Introduction

March 18 and 19, 2003
Cincinnati, Ohio
USA

An independent panel of expert scientists met in Cincinnati to review a risk assessment on the development of a reference dose (RfD) for resorcinol (CAS# 108-46-3). AMEC Earth and Environmental, Inc. wrote the assessment for the sponsor, Beazer East, Inc. Beazer East, Inc. was known as Koppers Company, Inc. prior to 1988, and, as such owned and operated a facility that manufactured resorcinol. This peer review meeting was conducted by Toxicology Excellence for Risk Assessment (*TERA*); a non-profit organization dedicated to the best use of toxicity data in risk assessment. Expert peer reviewers donated their time and talents to provide an independent review of the assessment. The objective was a comprehensive overall review of the materials as provided by the combined experience of all the reviewers. This meeting summary represents the major discussions and conclusions of the panel as a whole.

This review meeting followed a standard *TERA* process, beginning with a close examination of the supporting documentation and important references by the panel prior to the meeting. At the meeting, the authors of the assessment briefly presented their work. The panel then systematically discussed the assessment, starting with a discussion of the qualitative weight of evidence, followed by a discussion of the quantitative aspects of the assessment.

Full discussion and participation were encouraged and agreement was reached by consensus. Consensus for the purpose of these meetings is defined as "an opinion held by all or most, or general agreement." This meeting report is structured to reflect both the full discussion of the issues by different members of the panel and the consensus of the panel as a whole. The report will reflect when consensus was unanimous. The discussion is included to inform readers who were not present at the meeting the logic that the panel followed in arriving at consensus. However, it is only the panel consensus statements that represent the final outcome of the peer review.

The meeting was open to the public and an individual from Syracuse Research Corporation observed the proceedings.

Conflict of Interest

After brief introductions, the meeting began with a discussion of conflict of interest (COI). A brief general statement explaining the COI policy was given. Each reviewer had certified in writing prior to the meeting that he or she did not have a conflict (real or apparent) with the chemical under review and he or she had no affiliation with the sponsors and authors (identified to the reviewers before the meeting). Alternatively, the reviewers identified the potential for such conflicts prior to the meeting. *TERA* staff

discussed any potential conflicts with each reviewer to determine if measures were needed to manage a potential conflict (or appearance of conflict). *TERA* presented a plan for managing conflict of interest to the panel (see Appendix A).

On March 6, 2003 the *TERA* meeting manager conducted two conference calls with the panel members to present and discuss potential conflict of interest issues The conclusions from these calls were also presented to the panel and are summarized in Appendix A. During those conference calls, a consensus was reached on the selection of Dr. Lynne Haber as the panel chair. The issue of a potential conflict regarding the possible placing of the resorcinol RfD on the International Toxicity Estimates for Risk (*ITER*) database was not considered a concern once the panel realized that *ITER* is a free service for the public.

Each panel member gave a brief introduction and added any additional statements for inclusion in their previous COI disclosure. The panel agreed to each participant's participation as documented in Attachment A.

Description of a Proposed Reference Dose for Resorcinol

The meeting was attended by the following parties:

Sponsor: Ms Jane Patarcity, Beazer East, Inc.
Mr. Timothy Wolfson, Beazer East, Inc.

Presenter: Dr. Bradley Schwab, AMEC Earth and Environmental, Inc.
Dr. Brian Magee, AMEC Earth and Environmental, Inc.

Chair: Dr. Lynne Haber, *TERA*

Review Panel:

- Dr. Michael Kamrin, Professor Emeritus, Michigan State University
- Dr. Elaina Kenyon, U.S. Environmental Protection Agency (EPA)
- Dr. Steven Lamm, Consultants in Environmental and Occupational Health
- Dr. Randall Manning, Georgia Department of Natural Resources
- Dr. Patricia McGinnis, Syracuse Research Corporation
- Dr. Richard Pleus, Intertox, Inc.
- Dr. Allan Susten, Agency for Toxic Substances and Disease Registry
- Dr. Douglas Wolf, U.S. EPA

Author Presentation

A representative of AMEC Earth and Environmental, Inc. presented an overview of the assessment for resorcinol (the presentation slides can be found in Appendix B). He indicated that the purpose of the assessment is to develop a RfD that can be available to

inform risk-based clean up decisions under Pennsylvania Department of Environmental Protection regulations. Resorcinol is used in the manufacture of adhesives, pharmaceuticals, and cosmetics. Resorcinol is also found naturally in some products such as coffee, molasses, and groundwater in some regions. The assessment relies heavily on information published by the Cosmetic Ingredient Review (1985), a NTP report (1992), and Lynch et al. (2002). In addition, a search of PubMed was conducted. Resorcinol is well absorbed by the oral route – about 90% is absorbed following ingestion. In contrast, only about 0.5-3% of resorcinol is absorbed following dermal exposure. Following absorption, resorcinol is generally well distributed, although in some studies, slightly more resorcinol was identified in liver and kidney, than other tissues or organs. Resorcinol is eliminated in the urine as glucuronide or sulfate; elimination of a subcutaneous dose is biphasic and rapid.

Acute poisoning in humans indicates that CNS, respiratory effects, and cardiac depression are the primary acute symptoms of resorcinol. In addition hemolysis has been observed in some patients and methemoglobinemia has been observed in infants exposed dermally to preparations containing 5% of resorcinol or higher. In humans, dermal exposure occurs from the use of resorcinol in chemical peels and other dermatological treatments. Sensitization and contact dermatitis, but not irritation, have been observed following treatment with 1.4 % resorcinol ointment.

In addition, goiter and hypothyroidism have been observed following dermal exposure to high concentrations (>5% and up to 50%) of resorcinol, although the thyroid effects appear to be reversible with cessation of exposure. No thyroid hormone changes have been observed in volunteers exposed dermally to a 1.4% solution of resorcinol, or in workers exposed by inhalation. Epidemiology studies have identified endemic goiter in areas where resorcinol is present in the drinking water; however, other chemicals were also present in the water and the goiter could not conclusively be attributed to resorcinol. Thyroid effects have not consistently been observed in animal studies. However, it appears that a continuous, prolonged treatment with an oil-based, rather than water-based, vehicle is required for resorcinol to cause thyroid effects.

Several studies have examined the developmental and reproductive effects of resorcinol. A 3-generation reproduction study (Burnett and Goldenthal, 1988) in rats by the dermal route showed no effects. In addition, three oral rat teratology studies (DiNardo et al., 1985; Hazelton, 1982a; Kavlock, 1990) and one oral rabbit (Hazelton, 1982b) teratology study showed no effects.

The NTP (1992) conducted both a subchronic and chronic study of resorcinol. In the 90-day study, rats and mice (10/sex/species/dose) were exposed to resorcinol by gavage in water for 5 days/week, resulting in doses of 28 to 420 mg/kg-day in mice and 32-520 mg/kg-day in rats. The following effects were observed: increased mortality; relative organ weight changes of liver, adrenal, kidney, and brain; and CNS clinical signs. No effects were observed on thyroid hormone levels, or histopathology. In the 2-year study, rats and mice (60/sex/species/dose) were exposed to resorcinol by gavage in water for 5 days/week, resulting in doses of 0, 112, and 225 mg/kg-day in mice and male rats and 0,

50, 150 mg/kg-day in female rats. There were no neoplastic changes and no effects were observed on thyroid histopathology. Relative liver and brain weights were increased at the 15-month interim sacrifice, and CNS clinical signs were observed. Finally, mortality was increased. It was determined that the liver effects observed were not treatment-related because they were not reproduced in the 2-year study, they appeared to be due to the decreased body weight, and there was no corresponding liver histopathology. The incidence of CNS effects was not reported; therefore it was not possible to quantify this response. However, it was considered to be a data gap.

Two short-term drinking water studies (Cooksey et al., 1985; Seffner et al., 1995) identified thyroid effects at doses ranging from 6-10 mg/kg-day. Although these effects occurred at doses lower than those that identified effects in the NTP study, these studies were considered inadequate because they had small numbers of animals and a single dose. Finally, Lynch et al. (2002) estimated a NOEL of 10 mg/kg-day for thyroid effects in humans. However, this study was not selected as the critical study because exposure was not accurately measured and was by the dermal route.

Therefore, the NTP (1992) 2-year study was selected as the critical study. The NOAEL was identified as 100 mg/kg-day; adjusted for continuous exposure the NOAEL is 71 mg/kg-day. A total uncertainty factor of 1000 was applied – 10 each to account for inter- and intraspecies variability and 10 to account for database uncertainties. The resulting RfD is 71/1000, or 0.07 mg/kg-day.

Panel Clarifying Questions

One panel member asked to clarify the study design of the 3-generation study (Burnett and Goldenthal, 1988), because it is discussed as a 2-generation study in the report. In addition, this panelist noted that the study was primarily a study of hair dye mixtures and asked whether a resorcinol-only group was included. Another panelist asked whether the resorcinol used in cosmetic products such as hair dyes was pure or part of a coal-tar product. AMEC indicated that the study examined the F0, F1, and F2 generations, and that the study was conducted with hair dye mixtures; there was no resorcinol only group. Resorcinol was present in the mixture at 0.5 to 1%. AMEC indicated that they believe pure resorcinol is used in cosmetic products.

Other panelists asked how resorcinol was administered in the oral absorption study and how the studies to determine dermal absorption were conducted. AMEC indicated that in the oral study, resorcinol was administered by gavage. The dermal absorption studies were conducted in human volunteers in which resorcinol in a hydroalcoholic vehicle was administered to the face and upper body 2 times per day for 14 days. In addition, there was an *in vitro* dermal absorption study using human cadaver skin. No dermal absorption studies were conducted using ointment as a vehicle.

One panel member asked whether the authors had searched FDA archives for data on resorcinol, and indicated that resorcinol was probably classified as "Generally Recognizable as Safe (GRAS)". AMEC did not search FDA.

Another panel member asked how the authors had conducted their literature review and how they evaluated studies and determined whether to include them. AMEC indicated that they started with existing literature reviews for the basic titles and then followed up with a PubMed search. From this, the authors obtained and reviewed about 60 additional papers. AMEC noted that much of the information found in the literature searches was redundant with the existing review documents or repeated studies that had been included in the document already.

One panelist asked why a NOAEL of 100 mg/kg-day based on mortality was selected. This person also asked for other examples where RfDs were based on a mortality endpoint, and indicated that the effect level was a "frank effect level" rather than an "adverse effect level". Another panel member replied that there were approximately five other values on IRIS that used mortality as the critical effect, with the RfD based on a NOAEL, and that none of these values included an extra uncertainty factor for severity. The panel also questioned the cause of the mortality in the NTP study and noted that examining the raw data may help to answer that question.

AMEC indicated that all other endpoints in the NTP study were either not dose-related or not repeated from the subchronic to the 2-year study. There were no suitable effects other than mortality on which to base the RfD. Mortality was increased at doses of 150 mg/kg-day or higher. Therefore, the 100 mg/kg-day dose level was the no effect level. AMEC did not consider this dose level to be a frank effect level because no mortality was seen at this dose level. Finally, the NTP report did not suggest a cause of the mortality; it just noted that there was a decrease in the average number days of life in the treated animals.

A panelist asked AMEC to compare the NOAEL of 100 mg/kg-day to the doses at which dermal effects in humans and CNS effects in animals were observed. Another panel member asked how the dermal NOAEL in humans was estimated. AMEC explained that Lynch et al. (2002) estimated an effect level in humans of 30 mg/kg-day and a no effect level of 10 mg/kg-day by the dermal pathway. These estimates were based on the compilation of many case reports (some of which were unpublished), including estimates of applied doses, and estimates of dermal absorption. However, AMEC noted that this NOAEL was not a measured dose. Based on the differences between dermal and oral absorption, a dermal dose of 10 mg/kg-day would be equivalent to an oral dose as low as 0.2 mg/kg-day and the proposed RfD is lower than this. AMEC also indicated that CNS clinical signs were observed in rats at doses of 25 mg/kg-day, although no incidence data were reported (NTP, 1992). However, if 25 mg/kg-day were selected as a LOAEL, the uncertainty factor for database would be 3 rather than 10, so the resulting RfD would be about the same as the one proposed.

A panel member asked what concentrations of resorcinol have been measured in groundwater, specifically at the site in Pennsylvania. AMEC answered that they had not reviewed that information, but that concentrations in coal leachate were approximately 30 mg/L.

One panelist asked what the typical procedure was when resorcinol chemical peels were used. AMEC replied that the peel is applied all over the affected surface; therefore, the percentage of body surface covered was unique for each patient, but could be a significant portion of the body surface. The peel is left in place for 6 hours, but no information was available on whether the peels were covered. Treatment usually continued daily for up to 6 months. Therefore, very significant exposures to resorcinol could occur.

Someone asked how the kinetics studies using radiolabeled resorcinol were conducted, how distribution was reported, and how the brain was examined. AMEC was unsure of the protocol or whether brain was examined, but noted that the study showed a generally even distribution across all tissues.

A panelist asked the authors to comment on the observation of methemoglobinemia and why this was not considered as the critical effect. AMEC indicated that it is only observed following acute dermal dosing. Therefore route extrapolation and duration issues prevented consideration of this endpoint.

One panel member asked about the liver weight effects observed in the 90-day NTP study (p. 200, Table 2) and indicated that there was a good dose-dependent trend and liver weight was even increased at 32 mg/kg-day. AMEC indicated that this effect was not repeated in the 2-year study. Some panel members suggested that lack of reproducibility between the 90-day and 2-year studies was not a concern in selecting a critical effect.

The panelists asked the authors to comment on the role of drinking water vs. gavage exposure in observing potential thyroid effects in chronic animal studies. Since resorcinol inhibits thyroid peroxidase (TPO, an enzyme important to the synthesis of thyroid hormones), supporting the thyroid as a target tissue, the panelist wondered if the difference between the effects of gavage and drinking water exposure is related to the elimination kinetics. AMEC indicated that the differences may arise from the rapid elimination rate of resorcinol. With a gavage study, the compound would be cleared within 3-4 hours following dosing. In contrast, following drinking water exposure, assuming that rats drink at a constant rate, there will be lower peak concentrations of resorcinol but a longer overall duration of resorcinol in the body. Therefore, drinking water exposure was probably more conducive to promoting thyroid effects. An alternative interpretation might arise from reports that resorcinol actions on the thyroid may result from suicide substrate inhibition of TPO. If this is the case, *de novo* synthesis of TPO protein would be required to reverse the effect of resorcinol, regardless of its clearance rate. AMEC was unaware of protein turnover rates for TPO, but expected they would be longer than the resorcinol clearance rate. Under this hypothesis, gavage versus drinking water exposure might not be as important.

One panelist asked what percentage of resorcinol was found in each phase of the biphasic elimination curve. AMEC indicated that based on Merker et al. (1982), most of resorcinol (90%) of the compound is eliminated in the first phase within 2 hours.

Hazard Identification

The panel opened the meeting with a discussion of issues related to the hazard identification for resorcinol. To guide this discussion, the panel considered the following charge questions:

> 1. Was the literature search/document review complete enough to locate all studies pertinent to developing a RfD for resorcinol? Can you recommend any studies or data that should be included in this assessment?
>
> 2. Is the database sufficient to develop a RfD for resorcinol?
>
> 3. What do the data on resorcinol absorption, distribution, metabolism, elimination, and mode-of-action tell us about interpreting the potential for critical effects in humans and animals?
>
> 4. Are the human case reports and epidemiology studies of sufficient quality to support the conclusion that resorcinol has the potential to cause thyroid effects in humans at environmentally relevant doses?
>
> 5. Are the animal studies sufficient to draw conclusions regarding the target organ and critical effect(s) of resorcinol?
>
> - How should clinical signs suggesting CNS effects be interpreted?
> - Do animal studies support the conclusion that resorcinol is a thyroid agent? If not, what does that mean in light of the humans studies?
>
> 6. What is the critical effect of resorcinol and what is the appropriate choice of critical study?

The panel's discussions have been grouped into topic areas that roughly follow the content of the questions above.

Database

At least two panel members indicated that they conducted their own literature searches on resorcinol in preparing for this meeting. While the searches were not as extensive as would be done if these panelists were writing a document, the searches found approximately 800 cites, including many papers not reviewed by the document authors. The panel recommended that the document should include more data on the mode-of-

action and the mechanism of resorcinol toxicity. One member suggested that perhaps the authors should conduct a targeted literature search using key words specific to mode-of-action issues or to specific target organs such as thyroid. The panel recommended that the document authors need to more completely and thoroughly review all pertinent studies in the database, even if the studies are redundant with the information already included. The panel indicated that all primary studies should have been reviewed, particularly key studies on toxicity and mode-of-action issues. One panel member suggested that data from the IARC (1999) document on resorcinol should have been described in the document, particularly some dietary studies described in the IARC document that were not reviewed by the authors. Other panel members suggested the TLV documentation (ACGIH, 1992) as a secondary sources that all contain primary studies that are pertinent to the development of a RfD for resorcinol, including some pivotal kinetics studies that address the issue of vehicle (oil vs. water) and dosing strategy (gavage vs. drinking water) pertinent to resorcinol.

Other panelists suggested that additional data regarding other phenolic compounds with structural similarity to resorcinol should have been included. These data would give insight to the neurotoxicity issues and would help provide a stronger basis for supporting the critical effect. Another panelist agreed, stating that including data on structural analogs would contribute to the weight-of-evidence (WOE) for choosing a point of departure.

The panel reached unanimous consensus that the database was strong enough to support the development of a RfD for resorcinol; however, more of that data needs to be included in the document in order to support the RfD and allow the reader to independently evaluate its appropriateness.

Kinetics Studies

To help focus the discussion, the Chair reminded the panel of the ways in which mechanistic data is used in risk assessment. Such data can be used to help determine the relevance of animal data to humans. They can be used to develop "chemical-specific adjustment factors", in which actual data on toxicokinetic and toxicodynamic differences between species and among humans replace default uncertainty factors. Finally, mechanistic data can be used to assess whether the toxic effects are due to parent compound or metabolite, so that the appropriate dose metric can be used for the point of departure.

The panel discussed several key issues related to the kinetics data including the choice of appropriate dose metric and adjustment for continuous exposure, the role of drinking water vs. gavage exposure in the observation of thyroid effects, the support of a mode-of-action for resorcinol, and the Merker et al. (1982) study.

Choice of Dose Metric/Continuous Exposure Adjustment. One panelist summarized the available kinetics data by indicating that there is no evidence that resorcinol either stimulates or inhibits its own metabolism and there is no evidence of significant

interspecies differences to take into account. This panelist noted that the key issue regarding the kinetics data is choosing the appropriate dose metric to describe the various types of toxicity observed following resorcinol exposure. CNS effects are observed immediately after dosing and then subside. Therefore, the panelist concluded that these effects are likely to be due to parent compound and related to peak concentrations of resorcinol. The available data on thyroid effects suggested to this panelist that the appropriate dose metric is "time above a critical concentration". However, this reviewer was uncertain that even with drinking water studies the resorcinol concentration would exceed the critical point for long enough. Other panelists agreed that observation of thyroid effects may depend on the amount of time that resorcinol concentrations are above a critical concentration, because this same phenomenon has been observed with other compounds. Studies by Larson and Butterworth (1995) with chloroform also show that time above a critical concentration is important.

The panel discussed how to choose a dose metric if one has no data to inform the choice. One panelist noted that choice of dose metric is partly dependent on choice of critical effect. Generally, C_{max}, or peak concentration, is appropriate for an acute effect. Another panel member suggested that using area under the curve is appropriate. Although general toxicity is observed in some of the studies, the data do not clearly suggest an appropriate dose metric for general toxicity. Another panelist suggested that using applied dose would probably be the best dose metric when no data are available.

It was also noted that, for effects related to peak concentration, adjustment to continuous exposure may not be appropriate. For example, the panel noted that the CNS effects appear to be an acute effect because they do not show increasing severity with continued dosing. Since the effects appear to be an acute endpoint that is related to peak concentration, then it would not be appropriate to adjust the doses for continuous exposure, if this were selected as the critical effect. However, if severity did increase with duration, this could indicate cumulative damage by some mechanism; adjustment for continuous exposure would be appropriate in this case. Another panel member noted that according to EPA policy, when the appropriate dose metric cannot be determined the doses should be adjusted for continuous exposure, as this is a more conservative approach.

Panelists also noted that evaluating the data on structural analogs, such as phenol or catechols may help answer these questions regarding kinetics and dose metric. It was noted that similar CNS clinical signs are observed following phenol exposure and that the critical effect for the phenol RfD is decreased maternal weight gain in a developmental toxicity study, supported by developmental toxicity (decreased pup weight) at a similar dose, and decreased motor activity in adult animals at slightly higher doses. For phenol, the CNS effects are clearly related to peak concentration.

Mode-of-Action. One panel member commented that there were little data to conclusively support a mode of action and that a more detailed mode of action analysis was needed. Although it appears that resorcinol inhibits TPO, it is not clear whether the doses evaluated were large enough to inhibit TPO. In addition, the developmental studies

only looked at animals dosed on days 6-18 of gestation, so they are questionable for detecting thyroid effects in embryos. Other panel members noted that the thyroid in the fetus and in rats does not have a large storage capability. In contrast, the thyroid in the adult human has a large storage of thyroglobulin and so it takes more than 2 weeks of continuous hypothyroidism to begin to see significant colloid depletion and potential changes in circulating hormones. The panel also noted the species differences between rat and human thyroid homeostasis.

Merker et al. Study. The panel then discussed the studies contributing to the knowledge of resorcinol half-life. The primary study was the Merker et al. (1982) study in which resorcinol was administered to rats by subcutaneous injection. There are also oral studies that demonstrated rapid elimination, which is typically seen with phenolic compounds. However, the kinetics of resorcinol is very different across these two routes, so the data are not comparable. One reviewer indicated that a more detailed analysis of the available studies was needed in order to determine whether the data from the subcutaneous studies could support the oral studies. For phenol, route differences determine when the peak blood concentration occurs. However, this reviewer would expect that although elimination would be relatively quick by both routes, peak concentrations are generally lower and the half-life is generally longer by the subcutaneous route than oral route, depending on the compound. The route differences appear to be more important when developing acute toxicity values. This panelist also noted that as far as the observation of thyroid effects is concerned, as long as the critical concentration is maintained for the appropriate length of time, it would not matter what the route of exposure is. The panel also noted that the Merker study was summarized in the NTP report and that different half-life values were reported there than in the RfD document. AMEC indicated that they had reported the ranges overall across the single-dose and repeated dose studies in Merker and rounded the time estimates, while NTP gave just the range for the single-dose study.

AMEC indicated that the Merker study does not provide information on accumulation of resorcinol. Rather, it indicates the effects that pre-treatment with unlabeled resorcinol for 14 or 30 days has on the kinetics of radiolabeled resorcinol. Then one panel member clarified that the study does not provide information on what form the radioactivity is in, and so the study could not differentiate radiolabel that is in the form of the parent from metabolites.

The panel discussed some of the specific results in the Merker study, with particular attention to the levels in the brain, noting that the radioactivity levels at 1 hour were higher following resorcinol pretreatment than in the one-dose study. Several possible explanations for the observation were noted, but a panelist stated that the only conclusion that can be drawn from this study is that distribution does not change over time and that resorcinol does not affect its own metabolism. Another panel member indicated that since the study gives no information on standard deviations, it is impossible to draw conclusions about the study. In addition, there were only 3 animals/dose for each time group.

The panel evaluated the minimal information provided in the Merker study on CNS effects and the associated dose-response, and compared the findings in this study with the results of the NTP study. This comparison both evaluated dose-response in the two studies, and considered whether toxicity increased with repeated dosing. One panel member indicated that normally with short acting compounds one sees a series of acute responses over several days; however, the Merker study, for example on page 372, suggests that there may be a cumulative effect so that adjustment for continuous exposure is appropriate. Other panel members agreed, noting a statement in the NTP report that also suggests cumulative effects, even though there are no data to support the statement. A different panelist noted that the peer review comments to the NTP report supported this conclusion, and suggested that the document authors get clarification from NTP. One panel member noted that although the NTP chronic study suggests CNS effects at doses of 100 to 150 mg/kg-day, the 17-day study showed the same effect at 55 mg/kg-day and higher. However, the 13-week study showed CNS effects at higher doses than the chronic study. The panel was not able to explain the apparent inconsistency between the 17-day and subchronic studies.

Drinking Water vs. Gavage Exposure. The panel discussed the issue of the impact of drinking water exposure compared with gavage exposure on the observation of thyroid effects. It was noted that there is a good rationale to think that bolus dosing produces different kinetics than drinking water exposure, which could account for the lack of thyroid effects in the NTP study. This information would not necessarily affect the choice of NOAEL but would affect the selection of uncertainty factors. One panelist asked whether the gavage dosing would have lead to missing other important target organs for resorcinol. Other panel members indicated that there was no biological rationale to think that would be true.

One panel member questioned the significance of the dosing scheme in the NTP study (only 5/7 days) with the short half-life of resorcinol. If resorcinol is eliminated so rapidly, then a 2-day break from dosing would give the animals time to repair any damage done. Another panelist indicated that there is still no information about time needed to repair damage (recovery time).

Several panel members questioned whether critical concentrations could have been reached even by drinking water exposure. Panel members questioned whether animals would drink enough water containing resorcinol to see adverse effects. AMEC reported that they recollected either an odor or taste threshold of 2 ppm (2000 ppb). Subsequent to the meeting, it was found that resorcinol has an odor threshold in humans of 6 ppm (Verschueren, 1983). However, it is not known if the odor threshold in rats is the same. This concentration is substantially lower than the concentration of resorcinol in aqueous gavage doses used by NTP (1992) and slightly lower than concentrations used in short-term drinking water studies by Seffner (1995; 40 ppm)[1]. This means that it is possible that the animals in the NTP (1992) study (but not the Seffner (1995) study, could have detected a strong odor of resorcinol

[1] The other drinking water study, Cooksey, et al (1985) reports only total dose, not water concentrations.

Conclusions on Kinetics. One panel member indicated that in spite of the limited data, there is some information that can be obtained from the mechanistic data. It is known that resorcinol is absorbed, that it is eliminated, that it is evenly distributed in the body, and the half-life has been measured. In addition, absorption, distribution, metabolism, and elimination in animals seem similar to humans. Data are insufficient to definitively establish all potential modes-of-action and target organs. The panel concluded that TPO inhibition is a likely mode-of-action for thyroid effects, but that it is unlikely to be related to other potential effects.

Human Studies

In general, the panel suggested that a more detailed analysis of the human studies, including case reports, epidemiology studies, and occupational studies is needed in the RfD document in order to support conclusions regarding the utility of the human studies for risk assessment. Although, if one takes the Lynch et al. (2002) review at face value, then it is reasonable to conclude that resorcinol has the potential to cause thyroid effects in humans.

One panelist noted that several occupational studies (four studies by Tabershaw Occupational Medicine Associates [TOMA]) were cited in the Lynch article, but were not provided in the package supplied to the panel. The panel asked the sponsors to obtain these studies, and the two studies that were available to the sponsor were brought to the meeting for the panel to review. The two studies obtained provided general background information about the cohort (TOMA, 1981) and the results of the cancer mortality analysis (TOMA, 1980). The panel noted that TOMA (1981) suggests that lung, thyroid gland, liver and kidney are all potential target organs in humans. However, the panel also notes that these conclusions are all based on secondary references. The panel recommended that AMEC obtain the primary references to determine if they provide any useful information. One panel member suggested that this study was not useful for a resorcinol risk assessment because no information is provided on resorcinol exposure and the study did not evaluate any measures specific to resorcinol, such as the presence of resorcinol or metabolites in the urine. In addition, this panel member discussed the cancer mortality study and noted that one case of thyroid cancer was observed in the cohort. However, this case was not in the population with high resorcinol exposure. Therefore, this study was also not informative for the resorcinol risk assessment. The panel agreed and recommended that if the remaining two TOMA (1978, 1982) studies could be obtained, they should also be reviewed in the document.

The same panelist also indicated that a review of the case reports cited as the Gans memo by Lynch would have been desirable. (Note – *TERA* contacted Lynch regarding obtaining this memo for the panel, but was told that it is not available to the public.) Finally, this panelist noted that there are extensive human data regarding the potential for contact dermatitis following dermal exposure to resorcinol that should have been

included in the RfD document. This information could be important for addressing the issue of bathing in water that may contain resorcinol.

Another panel member suggested that the authors review the older literature on resorcinol because it could be very informative about the effects in humans.

The only data on occupational exposure are from the Roberts et al. (1990) study (as reported by Lynch), which reported a resorcinol concentration of <20 ug/m^3. This dose was converted to an equivalent systemic dose using the following calculation. Absorption was conservatively assumed to be 100% and exposure was converted from an occupational scenario to an ambient exposure scenario by multiplying by 10 m^3 (for an 8-hour shift with mild exertion) over 20 m^3 (ambient daily volume inhaled, or minute volume). This was then converted to a systemic dose by multiplying by the daily volume inhaled (20 m^3/day) and dividing by the default body weight of 70 kg. A dose of 2.8 ug/kg-day results indicating that the estimated inhalation dose would be much lower than the NOAEL proposed by Lynch for thyroid effects of resorcinol, and that this exposure in the occupational study is likely to have been too low to be informative regarding the doses at which resorcinol has thyroid effects. Another panelist reported doing a similar calculation and coming up with the same answer.

The panel reached unanimous consensus that sufficient human data exists to reach the hazard identification conclusion that resorcinol has the potential for thyroid effects in humans. However the panel also concluded that there was insufficient information presented in the AMEC document to identify other potential target organs in humans. The panel also reached unanimous consensus that there are insufficient data to draw conclusions regarding the dose response for thyroid effects in humans.

Animal Studies/Critical Effect

In general, the panel concluded that the discussion of critical effect was incomplete and that the document could be strengthened by including a table that clearly identifies the NOAEL or LOAEL for each study/endpoint, possibly also with the NOAEL identified for multiple key endpoints in the NTP studies. The table should convert all doses to units of mg/kg-day, include the shorter-term studies, and organize the data by target organ.

One panel member indicated that although NTP studies are overall the best studies, they are only designed for cancer hazard identification. They are not designed to find mechanistic endpoints or subtle changes in target organs. Therefore, NTP studies are hard to interpret for short term and subtle responses. Therefore, this panel member has no problem choosing a different study than the NTP study as the critical study, or in the fact that effects observed in the 90-day study were not observed in the 2-year study. For example, aging or masking by other effects could be reasons why liver effects were not observed in the 2-year study. Thus, this panel member concluded that the appropriate approach is to synthesize the information available in all studies and use the total weight of evidence for determining the critical effect.

The panel started this discussion focusing in on the potential critical effects identified by the animal studies and discussing the studies that support the choice of critical effect. The panel's summary of key critical effects, with identification of NOAEL/LOAEL is presented in Table 1.

CNS. The panel members discussed the WOE that suggests CNS as a critical effect. The panel noted that three studies suggest the potential for CNS effects by resorcinol: NTP, Gautgonis and Walton (1962), and Merker et al. (1982). The panel suggested that the Gautgonis and Walton (1962) study be reviewed in detail. In addition, the WOE is supported by the structural relationship to phenol and catechols. One panel member noted that, based on this information, resorcinol could have resulted in CNS effects. However, the studies do not provide enough information to conclusively say that CNS effects are the critical effect. It is likely that the acute deaths in the NTP study are due to CNS effects, but this is probably a high-dose phenomenon, rather than a low dose effect. Resorcinol appears to behave like a typical solvent in that it causes hyperactivity followed by depression.

Panel members noted that most of the information on CNS effects was obtained from secondary sources and therefore data are missing. However, it appears that doses ≤100 mg/kg-day do not produce effects, based on limited information from Merker et al. (1982) and NTP (1992, p 27). In Merker et al. (1982), no effect was observed at 55 and 88 mg/kg-day; effects were observed at 140 mg/kg-day and higher. When a total daily dose of 100 mg/kg-day was administered for 14 or 30 days, divided into 2 injections of 50 mg/kg, there were no clinical signs. Some panelists noted that we could not definitely say 100 mg/kg-day is a NOAEL based on this, since these effects are likely related to peak concentration, and the dose should really be expressed as a divided dose of 50 mg/kg/dose. The NTP data are very inconsistent. In the 17-day study, males had effects at 225 mg/kg-day and higher, but females had effects (hyper excitability, no tremors) at 55 mg/kg-day and higher. In the 13-week study, effects were seen at the high dose (520 mg/kg-day) only. In the 2-year study, effects were seen in males and females at 100 and 150 mg/kg-day. In general, the panel concluded that 100 mg/kg-day, given at one time, is a LOAEL.

One panel member noted that in the NTP study, the clinical observations were not an objective measure of hyperactivity, and that the raw data or notes may help to clarify the exact nature of the effects observed. Another panel member agreed, noting that resorcinol could be an irritant, and that a better approach would have been to measure ataxia or salivation, as these are less subjective. Other panel members questioned the usefulness of such an effort, given the cost and time investment needed to obtain and review the study notes.

One panel member expressed the opinion that the CNS effects were more like an acute response, and perhaps related to the different kinetics that would result from gavage dosing. Therefore, this panelist indicated that the CNS effects were not appropriate as the basis of a RfD. Another person agreed, noting that the CNS effects were related to the peak concentration of resorcinol, and not directly relevant to the RfD. However, these effects do inform the choice of uncertainty factor.

Thyroid. One panel member noted that there are several acute and subchronic studies that show quantifiable, statistically significant, biologically relevant thyroid effects in rats at fairly low doses. Another panel member agreed that the Seffner et al. (1995) and Cooksey et al. (1985) studies qualitatively demonstrated that thyroid effects occur in animals. However, this panel member noted that the studies have deficiencies, particularly with respect to dose-response information. The panel discussed the significance of the effects identified – it was noted that in Seffner, an increase in the height of follicular cells and a decrease in the follicle diameter indicate thyroid hypertrophy. One panel member indicated that these effects were adaptive effects, not adverse. Another replied that the adversity is unclear because no measurements of thyroid hormones were taken in the study. Without this, it is not possible to assess whether the thyroid would be able to maintain adaptation during continuous exposure.

The panel also noted that the Cooksey study found increased thyroid weight and a decrease iodine uptake into thryroid hormone compared to controls. However, one panel member noted that in the Cooksey study, the animals were on a low iodine diet, which severely compromised the results. Another member disagreed, stating that the results are consistent with Seffner and are what one would predict for a thyroid agent. It was also noted that both Cooksey and Seffner were drinking water studies, so they are by a more relevant route of exposure than the NTP gavage study. One panel member noted that these studies were also designed to examine specific indicators of thyroid toxicity and asked if these were more sensitive studies than those that just examined thyroid weight and histopathology. Other panel members noted that the studies were designed to evaluate more quantitative endpoints, such as thyroid morphometry and iodine uptake, but that they are not necessarily more sensitive. Several panel members indicated that the pair of studies had design deficiencies, compared with the NTP study and that it is unclear how much weight to give them because of the deficiencies. Another panelist indicated that since only one dose was tested, it is not possible to determine where on the dose-response curve the doses lay. Two panelists speculated that the effects in these two studies may be at the low end of the dose-response curve, even though there are no data to support this conclusion.

It was also noted that the Cooksey study (see Table 1of the Cooksey study) contributes to understanding the mode of action for resorcinol. One panel member noted that there appears to be 3 different steps to resorcinol action – inhibition of iodine uptake, TPO inhibition, and decreased iodine organification. Cooksey demonstrates that resorcinol inhibits iodine uptake to some degree, decreases iodine organification, and inhibits TPO.

With inhibition of TPO, one would expect to see effects typical of hypothyroidism including increased TSH and decreased T_3 and T_4. Based on the Cooksey study, resorcinol appears to be about 30-fold more potent at inhibiting TPO in vitro than the other known TPO inhibitors methimazol (MMI) and propylthiouracil (PTU). The panel also discussed how well the rat served as a model for human thyroid toxicity. One panel member indicated that qualitatively, the rat is a good model for humans, since rats and

humans both develop the same changes in the thyroid following exposure to thyroid agents. However, quantitatively, the rat is a sensitive model for humans because the animal dose of thyroid agents cannot be extrapolated to humans. Quantitatively, rats are more sensitive to the effects of thyroid agents because they have no binding proteins and a lower degree of iodine storage. One panel member also noted that there is no information for rats about the critical resorcinol concentration and the time above this concentration needed to induce thyroid effects. This panel member noted that TPO inhibition is clearly one mode-of-action, but it is not clear if this is the only one.

Another panel member indicated that rats are a sensitive, conservative model for thyroid effects because if effects are seen in rats, one can be more confident that the RfD be protective of the general human population.

Two panel members suggested that Seffner identified an effect level, but that it was not adverse. In addition, Cooksey identified a LOAEL in a sensitive population, because the low iodine diet would make the animals more sensitive to thyroid effects. However, another panel member questioned this, indicating that in unrelated studies designed to evaluate the effects of dietary iodine on thyroid, a 100% iodine deficiency in the diet had no effect on the pups born to dams. Therefore, it does not take much iodine in the diet to maintain normal thyroid function.

Panelists discussed the concept that a critical systemic level of resorcinol that is maintained for a critical time period is needed to see thyroid effects. The argument raised by the resorcinol database is that "more prolonged" systemic levels will occur as a result of rats repeatedly drinking water during the day and that these more prolonged and elevated levels are more likely to effect the thyroid as compared to gavage administrations. However, one panelist suggested that the levels achieved by drinking water would tend to be low and given the half-life, repeated drinking would give a series of small spikes that never get as high as the spikes seen with gavage. Therefore, a drinking-water study may be no more likely to identify thyroid effects than a gavage study. The panel then discussed the indicators of thyroid toxicity that were observed in the NTP study. It was noted that thyroid weights were not measured in either the 90-day or the 2-year study. Also, thyroid histopathology, T_3 and T_4 were measured in the 90-day study but only thyroid histopathology was evaluated in the 2-year study; thyroid hormone levels were not measured in the latter study. Neither study measured TSH. One panelist noted that in NTP studies colloid depletion, thyroid hypertrophy, and thyroid hyperplasia would not typically be evaluated in a quantitative manner and in a 2-year study, unless the lesions were moderately severe in the high dose group, may not be reported.

One panel member concluded that in a weight of evidence analysis, the most weight goes to thyroid effects as the critical effect. Thyroid effects are seen in humans, in animals following continuous exposure, and are not seen following bolus dosing, when time above a critical concentration is not achieved. Therefore, the data give a cohesive story that thyroid effects are real. There is a plausible mode of action, the data demonstrate a level of consistency and there are good reasons for not seeing effects in the animal studies that did not demonstrate thyroid effects. Although the dose response for this

effect is poor, an attempt should be made to estimate a RfD based on these effects, or at least ensure that a RfD is below the doses that cause these effects. The panel unanimously agreed with this statement.

Mortality. One panel member suggested that mortality appeared to be an acute effect related to the kinetics of the compound, and did not believe that this was an appropriate endpoint on which to base the RfD. Another panel member agreed that mortality was not an appropriate endpoint, indicating that in the NTP study, survival was variable across gender and species. Therefore, there was no clear dose-response for mortality either. This panelist also agreed that this could be a high-dose effect.

A different panel member indicated more comfort in selecting mortality as the critical effect because there are no other effects that have a good dose-response curve. In addition, the dose response curve for mortality is steep, providing more comfort that a NOAEL for mortality really is a NOAEL (i.e., that not only is mortality absent at this dose, but all adverse effects are absent). A different panel member indicated some discomfort at using mortality as the basis of the RfD, but noted that this approach has been used before. This person agreed that there were no other effects with good dose response data, so mortality is the only effect available. However, this panelist also indicated that if a series of studies could be used as co-critical, that would be preferable.

Organ Weights. One panel member asked why the brain weight changes observed in the NTP study at the 15-month sacrifice (p 24) were not considered adverse. Other panel members replied that the change is in relative brain weight and appears to be related to decreased body weight.

The panel noted that in the subchronic NTP study, rats had increased relative and absolute adrenal weights, but mice had decreased weights. These changes occurred in the absence of body weight changes. One panel member indicated that even though the weight changes occurred in different directions in the different species, the concordance of observation of an effect in the same organ in 2 species indicates that the effect should be considered further. Another panel member expressed discomfort at calling these effects adverse without supporting data, such as histopathology. The preponderance of the data for adrenal gland is negative and steroid levels were not measured, so the effect could be compensating for other effects. A different panelist indicated that, often, the observation of adrenal weight changes without histopathology effects are related to a change in the pituitary. It is hard to determine why the change in adrenal weight occurred, but this panelist agrees that the effect is adverse in the absence of information indicating that it is not biologically relevant. A panel member asked if adrenal weight changes could be related to a stress response, and noted that in the chronic study, no changes were observed in female rats and that adrenal weights were increased in male rats. However, in males, the values for controls appeared to be lower than normal. If the treated animals were compared to historical controls, there may be no effect on adrenal weights. A different panel member indicated that adrenal weights are too variable to use historical controls. For this endpoint, the concurrent control is the best. One panel

member asked what was considered to be a clinically significant effect on adrenal weights, but no one could answer. Another panel member asked what other effects might be expected that would be correlated with adrenal effects. A panelist replied that changes in white blood cell differentials, hypoglycemia, and sugar in urine could be expected, but that toward the end of the chronic exposure, all measured endpoints tended to equilibrate. Therefore, it is not unexpected that these changes were not observed. It was also noted that no histopathologic changes were seen in the NTP study to support the adrenal weight changes. The panel identified a LO(A)EL for adrenal effects of 32 mg/kg-day from the NTP 13-week rat study and 28 mg/kg-day from the 13-week mouse study, but there was not a clear consensus on whether the effect was adverse. However, since there was no dose-response, there was unanimous consensus that this is not the critical effect.

One panel member noted that absolute and relative liver weights were increased at doses of 65 mg/kg-day and higher in female rats, so that (based on a statistically significant increase) the LOAEL for this effect would be 65 and the NOAEL would be 32 mg/kg-day. Another panel member noted the absence of a clear dose-response in the females, and recommended a LOAEL of 130 and a NOAEL of 65, again based on a statistically significant increase. Another member indicated that it is not clear if this effect should be considered to be adaptive or adverse. However, since there is no indication of enzyme induction, there is nothing to suggest that the change is adaptive. Another member indicated that all of the clinical chemistry is normal, and questioned whether the effect was clinically significant. A different person noted that liver changes can occur without accompanying changes in clinical chemistry, so that the absence of clinical chemistry is not informative. Other panel members replied that the effect should be considered adverse, so that the overall assessment is health protective. One panel member asked about the mechanisms by which liver weight could be increased without accompanying hypertrophy or hyperplasia. A different panelist replied that the effect was probably an early mitogenic response. This person noted that liver foci were observed in the study; however, there was not a dose response for the foci or a comparison of volume between the treated and control animals. Overall, the panel concluded that liver weight changes were not the critical effect.

Methemoglobinemia. Some human case reports suggest that methemoglobinemia is an effect of resorcinol. One panel member asked the document authors if there was any additional information, other than the few human case studies. In addition, panel members asked what doses resulted in this effect in children. AMEC answered that they were not aware of other studies. Methemoglobinemia was observed following dermal treatment with ointment containing 5-12.5% resorcinol; typical ointments contain 0.5 to 1% resorcinol. One panel member suggested that the document authors attempt to quantify the doses in the document by estimating treated surface area and application rate.

The information in humans is supported in part by the NTP study, which reported sporadic (not dose-related and not statistically significant) increases in methemoglobin in male and female rats in the 13-week study. However, another panel member pointed out that NTP did not find any significant differences in clinical chemistry. One panel

member noted that resorcinol does have some activity inhibiting iodine uptake, and that other similar acting compounds, such as nitrate, also cause methemoglobinemia. The panel questioned whether resorcinol causes oxidative damage, and noted that other potent oxidants also caused methemoglobinemia. One panel member noted that resorcinol reacts with iron, so it has some oxidative properties. However, the panel concluded that one would expect to see effects in other hematology parameters if methemoglobinemia is an issue and those effects were not observed.

Another person noted a trend in increased cholinesterase in the NTP study and asked if this could be related to the CNS effects. However, a different panel member replied that this was most likely red blood cell cholinesterase, and not related to CNS effects. The panel concluded that methemoglobinemia is a potential critical effect, and one of particular interest for children, but that are no data to estimate a dose response.

Developmental and Reproductive Toxicity. Three developmental toxicity studies in rats (DiNardo et al., 1985; Kavlock, 1990; Hazleton, 1982a**)** and one developmental toxicity study in rabbits (Hazelton 1982b) were reviewed and discussed by the panel. One panel member noted that no reports of CNS clinical observations and no fetal abnormalities were reported in any of the rat studies. One panel member noted that if the CNS effects observed in other studies were due to the gavage dosing, then one would expect to see them in these studies too. Maternal weight gain was affected in the DiNardo study, but not the other two rat studies. The Hazelton study showed a slight increase compared to negative controls in skeletal malformations at the high doses of 250 mg/kg-day compared to negative controls, but this increase was not as marked as that observed in the positive controls. The slight increase was not statistically significant, but it was not clear if the statistical analysis considered individual pups or litter incidence. The study authors considered this increase to be incidental. One panel member asked whether the timing of the dosing (GD 9-15 in two studies and GD 11 in the other) was sufficient to cover all the critical periods for thyroid development. Another panel member replied that while rat thyroid gland development starts around GD 9, first fetal synthesis of thyroid hormone and development of neurobehavioral function happens after GD 15. Therefore, it is possible that these studies would have missed some time periods for development that might be affected by resorcinol. One panel member noted that the rabbit study, which was similar in design to the rat studies, did not demonstrate CNS clinical observations or fetal effects. However, this panelist questioned the sensitivity of the study. Only 50% of the matings resulted in pregnancy, so there were a low number of dams. In addition, only 2 malformations were observed in the positive controls, so the study is inadequate to evaluate the potential for developmental toxicity. This fact should be noted in the resorcinol RfD report. In general, the panel recommended that the RfD report include a more critical evaluation of the design of the developmental toxicity studies, as well as the reported results.

Another panel member reviewed the multigeneration study in Sprague Dawley rats (Burnett and Goldenthal, 1988). It was noted that in this study, resorcinol was present in 4 of the 6 hair dye formulations tested. However, there was no resorcinol only group – every formulation containing resorcinol also contained other compounds. Therefore this

study is not relevant to the resorcinol RfD, and this panel member suggested that it be given less emphasis in or excluded from the RfD document.

One panel member commented that the available developmental/reproductive toxicity studies were designed to evaluate gross developmental and reproductive toxicity, but not thyroid or developmental neurotoxicity. Other panelists commented that even though the studies were not specifically designed to see thyroid developmental toxicity, the studies as designed would have detected some effects on the thyroid. For example the visceral exam would have detected obvious defects in the thyroid gland. In addition, decreased fetal weight or delayed fetal development is associated with thyroid defects and these effects were not observed.

Another panel member asked if there were any data to indicate that resorcinol crossed the placenta, suggesting that if it is rapidly cleared, then there may have been no fetal exposure. A different panelist replied that the physical/chemical properties of resorcinol, as well as data on related chemicals, indicate that resorcinol would cross the placenta, but there are no data to support this conclusion.

The panel reached unanimous consensus that no NOAEL or LOAEL could be identified for developmental/reproductive toxicity effects. While the panel concluded that these studies need further critical evaluation and write-up before final conclusions could be drawn, the panel concluded that these studies suggest that resorcinol is not likely to be a reproductive or developmental toxicant in rats at doses of concern for other critical endpoints. The rabbit study is inadequate to draw any conclusions. The panel also indicated several data gaps that should be acknowledged for both reproductive and developmental toxicity, including lack of data on male reproductive effects, lack of evaluation of late gestation periods and early neonatal periods, and lack of developmental neurotoxicity evaluation.

Dermal Contact Sensitivity. One panel member indicated that there is clearly a large literature base in humans, including occupational studies, suggesting that resorcinol causes contact sensitivity. For example, studies in hairdressers and others who use hair dyes indicate that 1% of the population has contact dermatitis. However, there is no quantitative information on what dose is a sensitizing dose. One panel member asked if it was possible to extrapolate the dermal effect to an oral exposure. The first panelist replied that there were not enough data to do that. However, this person acknowledged the importance of considering this effect because of the possibility of bathing in water containing resorcinol and noted that resorcinol solutions of 1% or less generally do not result in contact sensitization. Other panel members noted that due to the properties of both resorcinol and the skin, any contact sensitization is likely to occur as a portal-of-entry effect rather than a systemic effect following dermal exposure. This means that contact sensitization may be a concern for dermal exposure, and should be considered in setting drinking water levels of resorcinol, but that contact sensitization is not of concern for the oral RfD.

Conclusions. After an in-depth, point-by-point discussion of the potential critical effects identified by the animal studies, the panel unanimously concluded that the weight-of-evidence points to thyroid effects as the critical effect for resorcinol. Thyroid effects are seen in humans, in animals following continuous exposure, and are not seen following bolus dosing, when sufficient time above a critical concentration is not achieved. Therefore the data give a cohesive story that thyroid effects are real. There is a plausible mode of action, the data demonstrate a level of consistency and there are good reasons for not seeing effects in the animal studies that did not demonstrate thyroid effects.

The CNS effects were not appropriate as the basis of a RfD because they appeared to be an acute response, and perhaps related to different kinetics resulting from gavage dosing. A majority of panel members concluded that mortality was not an appropriate endpoint on which to base a RfD. This conclusion was not unanimous, however, since other panelists indicated that a good dose-response relationship and a steep dose-response curve provide more comfort that the NOAEL for mortality in the NTP study really is a NOAEL overall. The panel identified a LO(A)EL for adrenal effects of 32 mg/kg-day from the NTP 13 week study, but there was not a clear consensus on whether the effect was adverse. However, since there was no dose-response, there was unanimous consensus that this is not the critical effect. Similarly, the panel identified an effect level for absolute and relative liver weight increase at 65 mg/kg-day; although there was no consensus on whether this effect was adverse. The panel concluded that methemoglobinemia is a potential critical effect, and one of particular interest for children, but that are no data to estimate a dose response. The panel reached unanimous consensus that no NOAEL or LOAEL could be identified for developmental/reproductive toxicity effects. Based on these studies, the panel concluded that resorcinol is not likely to be a reproductive or developmental toxicant in rats at doses of concern. However, the panel also noted that data gaps (lack of data on male reproductive effects, lack of evaluation of late gestation periods and early neonatal periods, and lack of developmental neurotoxicity evaluation) need to be addressed. Finally, the panel concluded that contact sensitization may be a concern for dermal exposure, and should be considered in consideration of drinking water levels of resorcinol, but that contact sensitization is not of concern for the oral RfD.

Dose Response

In evaluating dose-response issues, the panel considered the following charge questions:

1. What is the appropriate point-of-departure for a resorcinol RfD?
    - Is a NOAEL based on a dose that doesn't result in increased mortality the appropriate POD?
    - Can a different, appropriate NOAEL or LOAEL be identified?
    - Are any data amenable to modeling with benchmark dose software in order to estimate a POD?

2. Comment on the uncertainty factors applied to derive the RfD for resorcinol. Would you change the value of any UF applied by the authors? Would you use additional factors not applied by the authors?

In order to focus this discussion, the Chair started by asking the panel if they believed that the data on resorcinol were sufficient to develop a RfD. The panel reached consensus, although not unanimous, that a RfD could be developed with the existing data and that the remaining uncertainty could be addressed with the use of uncertainty factors. One panel member disagreed, suggesting that additional studies be completed in order to have confidence in a RfD. This person indicated that the existing database suggests thyroid effects that are not adequately characterized. An occupational study that linked thyroid status with occupational exposure level would provide the database necessary to describe for resorcinol the exposure relationship to thyroidal effect. In addition, a multi-dose, rat subchronic drinking-water study of resorcinol that completely examines the thyroid is important. Therefore, if a RfD were developed with the existing data without conducting these additional studies to describe the thyroid effects completely, then the RfD would not adequately reflect the potential for thyroid effects.

Point of Departure

The Chair opened this discussion by reminding the panel of the definition of critical effect as "The first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases." One member expressed the opinion that, while thyroid toxicity seems to be the "critical effect", there are no good quantitative data to develop a point-of-departure. The two animal studies (Cooksey and Seffner) that most clearly demonstrate thyroid effects are inadequate to use as the critical study and can only be used as supporting studies. This panelist expressed the opinion that the mortality data from the NTP was an appropriate choice for a point-of-departure because there are dose-response data, the dose-response curve is steep, and there are supporting NOAELs in the database. Using mortality as the point-of-departure, the NOAEL would be 100 mg/kg-day in female rats and 112 mg/kg-day in males. The frank effect level (FEL) would be 225 mg/kg-day in males and 150 mg/kg-day in females.

Another panel member disagreed, stating that choosing mortality for the point-of-departure presumes that one does not believe that there are adverse effects at lower doses. The database demonstrates that many effects are occurring at doses lower than the mortality NOAEL. Other panel members agreed, stating that the POD should be related to all relevant health effects and that selecting mortality as the POD ignores effects that are occurring at lower dose levels. The panel reached consensus, although not unanimous, that mortality is not an appropriate endpoint for the point-of-departure.

One panel member suggested that the POD should be based on a weight-of-evidence approach, and the WOE suggests that thyroid toxicity is the critical effect. In addition, this person argued that there must be a good biological argument for the final choice of POD that is well described in the document. The final choice of POD should be relevant to humans, have a plausible mechanistic basis and fit the best with the kinetic information

that is available. Mortality and the CNS effects do not satisfy these requirements because mortality is a frank effect and the CNS effects are most likely an acute effect due to gavage dosing. The goal of risk assessment is to select the lowest NOAEL/LOAEL boundary as the point of departure. The studies that identified thyroid effects are probably at the NOAEL/LOAEL boundary and it is clear that if one prevents thyroid effects, then all other effects will be prevented too. Another panel member agreed, noting that all of the identified NOAELs appear to be within a factor of 10 and a weight-of-evidence approach suggests a fairly consistent POD. Other panel members agreed that thyroid effects appear to be the critical effect, at least qualitatively. One person stated that using the thyroid effects as the POD is protective and is the most biologically relevant, scientifically defensible endpoint because it is consistently observed, even if the dose-response is weak. Some panel members considered the dose-response information for the thyroid effects to be too incomplete to make the thyroid effects the POD.

One panel member mentioned that none of data sets were amenable to benchmark dose modeling. However, the panel did not have time for a complete discussion of this issue.

The panel discussed each possible POD with its associated uncertainty factor (summarized in Table 2). The panel eventually reached unanimous consensus that the thyroid effects were the critical effect, and that the appropriate POD is the 10 mg/kg-day effect level identified by the Cooksey and Seffner studies. However, a consensus was not reached on whether this effect level is adverse, or whether it should be considered an effect level in a sensitive population. The panel acknowledged the uncertainties associated with using these studies, but considered that these uncertainties could be addressed with appropriate uncertainty factors.

Uncertainty Factors

Uncertainty factors are used in a non-cancer risk assessment to account for inherent variability in data or in situations where key data are missing. Generally, five areas of uncertainty are considered when developing a RfD:

UF_A – accounts for variability between species and is used when extrapolating from and animal study

UF_H – accounts for the inherent variability in human populations and is used to protect sensitive individuals

UF_S – accounts for uncertainty in extrapolating from a less-than-lifetime study, when the database does not contain any information regarding lifetime exposure

UF_L – accounts for uncertainty in basing a RfD on a LOAEL rather than a NOAEL

UF_D – accounts for the lack of key studies in the database

The panel first discussed the document author's choice of uncertainty factors that were applied when mortality was selected as the critical effect. The panel then considered the appropriate choice of uncertainty factors to be applied when the POD is based on thyroid effects.

The panel first discussed which uncertainty factors would be appropriate if the RfD was based on a mortality endpoint. One panel member indicated that a UF_L should be used to account for using a severe endpoint. Another person suggested using a modifying factor of 10 to account for severity. In addition, a panel member suggested that UF_D should be 10. However, since the panel had earlier concluded that mortality was not a suitable endpoint for the POD, it did not reach any conclusions regarding uncertainty factors for this endpoint.

A panel member suggested uncertainty factors appropriate for using a LOAEL of 10 mg/kg-day for thyroid effects. This person suggested using a UF_L of 10. Another panel member suggested 3, since the effect could be a minimal LOAEL. The first panelist agreed that a UF_L of 3 to 10 would be acceptable. This panelist suggested a value of 1 for UF_A because the toxicokinetics of resorcinol are likely the same between animals and humans, but rats are more sensitive dynamically. This person suggested a UF_H of 3, because the rat represents a sensitive human population. The rat is not representative of an adult human, but a 3 is still needed to account for pregnant women, fetuses and neonates. UF_S was suggested to be 1 and UF_D was suggested to be 10.

A different panel member suggested a different set of UFs for using the thyroid effects as the POD. While this panelist agreed that 10 mg/kg-day is the POD, this person designated this value as a NOAEL. Therefore, the UF_L would be one. This panelist suggested UF_A of 10, but a UF_H of 3 because the effects are not really adverse, but a precursor effect. UF_S was suggested as 3 because no long-term studies demonstrated whether thyroid effects would progress with time. UF_D was suggested as 3 to 10.

One panel member asked if there was any data on TPO variability in children compared with adults. Another panelist replied that the homeostatic mechanisms appear to be similar in children and adults, since all can maintain T4 levels.

The Chair then polled the panel for their opinions on the appropriate uncertainty factors for use with the thyroid POD.

UF_H. Two panel members indicated a value of 10 was appropriate for this factor; 7 panel members indicated that a value of 3 was appropriate. One panel member indicated that a value of 3 was appropriate for UF_H because of issues related to need for free T4 in the second trimester. Another panel member suggested that the document better describe potential sensitive subpopulations, such as the elderly or people with compromised renal clearance.

UF_A. Two panel members indicated a value of 3 was appropriate for this factor, because there is no information on the dynamic differences between animals and humans. One panel member also indicated this choice reflected the poor quantitation in the Cooksey and Seffner studies as well as the lack of information on quantitative differences between animals and humans. Seven panel members indicated a value of 1 was appropriate for this value since rats seem to be more sensitive than humans to thyroid

effects. In addition, the rats in the Cooksey study were fed a low iodine diet and therefore represent a sensitive model for thyroid effects.

UF_S. Two panel members indicated a value of 1 was appropriate for this factor because there are chronic studies that do not show progression of effects and because resorcinol is cleared quickly. Seven panel members suggested that a value of 3 was appropriate because the critical effects were only demonstrated in subchronic studies and the chronic study was incomplete for thyroid evaluation. However, a full 10 was not needed due to the rapid clearance and lack of progression mentioned above.

UF_L. Three panel members suggested that a value of 1 was appropriate for this factor because the thyroid effects observed were adaptive, not adverse; alternatively these effects were precursors to an adverse effect, but were not adverse by themselves. Six panel members indicated that a value of 3 was appropriate because the effects observed could be considered a minimal LOAEL. Of these 6 panel members, two indicated that the value of this factor could go as high as 10.

UF_D. One panel member indicated a value of 1 was appropriate. One panel member indicated a value of 3 was appropriate. Two panel members indicated that a range of 3 to 10 was appropriate and five panel members felt that a value of 10 was appropriate. These panel members indicated that although the database for resorcinol was good, there was limited evaluation of the potential for thyroid effects. In addition, the database is missing a good multi-generation study, complete reproductive toxicity evaluation (no data in males), and a neurotoxicity study. Other panel members indicated that a 10 was warranted due to the poor quality of the existing studies of thyroid effects and the need for more studies.

With these various combinations, the overall composite uncertainty factor proposed by the panelists ranged from 100-1000. Only one panel member proposed a combination of factors that resulted in a range of 300-1000. The remaining panelists proposed combinations that resulted in composite factors of either 100, 300, or a range of 100-300. The panel recommended that the document expand on the documentation and justification for the choice of uncertainty factors.

In conclusion, the panel reached unanimous consensus that thyroid effects are to be considered the critical effect. The Cooksey and Seffner studies are to be considered as co-critical studies, supporting a point-of departure of 10 mg/kg-day. Using the composite uncertainty factor of 100-300, as discussed above, the resulting RfD for resorcinol ranges from 0.03 to 0.1 mg/kg-day.

Although the panel recognized that this value is similar to the value derived by the document authors, it concluded that this value has a more biologically plausible and scientifically defensible basis than a RfD based on mortality.

Conclusions

The panel reached consensus that clearly enough data exists on resorcinol to develop a RfD; however, more of that data needs to be included in the document in order to support the RfD and allow the reader to independently evaluate its appropriateness. Specifically, the panel concluded that the resorcinol document should include more data on the mode-of-action and the mechanism of resorcinol toxicity. In addition, the panel recommended that the document authors conduct a targeted literature search using key words specific to mode-of-action issues or to specific target organs such as thyroid. The panel also recommended that the document more completely and thoroughly review all pertinent studies in the database, even if the studies are redundant with the information already included. Finally, the panel recommended that the authors review all primary studies, particularly key studies on toxicity and mode-of-action issues.

The panel reached unanimous consensus that sufficient human data exist to reach the hazard identification conclusion that resorcinol has the potential for thyroid effects in humans. However the panel also concluded that there was insufficient information presented in the document to identify other potential target organs in humans. The panel recommended that if the remaining two TOMA (1978, 1982) studies could be obtained, they should also be reviewed in the document. The panel also reached unanimous consensus that there are insufficient human data to draw conclusions regarding the dose response for thyroid effects in humans.

After an in-depth, point-by-point discussion of the potential critical effects identified by the animal studies, the panel unanimously concluded that the weight-of-evidence points to thyroid effects as the critical effect for resorcinol. Thyroid effects are seen in humans, in animals following continuous exposure, and are not seen following bolus dosing, when time above a critical concentration is not achieved. Therefore, the data give a cohesive story that thyroid effects are real. There is a plausible mode of action, the data demonstrate a level of consistency and there are good reasons for not seeing effects in the animal studies that did not demonstrate thyroid effects. For reasons discussed in detail in the section on animal studies, the panel concluded that mortality, CNS effects, organ weight changes, developmental/reproductive effects, and contact dermatitis were not critical effects for the development of an oral RfD. The panel noted that methemoglobinemia could potentially be a critical effect, but there are no data to estimate a dose response.

The panel made several recommendations that focused on strengthening the discussion of critical effect in the resorcinol document. The panel recommended that the document include a table that clearly identifies the NOAEL or LOAEL for each study/endpoint, including the NOAEL identified for multiple key endpoints in the NTP studies. The table should convert all doses to units of mg/kg-day, include the shorter-term studies, and organize the data by target organ. The panel recommended that the document authors review the Gautgonis and Walton (1962) study in detail to provide additional information about the potential for CNS effects. In addition, the panel recommended that the document include a more critical evaluation of the design of the developmental toxicity

studies, as well as the reported results. The document should acknowledge the data gaps for both reproductive and developmental toxicity, including lack of data on male reproductive effects, lack of evaluation of late gestation periods and early neonatal periods, and lack of developmental neurotoxicity evaluation.

The panel recommended that the document expand the discussion of the point-of-departure to describe a good biological argument for the final choice of POD. The discussion should demonstrate how the final choice of POD is relevant to humans, has a plausible mechanistic basis and fits the best with the kinetic information that is available.

Although the panel members had wide-ranging opinions on the values for individual uncertainty factors in each of the five areas of uncertainty, the panel reached consensus that a composite uncertainty factor with a range of 100-300 would be protective of human health. The panel recommended that the document expand on the discussion of rationale behind the choice of uncertainty factors.

In conclusion, the panel reached unanimous consensus that thyroid effects are to be considered the critical effect. The Cooksey and Seffner studies are to be considered as co-critical studies, supporting a point-of departure of 10 mg/kg-day. Using the composite uncertainty factor of 100-300, as discussed above, the resulting RfD for resorcinol proposed by the panel ranges from 0.03 to 0.1 mg/kg-day.

The panel unanimously agreed that it should review a revised document, which incorporates the conclusions of the panel and provides additional narrative support as discussed above in this section before the panel would approve this RfD for inclusion on ITER.

Suggestions from Individual Panel Members

Many individual panel members made specific suggestions for improvements to the resorcinol document. While these suggestions do not carry the weight of panel consensus, they have been included in the report to provide additional guidance to the document authors as they consider revisions.

- One panel member suggested that data from the IARC (1999) document on resorcinol should have been described in the document, particularly some dietary studies described in the IARC document that were not reviewed by the authors. Other panel members suggested the TLV documentation (ACGIH, 1992) as a secondary source that contains primary studies that are pertinent to the development of a RfD for resorcinol, including some pivotal kinetics studies that address the issue of vehicle (oil vs. water) and dosing strategy (gavage vs. drinking water) pertinent to resorcinol.
- One reviewer indicated that a more detailed analysis of the available kinetics studies was needed in order to determine whether the data from the subcutaneous studies could support the oral studies.

- One panel member suggested contacting the NTP and obtaining the raw data and notes to clarify the incidence of CNS clinical observations. However, other panelists also acknowledged that this will be a labor-intensive exercise, and may not provide any additional information on the CNS effects.
- A panel member suggested that the extensive human data regarding the potential for contact dermatitis following dermal exposure to resorcinol that should have been included in the RfD document.
- Another panel member suggested that the authors review the older literature on resorcinol because it could be very informative about the effects in humans.
- One panel member suggested that the document authors attempt to quantify the doses received by subjects in the human studies in the document by estimating treated surface area and application rate.
- One panel member suggested that the three-generation study was not relevant to the resorcinol RfD because it did not include a resorcinol-only treated group. Therefore, this study should be given less emphasis in or excluded from the RfD document.
- One panel member suggested that the document include additional data about other, structurally similar, phenolic compounds with structural similarity. These data would give insight to the neurotoxicity issues and would help provide a stronger basis for supporting the critical effect. They would contribute to the weight-of-evidence (WOE) for choosing a point of departure.

- One panel member suggested that additional studies, including a thyroid study in animals and an occupational study, would provide better dose-response data on the thyroid effects and improve confidence in a RfD.

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Table 1. Summary of Potential Critical Effects for Resorcinol

Effect	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Study	Comments
CNS	88	100	Rat gavage and subcutaneous	Endpoint is an acute effect that may not be relevant to human exposure
Developmental Toxicity	Not identified	Not identified	Rat oral	No evidence of dev. toxicity, but data gaps exist
Relative brain weight changes	Not identified	Not identified	Rat gavage, 13-week	Due to body weight changes, determined to be not adverse
Adrenal gland weight changes	NA	32, rat 28, mouse	Gavage, 13-week	
Liver weight changes (rel and abs)	32, female 65, male	65, female 130, male	Rat gavage. 13-week	No consensus of adversity of effect. Effect not seen at 15 month interim sac.
Methemoglobinemia	Not identified	Not identified		No data available to estimate dose.
Thyroid	5-10	---	Rat drinking water, short-term	Dose level likely at the NOAEL/LOAEL boundary. Rats on low I diet in one study, represent a sensitive subpopulation
Contact dermatitis	Not identified	Not identified		No data from oral exposure
Mortality	100, female 112, male	150, female 225, male	Rat gavage, 2-year	

Table 2. Summary of Potential PODs and UFs

POD (mg/kg-day)	UF_H	UF_A	UF_S	UF_L	UF_D	MF	Composite UF	RfD (mg/kg-day)
71 Mortality, NOAEL[1]	10	10	1	1	10	1	1000	0.07
71 Mortality, NOAE[2]L	10	10	1	1	10	10	10,000	0.007
32, Organ weight changes, NOAEL	10	10	3	1	10	1	3,000	0.008
10, Thyroid, LOAEL[3]	3	3	3	1	10	1	300	0.03
	3	1	3	1	10	1	100	0.1
	3	1	1	3-10	10	1	100-300	0.03-0.1
	10	3	3	3-10	1	1	300-1000	0.01-0.03
	3	1	3	3	3-10	1	100-300	0.03-0.1
	3	1	3	3	3	1	100	0.1
	3	1	1	3	10	1	100	0.1
	10	1	3	1	10	1	300	0.03
	3	1	3	3	3-10	1	100-300	0.03-0.1

1. The POD, UFs, and RfD proposed by the document authors.
2. Modifying factor to account for severity, proposed by some panel members.
3. The panel reached unanimous consensus on POD for thyroid effects. However, each panel member suggested a different combination of UFs. Each different combination is shown in table.

Appendix A
Conflict of Interest Disclosures

Peer Review of
"Description of a Proposed Reference Dose for Resorcinol"
March 18 and 19, 2003

An essential part of panel selection is the identification and disclosure of conflicts of interest to ensure credible results and confidence in the panel's recommendations. Prior to selecting the panel, *TERA* determined that a conflict of interest that would prevent a person from being considered for the panel would include authorship or previous review of this document; anyone employed by the Sponsor or AMEC, the organization that developed this document; anyone currently receiving financial support, e.g., thru contracts or grants, from the Sponsor or AMEC; and those with direct personal financial interests in the outcome of the review. Each panel member was asked to complete a questionnaire to determine whether his or her involvement in certain activities could pose a conflict of interest or could create the appearance that the peer review lacks impartiality. An answer of "yes" to any of these questions does not necessarily mean that the individual has a conflict of interest, but that additional information needed to be gathered. *TERA* staff carefully reviewed these forms and discussed the answers with the panel members to ascertain whether conflicts of interest might exist. *TERA* determined that none of the panel members has a conflict of interest as defined above. However, some of the panel members have past experience with either resorcinol or the Sponsor or Author that may be perceived as a conflict. Information from each panel member relevant to these activities is summarized below to make sure the other panel members and the public are fully aware of these activities.

While these activities are not conflicts of interest, they are disclosed here as they may create an appearance that a panel member lacks impartiality because they have previously reached conclusions on similar issues or questions. The panel members were asked to objectively evaluate the materials for this review, and use this information, along with their personal knowledge and expertise, to independently reach conclusions on this document. The panel was also informed that if a panel member felt at any time that another member was trying to influence the outcome of the review in an inappropriate way, he or she should bring this to the attention of the Chair so that it may be addressed. These disclosures were discussed by the panel at the beginning of the meeting. The panel reached unanimous consensus that no panel member had a conflict that would prevent him or her from serving on the panel.

The peer reviewers have donated their time and talents to this effort. They were selected based upon their expertise and qualifications and are employed by many types of organizations. *TERA* strives to create a balance of expertise and affiliations for each meeting. However, individual peer reviewers were representing their own expertise and views, not those of their employer, of any group who may have nominated them, or any group with which they may be associated. This peer review panel was a distinguished group, with many years experience in a wide range of disciplines.

Dr. Lynne Haber, Chair. Toxicology Excellence for Risk Assessment. Dr. Haber is the Manager of *TERA*'s Risk Assessment Research Program. She has authored numerous RfD documents, including EPA's IRIS assessment for phenol. She has served on several peer review panels, including the panel that reviewed the benzene noncancer risk assessment for U.S. EPA. Dr. Haber was selected for the panel based on her extensive risk assessment expertise, experience with peer review panels, and knowledge of phenol metabolism (resorcinol and phenol are metabolized via similar pathways). Dr. Haber has no personal conflicts of interest; although she has a corporate conflict in that other TERA employees conducted a review of an earlier of this resorcinol document. Dr. Haber was not involved in this earlier review; has not been informed of the content of the earlier review, and appended a memo documenting this to her COI questionnaire. In addition, the Director of TERA attached a memo to the COI questionnaire indicating that the outcome of a review chaired by Dr. Haber is not a factor in evaluating her performance.

This information was disclosed to the panel on March 6, 2003, prior to the peer review meeting; the panel was asked to reach consensus on whether Dr. Haber could serve as the panel chair without compromising the independence of the peer review. One panel member expressed concern with the appearance of conflict and suggested that Dr. Haber facilitate the meeting, but not be polled for consensus. Another panel member was concerned that if the Sponsor's primary goal is to have its value included on *TERA'*s *ITER* database, this would constitute an ongoing business relationship. Thus, any *TERA* staff member serving on the panel would have the appearance of being biased. This panelist's concern was lessened when it was made known that *ITER* is a free Internet database that compares risk levels developed by organizations as environmental guidance. In addition to regulatory agencies, any independent value can be included on *ITER* if it has undergone a rigorous independent peer review. The remaining seven panel members had no concerns about Dr. Haber serving as panel chair. The first two members indicated that they could support the majority position; the panel reached unanimous consensus that Dr. Haber will serve as panel chair.

Dr. John Christopher. California Environmental Protection Agency. Dr Christopher is a Toxicologist with CalEPA's Department of Toxic Substances Control. He has conducted risk assessment at the state level for several years, and is certified as a Diplomat of the American Board of Toxicology. In addition, Dr. Christopher has extensive experience serving on peer review panels, including a recent panel convened to review a health benchmarks document developed for the World Trade Center clean-up. Dr. Christopher was selected for the panel due to his expertise in risk assessment his experience as a peer reviewer. He did not have any conflicts.

Dr. Michael Kamrin. Michigan State University. Dr. Kamrin is a Professor Emeritus from MSU's Institute of Environmental Toxicology and a consultant in Toxicology and Risk Analysis. He has published widely on a variety of risk assessment topics such as developing fish consumption advisories, evaluating the health risks posed by hazardous wastes, and assessing the risks of pesticides. Dr. Kamrin was selected for the panel based on his risk assessment expertise and has no conflicts of interest. A project completed by

Dr. Kamrin in 2001 for Scientific Certification Systems was partially funded by the Hickson Corporation. However, since the project was not ongoing, was not related to resorcinol, and was not related to the BCAS, *TERA* determined that this activity does not constitute a conflict. However, this information was disclosed during the meeting.

Dr. Elaina Kenyon. U.S. Environmental Protection Agency. Dr. Kenyon is a toxicologist with EPA's National Health and Environmental Effects Research Laboratory. She has conducted research into the metabolism of phenolic compounds and was select for the panel based on this expertise. She has no conflicts.

Dr. Steven Lamm. Consultants in Environmental and Occupational Health, Inc. Dr. Lamm is the President and Chief Scientists of CEOH, Inc. He is an epidemiologist and occupational medicine physician. He has conducted numerous epidemiology studies, including several evaluating the potential for thyroid effects in populations exposed to thyroid agents in the environment. He was selected for the panel based on his experience evaluating epidemiology studies of thyroid agents. Dr. Lamm provided the following information regarding potential conflict of interest:

> "There are two areas where a "Conflict-of-Interest" perception might arise concerning myself, Beazer, and Resorcinol.
>
> 1. From 1977-1980, my employer, Tabershaw Occupational Medicine Associates [TOMA], served as the occupational and environmental consultants to Koppers Company, the predecessor of Beazer, Inc. I was the principle director of that project under Dr. Tabershaw. In 1981, when I formed Consultants in Epidemiology and Occupational Health, Inc., I became a direct consultant to Koppers, extending the analysis of previous epidemiological studies, particularly concerning cancer risk in coal-tar plant workers. I recall attending an FDA hearing on dermatological coal-tar preparations at that time for Koppers, though I no longer remember the specifics of that meeting. My recollection is that the issue related to carcinogenic risk from dermal applications rather than any thyroidal issues. The consultancy ended before or at the time that Beezer took over. About two years ago, I was contacted by Beazer Corp. concerning work that had developed at TOMA with Koppers on projects whose initiation I had participated in. I was prepared to testify at a trial on that matter last April, but I was not called to the stand. The issue related again to the interpretation of occupational epidemiological studies on coal-tar plants. There was no mention of resorcinol in these discussions.
>
> 2. I had been asked to update the chapter on environmental goitrogens that Dr. Eduardo Gaitan had written in the first edition of Braverman's "Diseases of the Thyroid". Dr. Arnold Engle and I did so, and this chapter now titled "Goitrogens in the Environment" was published in January 2003 in the second edition of Braverman's "Diseases of the Thyroid". I have attached a copy of the uncorrected proof copy. You will find the discussion of Resorcinol at the top of page 314. While these paragraphs are included in document of which I am a co-

author, this section had been written by Dr. Eduardo Gaitan and does not differ from his version in the first edition.

Neither of these issues should influence my consideration of the Resorcinol risk assessment, since I have no on-going work with Beazer (nor foresee any) and I have personally never made any assessment concerning resorcinol."

TERA determined that these activities are not a conflict because they are not currently ongoing.

Dr. Randall Manning. Georgia Department of Natural Resources. Dr. Manning is the Coordinator of GA DNR's Environmental Toxicology Program. He is a toxicologist who is certified as a Diplomate of the American Board of Toxicology. He has conducted research on the metabolism of environmental contaminants and been extensively involved with risk assessment of environmental contaminants at the State level. In addition, he has experience serving on ITER peer review panels. Dr. Manning was selected for the panel based on his risk assessment and peer review panel expertise. He has no conflicts.

Dr. Patricia McGinnis. Syracuse Research Corporation. Dr. McGinnis is an Associate Director of SRC's Environmental Science Center. She is a certified Diplomat of the American Board of Toxicology and has worked on over 200 chemical assessments for various offices of U.S. EPA. In addition, Dr. McGinnis has experience serving on peer review panels, including an ITER panel reviewing acrylonitrile. She was selected for the panel based on her extensive risk assessment and peer review panel expertise. Dr. McGinnis has no personal conflicts of interest. SRC has prepared risk assessment documents on resorcinol for U.S. EPA, including an ongoing project to prepare a hazard profile for resorcinol; Dr. McGinnis is not involved in this project. This work was disclosed to the panel; it was determined that this is not a conflict that would prevent Dr. McGinnis from participating on the panel.

Dr. Richard Pleus. Intertox, Inc. Dr. Pleus is the Founder and Director of Intertox. He is a toxicologist with special expertise in neurotoxicology. In addition, Dr. Pleus is the co-author of a human study designed to quantify the thyroid effects of an environmental contaminant known to affect the thyroid in animal studies. As such, he has extensive experience in the environmental risk assessment of thyroid agents. Dr. Pleus was selected for the panel based on his expertise in neurotoxicology and risk assessment of thyroid agents. He does not have any conflicts.

Dr. Allan Susten. Agency for Toxic Substances and Disease Registry. Dr. Susten is the Assistant Director for Science in ATSDR's Division of Health Assessment and Consultation. He is a toxicologist who is certified as a Diplomate of the American Board of Toxicology. Dr. Susten has extensive experience developing Minimal Risk Levels (ATSDR's equivalent of the reference dose), with specific expertise in phenolic compounds. He was selected for the panel based on his experience with developing health benchmarks and phenolic compounds. At the meeting, Dr. Susten clarified that his agency works with the state health departments, including Pennsylvania. He had recently

received a mass e-mail from a colleague requesting toxicological information on resorcinol. He has not seen any documents related to this work, but may see them in the future. *TERA* determined that this was not a conflict because it was not related to the site in question.

Dr. Douglas Wolf. U.S. Environmental Protection Agency. Dr. Wolf is an Acting Branch Chief in EPA's National Health and Environmental Effects Research Laboratory. As a Veterinary Pathologist, Dr. Wolf has extensive experience in designing, conducting, and interpreting animal toxicity studies. Specifically, Dr. Wolf has experience in evaluating the thyroid pathology of an environmental contaminant known to have thyroid effects in animals. He was selected for the panel based on his expertise in animal study design and thyroid agents. He has no conflicts.