potential concern.

The minimal database needed for the development of an RfC is a well-conducted subchronic inhalation study that adequately evaluates a comprehensive array of endpoints, including the respiratory tract, and establishes a NOAEL and a LOAEL (U.S. EPA, 1994). This criterion was not met for phenol. Neither of the two available subchronic studies (Deichmann et al., 1944; Sandage, 1961) are adequate for exposure-response assessment because neither included adequate documentation of the histopathology results and neither used modern methods for generating or monitoring exposure levels. These studies can, however, be used for hazard identification, and they identify the respiratory tract, liver, and kidney as targets of inhalation exposure to phenol.

The phenol database also includes a well-conducted, 2-week inhalation study with rats that used modern exposure methods, evaluated a wide array of endpoints, and included a thorough histopathology evaluation of the respiratory tract (Hoffman et al., 2001; the full unpublished study report is available as Huntingdon, 1998). The only treatment-related effect observed was a red nasal discharge in male rats, which was observed with a statistically significant duration-related, and concentration-related incidence in the mid- and high-concentration groups. However, because the red nasal discharge was likely due to a nonspecific response to stress, this response is not considered adverse. The 2-week study is of insufficient duration for the derivation of an RfC.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Not applicable.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

Not applicable.

I.B.4. Additional Studies/Comments (Inhalation RfC)

Not applicable.

I.B.5. Confidence in the Inhalation RfC

Not applicable.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2002

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for phenol conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Phenol
CASRN — 108-95-2
Last Revised — 09/30/2002

Section II provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per $\mu g/m^3$ air breathed. The third form in which risk is presented is as a concentration of the chemical in drinking water or in air that is associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in the risk assessment guidelines of 1986 (EPA/600/8-87/045) and in the IRIS background document. IRIS summaries developed since the publication of EPA's more recent *Proposed Guidelines for Carcinogen Risk Assessment* also use those guidelines where indicated (Federal Register 61[79]:17960-18011, April 23,

1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

This carcinogenicity assessment replaces the previous assessment of 11/01/90.

Under the current guidelines (U.S. EPA, 1987), phenol would be characterized as Group D, not classifiable as to human carcinogenicity. Under *Draft Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), 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.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Inadequate.

The epidemiology data on phenol are limited. Kauppinen et al. (1986) reported a significant increase in respiratory cancer in phenol-exposed workers, but this observation appears to be due to confounding exposures, as there was no dose-response and the effect decreased after accounting for latency. No effect on cancer mortality was observed in workers exposed to phenol in the rubber industry (Wilcosky et al., 1984) or in workers exposed to formaldehyde and phenol (Dosemeci et al., 1991). However, the usefulness of each of these studies for risk assessment is limited by (depending on the study) an absence of an effect when latency was considered, a lack of a dose-response, and the potential for confounding. Because all of the subjects were also exposed to other chemicals and there was no correction for smoking, these studies are not adequate for reaching conclusions on the carcinogenic potential of phenol.

II.A.3. Animal Carcinogenicity Data

Inadequate.

NCI (1980) conducted a carcinogenicity bioassay in which F344 rats (50/sex/group) received phenol in drinking water at concentrations of 0, 2500, or 5000 ppm for 103 weeks and were sacrificed 1-2 weeks later. Using the reference water intake of 0.13 and 0.14 L/kg-day for chronic exposure of male and female F344 rats, respectively (U.S. EPA, 1988), the doses can be estimated as 0, 260, and 585 mg/kg-day for male rats and 0, 280, and 630 mg/kg-day for female rats. The doses shown here were adjusted to account for the reported water consumption of 80% and 90% of control at the low and high doses, respectively. The animals were observed daily for clinical signs and examined weekly for palpable masses. Body weights and food consumption were recorded every 2 weeks for the first 12 weeks and monthly thereafter; water consumption was recorded weekly.

At the end of study, the animals were sacrificed and complete gross and histopathological examinations were performed. Organs and tissues examined included the bone marrow, spleen, cervical and mesenteric lymph nodes, heart, liver, kidney, thyroid, reproductive organs, brain, and other major tissues. The survival rate at study termination was comparable among all three groups of males (approximately 50%) and females (approximately 75%). Dose-related decreases in body weight as compared with the controls were observed in male and female rats, with a decrease of approximately 15% in high-dose males and approximately 10% in high-dose females. Water consumption was reduced by approximately 10% at the high dose.

The authors stated that the non-neoplastic lesions were similar to those naturally occurring in aged F344 rats. However, an analysis conducted for this assessment found statistically significant increases in chronic kidney inflammation in high-dose males and females; there were no significant changes at the low dose. No other differences in the incidence of non-neoplastic lesions between the controls and the exposed rats were observed. The increased kidney inflammation and the decreased body weight as compared with controls at the high dose of 5000 ppm (585 mg/kg-day for males and 630 mg/kg-day for females) indicate that the MTD was reached.

There were no dose-related trends in cancer incidence in male or female rats, but the study authors reported several tumors for which statistically significant increases were seen in low-dose males only, as indicated by pairwise comparisons. These increases were seen in the incidences of pheochromocytomas of the adrenal medulla (13/50, 22/50, and 9/50 in the control, low-, and high-dose groups, respectively) and "leukemias or lymphomas" (18/50, 31/50, and 25/50). The incidence of interstitial cell tumors of the testes was also elevated in

the low-dose group (42/48, 49/50, and 47/50). The historical control incidence of pheochromocytomas in the bioassay program was 9% (data for the test laboratory were not reported), and the historical control incidence of leukemias or lymphomas in the test laboratory was 26%. The authors stated that the leukemias were "of the type usually seen in untreated F344 rats." There were no significant increases in tumor incidence in any tissue in female rats.

In light of the absence of a clear dose-response in males, the high spontaneous testicular tumor rate in the matched controls and the absence of tumors in female rats, an association between the tumors and phenol exposure cannot be established. NCI concluded that phenol was "not carcinogenic in male or female F344 rats." However, the report noted uncertainties regarding the possible increase in leukemia in male rats, and the NCI reviewers recommended that phenol be considered for a retest. The increases in leukemia are of particular interest in light of the leukemogenic effects of benzene (for which phenol is a metabolite) in humans. (Benzene has not been shown to induce leukemia in experimental animals, although increases in lymphoma have been observed [e.g., NTP, 1986].)

In a parallel study, NCI (1980) administered phenol at 0, 2500, or 5000 ppm in drinking water to B6C3F1 mice (50/sex/group) for 103 weeks and sacrificed the mice 1-2 weeks later. For B6C3F1 mice, the reference water intake is 0.24 L/kg-day for both sexes. The study reported that water consumption was decreased to 75% and 50-60% of the control levels at the low and high doses, respectively. The resulting doses (adjusting for decreased water intake) were 0, 450, and 660 mg/kg-day for both sexes. Dose-related decreases in body weight as compared with the controls were attributed to the decrease in water consumption. Besides the decreased water consumption, no clinical signs of toxicity were observed, and mortality rates (approximately 10% in males and 20% in females) were comparable between experimental and control groups. Histopathological examination and statistical analyses revealed no phenol-related signs of toxicity or carcinogenicity; lesions in all systems observed in the dosed groups were comparable with those in the controls. NCI concluded that, under the conditions of the assay, phenol was not carcinogenic in male or female B6C3F1 mice (NCI, 1980).

Although the only sign of toxicity in the mouse study was decreased body weight (compared to the controls) secondary to decreased water consumption, higher doses probably could not have been tested in light of the decreased water consumption. If the authors had attempted to overcome the palatability issue by administering the high dose in the NCI (1980) mouse study by gavage instead of in drinking water, high toxicity would have been expected, considering the higher toxicity of phenol administered by gavage than that of phenol in drinking water. These considerations suggest that an MTD was also reached in mice, although a definitive conclusion is difficult. No other long-term oral carcinogenicity studies of phenol are available. No inhalation studies of phenol were of a sufficient duration to assess phenol carcinogenicity.

II.A.4. Supporting Data for Carcinogenicity

In contrast with the negative carcinogenicity results for oral administration of phenol, dermally administered phenol has been consistently observed to be a promoter. Several authors (Salaman and Glendenning, 1957; Boutwell and Bosch, 1959; Wynder and Hoffmann, 1961) observed that dermally applied phenol promoted DMBA-initiated skin tumors. These studies have generally reported significant skin ulceration at all doses tested. The exception is Wynder and Hoffman (1961), who reported that 5% phenol promoted DMBA-initiated tumors in mice in the absence of any toxic reactions. When the same phenol dose was administered in different volumes, higher promotion activity was exhibited by the more concentrated solution, which also produced severe skin ulceration, suggesting that some of the promotion activity may have been related to the rapid cell division in the repairing of skin damage (Salaman and Glendenning, 1957). The observed response was dose-related (Boutwell and Bosch, 1959), but marked systemic toxicity was also observed at these doses.

Co-carcinogenesis with dermally administered benzo[a]pyrene has also been observed (Wynder and Hoffmann, 1961). Because the benzo[a]pyrene was co-administered with the phenol, this assay cannot be classified as a true initiation/promotion assay. Production of papillomas by dermally administered phenol (in the absence of an initiator) was observed only at a concentration that caused ulceration and hence was above the MTD.

Genotoxicity studies have found that phenol tends not to be mutagenic in bacteria (Pool and Lin, 1982; Rapson et al., 1980; Haworth et al., 1983), but positive or equivocal results have been obtained in gene mutation assays in mammalian cells (McGregor et al., 1988a, b; Paschin and Bahitova, 1982; Tsutsui et al., 1997). Increases were larger in the presence of S9 activation. Phenol tended to induce micronuclei in mice when administered intraperitoneally (Marrazzini et al., 1994; Chen and Eastmond, 1995; Ciranni et al., 1988), but negative (or positive only at very high doses) when administered orally (Ciranni et al., 1988; Gocke et al., 1981). This difference is likely due to the first-pass conjugation and inactivation of orally administered phenol. Phenol was also positive in vitro micro nucleus tests with human lymphocytes (Yarer et al., 1990) and Chinese hamster ovary (WHO) cells (Miller et al., 1995) and caused chromosome aberrations in the presence of S9 activation in WHO cells (Aviate et al., 1989). Phenol has been observed to act synergistically with hydroquinone in the production of genotoxic effects (Marrazzini et al., 1994; Barale et al., 1990; Chen and Eastmond, 1995).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not applicable.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not applicable.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2002

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in the finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Phenol. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation - Updated Health Effects Assessment for Phenol. Prepared by the Office of Health and Environment Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. U.S. EPA. 1988.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 08/28/2002

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for phenol conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Phenol
CASRN — 108-95-2

VI.A. Oral RfD References

Argus Research Laboratories, Inc. (1997). Oral (gavage) developmental toxicity study of phenol in rats. Horsham, PA. Protocol number: 916-011.

Berman, E; Schlicht, M; Moser, VC; et al. (1995). A multi-disciplinary approach to toxicological screening: I. Systemic toxicity. J Toxicol Environ Health 45:127-143.

Capel, ID; French, MR; Millburn, P; et al. (1972). Fate of C-14-phenol in various species. Xenobiotica 2:25-34.

Charles River Laboratories. (1986). Technical bulletin: baseline hematology and clinical chemistry values as a function of sex and age for Charles River Outbred Mice: Crl: CD-1(ICR)BR, Crl: CF-1 BR.

Charles River Laboratories. (1988). Embryo and fetal development toxicity (teratology) control data in the Charles River Crl:CD BR rat.

Clin Trials BioResearch. (1998). A 13-week neurotoxicity study of phenol administered in the drinking water to the rat, vol 1 and 2. Senneville, Quebec, Canada. Project ID: 97439.

Corti, M; Snyder, CA.(1998). Gender- and age- specific cytotoxic susceptibility to benzene metabolites in vitro. Toxicol Sci 41:42-48.

Deichmann, WB; Witherup, B. (1944). The acute and comparative toxicity of phenol and o-, m-, and p-creosols for experimental animals. J Pharmacol Exp Ther 80:233-240.

Dow Chemical Co. (1994). Pharmacokinetics, metabolism, and distribution of C^{14} phenol in Fischer 344 rats after gavage, drinking water, and inhalation exposure, with cover letter dated 07/13/1994. U.S. EPA/OPTS Public Files Fiche # OTS0557473; Doc#: 86940001296.

Eastmond, DA; Smith, MT; Irons, RD. (1987). An interaction of benzene metabolites reproduces the myelotoxicity observed with benzene exposure. Toxicol Appl Pharmacol 91(1):85-95.

Hsieh, GC; Sharma, RP; Parker, RD; et al. (1992). Immunological and neurobiochemical alterations induced by repeated oral exposure of phenol in mice. European J Pharmacol 228:107-114.

IIT Research Institute. (1999). Two-generation oral (drinking water) reproductive toxicity study of phenol in rats. Chicago, IL. IITRI Project No. L08657, Study No. 2.

Kenyon, EM; Seeley, ME; Janszen, D; et al. (1995). Dose-, route-, and sex-dependent urinary excretion of phenol metabolites in B6C3F1 mice. J Toxicol Environ Health 44(2):219-33.

Liao, TF; Oehme, FW. (1981). Tissue distribution and plasma protein binding of carbon-14-labeled phenol in rats. Toxicol Appl Pharmacol 57(2):220-225.

Luster, MI; Portier, C; Pait, DG; et al. (1992). Risk assessment in immunotoxicology. I. Sensitivity and predictability of immune tests. Fund Appl Toxicol 18:200-210.

Luster, MI; Portier, C; Pait, DG; et al. (1993). Risk assessment in immunotoxicology. II. Relationships between immune and host resistance tests. Fund Appl Toxicol 21:71-82.

Moser, VC; Cheek, BM; MacPhail, RC. (1995). A multidisciplinary approach to toxicological screening: III. Neurobehavioral toxicity. J Toxicol Environ Health 45(2):173-210.

Narotsky, MG; Kavlock, RJ. (1995). A multidisciplinary approach to toxicological screening: II. Developmental toxicity. J Toxicol Environ Health 45(2):145-71.

NCI (National Cancer Institute). (1980). Bioassay of phenol for possible carcinogenicity in F344 rats and B6C3F1 mice. Prepared by the National Cancer Institute, Bethesda, MD for the National Toxicology Program, Research Triangle Park, NC. NCI-CG-TR-203, DHHS/PUB/NIH80-1759.

NTP (National Toxicology Program). (1983a). Teratologic evaluation of phenol in CD rats. Prepared by Research Triangle Institute, Research Triangle Park, NC. NTIS PB83-247726.

NTP. (1983b). Teratologic evaluation of phenol in CD-1 mice. Prepared by Research Triangle Institute, Research Triangle Park, NC. NTIS PB85104461.

Ohtsuji, H; Ikeda, M. (1972). Quantitative relation between atmospheric phenol vapor and vapor in the urine of workers in Bakelite factories. Br J Ind Med 29:70-73.

Piotrowski, JK. (1971). Evaluation of exposure to phenol: Absorption of phenol vapor in the lungs through the skin and excretion of phenol in urine. Br J Ind Med 28:172-178.

Ryan, BM; Selby, R; Gingell, R; et al. (2001). Two-generation reproduction study and immunotoxicity screen in rats dosed with phenol via the drinking water. Inter J Toxicol 20:121-142.

Seaton, MJ; Schlosser, P; Medinsky, MA. (1995). In vitro conjugation of benzene metabolites by human liver: potential influence of interindividual variability on benzene toxicity. Carcinogenesis 16(7):1519-27.

Selgrade, MK. (1999). Use of immunotoxicity data in health risk assessments: uncertainties and research to improve the process. Toxicology 133:59-72.

Tanaka, T; Kasai, K; Kita, T; et al. (1998). Distribution of phenol in a fatal poisoning case determined by gas chromatography/mass spectrometry. J Forensic Sci 43(5):1086-8.

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and documentation of biological values for use in risk assessment. EPA 600/6-87/008. Available from: NTIS, PB88-179874/AS.

U.S. Environmental Protection Agency. (1998). Health effects test guidelines. Office of Prevention, Pesticides and Toxic Substances. OPPTS 870.7800 Immunotoxicity. Washington, DC.

U.S. Environmental Protection Agency. (2002). Toxicological review of phenol in support of summary information on Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available at http://www.epa.gov/iris.

Vieira, I; Sonnier, M; Cresteil, T. (1996). Developmental expression of CYP2E1 in the human liver: hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

VI.B. Inhalation RfC References

Deichmann, WB; Kitzmiller, KV; Witherup, BS. (1944). Phenol studies. VII. Chronic phenol poisoning, with special reference to the effects upon experimental animals of the inhalation of phenol vapor. Am J Clin Pathol 14:273-277.

Hoffman, GM; Dunn, BJ; Morris, CR; et al. (2001). Two-week (ten-day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. Int J Toxicol 20:45-52.

Huntingdon. (1998). Two-week (ten day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. Chemical Manufacturers Association. CMA Reference No. PHL-4.0-INHAL-HLS. U.S. EPA/OPTS Public Files Fiche #: OTS0559328; Doc#: 40-980000008.

Sandage, C. (1961). Tolerance criteria for continuous inhalation exposure to toxic material. I. effects on animals of 90-day exposure to phenol, CCl4, and a mixture of indole, skatole, hydrogen sulfide, and methyl mercaptan. Wright Patterson Air Force Base, OH. U.S Air Force systems command, Aeronautical Systems Division, ASD technical report 61-519(I).

U.S. Environmental Protection Agency (EPA). (1994b). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F.

U.S. EPA. (2002). Toxicological review of phenol in support of summary information on Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available at http://www.epa.gov/iris.

VI.C. Carcinogenicity Assessment References

Barale, R; Marrazzini, A; Betti, C; et al. (1990). Genotoxicity of two metabolites of benzene: Phenol and hydroquinone show strong synergistic effects in vivo. Mutat Res 244(1):15-20.

Boutwell, RK; Bosch, DK. (1959). The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res 19:413-424.

Chen, H; Eastmond, DA. (1995). Synergistic increase in chromosomal breakage within the euchromatin induced by an interaction of the benzene metabolites phenol and hydroquinone in mice. Carcinogenesis 16(8):1963-9.

Ciranni, R; Barale, R; Ghelardini, G; et al. (1988). Benzene and the genotoxicity of its metabolites. II. The effect of the route of administration on the micronuclei and bone marrow depression in mouse bone marrow cells. Mutat Res 209(1-2):23-8.

Dosemeci, M; Blair, A; Stewart, PA; et al. (1991). Mortality among industrial workers exposed to phenol. Epidemiology 2(3):188-93.

Gocke, E; King, M.-T; Eckhardt, K; et al. (1981). Mutagenicity of cosmetics ingredients licensed by the European communities. Mutat Res 90: 91-109.

Haworth, S; Lawlor, T: Mortelmans, K; et al. (1983). Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 5(Suppl 1):3-142.

Ivett, JL; Brown, BM; Rodgers, C; et al. (1989). Chromosomal aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. IV: Results for l5 chemicals. Environ Molec Mutagen 14:165-187.

Kauppinen, TP; Partanen, TJ; Nurminen, NM. (1986). Respiratory cancers and chemical exposures in the wood industry: A nested case-control study. Br J Ind Med 43:84-90.

Marrazzini, A; Chelotti, L; Barrai, I; et al. (1994). In vivo genotoxic interactions among three phenolic benzene metabolites. Mutation Research 341(1):29-46.

McGregor, DB; Brown, A; Cattanach, P; et al. (1988a). Responses of the L5178Y TK+/TK- Mouse Lymphoma Cell Forward Mutation Assay. 3. 72 Coded Chemicals. Environ Molec Mutagen 12:85-154.

McGregor, DB; Rlach, CG; Brown, A; et al. (1988b). Reactivity of catecholamines and related substances in the mouse lymphoma L5178Y cell assay. Environ Molec Mutagen 11:523-544.

Miller, BM; Pujadas, E; Gocke, E. (1995). Evaluation of the micronucleus test in vitro using Chinese hamster cells: results of four chemicals weakly positive in the in vivo micronucleus test. Environ Molec Mutagen 26(3):240-7.

NCI (National Cancer Institute). (1980). Bioassay of phenol for possible carcinogenicity in F344 rats and B6C3F1 mice. Prepared by the National Cancer Institute, Bethesda, MD for the National Toxicology Program, Research Triangle Park, NC. NCI-CG-TR-203, DHHS/PUB/NIH80-1759.

NTP (National Toxicology Program). (1986). Toxicology and carcinogenesis studies of benzene (CAS No. 71-43-2) in F344/N rats and B6C3F1 mice (gavage studies). NTIS PB86-216967/AS.

Paschin, YV; Bahitova, LM. (1982). Mutagenicity of benzo[a]pyrene and the antioxidant phenol at the HGPRT locus of V79 chinese hamster cells. Mutat Res 104(6):389-93.

Pool, BL; Lin, PZ. (1982). Mutagenicity testing in the *Salmonella typhimurium* assay of phenolic compounds and phenolic fractions obtained from smokehouse smoke condensates. Food Chem Toxicol 20:383-391.

Rapson, WH, Nazar, MA; Butsky, V. (1980). Mutagenicity produced by aqueous chlorination of organic compounds. Bull Environ Contam Toxicol 24:590-596.

Salaman, MH; Glendenning, OM. (1957). Tumor promotion in mouse skin by sclerosing agents. Br J Cancer 11:434-444.

Tsutsui, T; Hayashi, N; Maizumi, H; et al. (1997). Benzene-, catechol-, hydroquinone- and phenol-induced cell transformation, gene mutations, chromosome aberrations, aneuploidy, sister chromatid exchanges and unscheduled DNA synthesis in Syrian hamster embryo cells. Mutat Res 373(1):113-23.

U.S. Environmental Protection Agency (EPA). (1987). Risk assessment guidelines of 1986. EPA/600/8-87/045.

U.S. Environmental Protection Agency. (1988). Recommendations for and documentation of biological values for use in risk assessment. EPA 600/6-87/008. NTIS PB88-179874/AS.

U.S. Environmental Protection Agency. (1999). Guidelines for carcinogen risk assessment. Review Draft, NCEA-F-0644, July 1999. Risk Assessment Forum, Washington, DC.

U.S. Environmental Protection Agency. (2002). Toxicological review of phenol in support of summary information on Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available at http://www.epa.gov/iris.

Wilcosky, TC; Checkoway, H; Marshall, EG; et al. (1984). Cancer mortality and solvent exposures in the rubber industry. Am Ind Hyg Assoc J 45(12):809-811.

Wynder, EL; Hoffmann, D. (1961). A study of tobacco carcinogenesis. VIII. The role of the acidic fractions as promoters. Cancer 14(6):1306-1315.

Yager, JW; Eastmond, DA; Robertson, ML; et al. (1990). Characterization of micronuclei induced in human lymphocytes by benzene metabolites. Cancer Res 50(2):393-399.

VII. Revision History

Phenol
CASRN — 108-95-2

Date	Section	Description
12/01/1988	I.A.	Withdrawn; RfD verified (in preparation)
06/01/1989	I.A.	Oral RfD summary replaced; RfD changed
06/01/1990	I.B.	Data judged inadequate for derivation of inhalation RfD
07/01/1990	I.B.	Not verified; data inadequate
11/01/1990	II.	Carcinogen assessment on-line

Date	Section	Description
03/01/1991	I.B.	Inhalation RfC message on-line
09/30/2002	I.,II.,VII	RfD, RfC, cancer assessment sections updated.
10/28/2003	I.A.6, I.B.6, II.D.2	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Phenol
CASRN — 108-95-2
Last Revised — 01/31/87

- 108-95-2
- Benzenol
- Carbolic Acid
- Hydroxybenzene
- Izal
- Monohydroxybenzene
- Monophenol
- NCI-C50124
- Oxybenzene
- Phenic Acid
- Phenol
- Phenyl Alcohol
- Phenyl Hydrate
- Phenyl Hydroxide
- Phenylic Acid
- Phenylic Alcohol