Report of the Peer Review Meeting on Resorcinol

Sponsored by
Beazer East, Inc.

November 17-18, 2004
Harrisburg, PA

Peer Review Organized by
Toxicology Excellence for Risk Assessment
(http://www.tera.org/peer)

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Independent Peer Review:
Resorcinol Reference Dose

On November 17-18, 2004, an independent panel of expert scientists met in Harrisburg, PA to review a risk assessment document that presented a reference dose (RfD) for resorcinol (CAS# 108-46-3). This peer review was conducted as a follow-up to an earlier peer review of the document that took place in March 2003. The follow up review had two purposes: to evaluate revisions made to the document following the first review and to evaluate a new study and the impact of this study on the resorcinol RfD.

1.0 Introduction

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 organized 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.

In 2003, an independent panel of expert scientists met in Cincinnati to review the original assessment that developed a reference dose (RfD) for resorcinol (CAS# 108-46-3). The panel reached consensus that enough data existed on resorcinol to develop a RfD; however, more of that data needed 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 appear redundant with the information already included in the existing risk assessment. Finally, the panel recommended that the authors review all primary studies, particularly key studies on toxicity and mode-of-action issues. A full report of the 2003 peer review meeting is available at http://www.tera.org/peer/RSC/Resorcinol%20Meeting%20Report.pdf .

Since the original peer review, a new subchronic dose range finding study of resorcinol, conducted on behalf of the Resorcinol Task Force (RTF), has become available. The Sponsors and Authors revised the original document to incorporate both the new study and additional work done in response to the panel's original comments. This follow-up peer review had two purposes. The first was to evaluate the new study and its impact on the resorcinol RfD proposed in March 2003. The second was to evaluate how well the revised document addresses the recommendations made by the panel at the 2003 meeting. The

follow-up peer review did not reopen discussion on issues that had resolution following the 2003 meeting and were not affected by the new study.

The same panel was reconvened for the December 2004 peer review meeting. This 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 of all panel members were encouraged. This report completely characterizes the entire discussion of the panel in order to inform readers who were not present at the meeting about the logic that the panel followed in arriving at its conclusions. In addition, this report presents the major conclusions and recommendations that were reached by consensus of the panel as a whole. In this case, unanimous consensus was reached for all conclusions and recommendations. Unanimous consensus means that everyone agrees, or can "live with" the decision. Therefore, this report represents the final outcome of the peer review.

2.0 Participants

The meeting was attended by the following parties:

Sponsor: Ms. Jane Patarcity, Beazer East, Inc.
Mr. Timothy Wolfson; Babst, Calland, Clements & Zomnir, PC

Author: Dr. Brian Magee, AMEC Earth and Environmental, Inc.
Ms. Jane Hamblen, 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, Retired
Dr. Douglas Wolf, U.S. EPA

* Due to personal circumstances, these panel members were unable to attend the meeting and were not able to provide pre-meeting comments.

Observers: Mr. Paul Ashford, Manager, Resorcinol Task Force
Mrs. Barbara Buchner, INDSPEC Chemical Corp.
Dr. Samuel Fang, Pennsylvania Department of Environmental Protection

Dr. Frank Welsch, Resorcinol Task Force, Study Director
Mr. Richard Wiedman, Eckert Seamans

3.0 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 completed a questionnaire to identify potential COI or bias issues. *TERA* staff discussed any potential conflicts with each reviewer prior to the meeting to determine if measures were needed to manage a potential conflict (or appearance of conflict). Each panel member 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}. *TERA* presented a plan for managing conflict of interest to the panel (see Appendix A).

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 Appendix A.

4.0 Author and Observer Presentations

Presentations were made by the Authors (AMEC Earth and Evironmental, Inc.) and by Observers from the Resorcinol Task Force (RTF).

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). The first part of the presentation functioned as a disposition of comments, informing the panel of how AMEC had responded to each of the comments from the 2003 review and where in the document the revisions could be found. The Authors then discussed the dose-range finding drinking water study conducted for the RTF by WIL Laboratories in 2003 subsequent to the 2003 resorcinol peer review. This study (WIL, 2003) was designed to determine appropriate doses for a full, guideline-compliant, two-generation study. In addition to reproductive performance, the WIL (2003) study evaluated thyroid effects (hormone alterations and histopathology) in adults and F1 pups as well as a developmental neurobehavioral battery in F1 pups. At the doses tested, resorcinol had no effect on reproductive performance, mortality, body weight, or organ weight. AMEC concluded that there were no statistically significant increases of TSH or statistically significant decreases in T3 or T4 in any groups. Minimal microscopic changes characterized as follicular hyperplasia were reported; however, these changes were not statistically significant when individual dose groups were compared to concurrent controls. A statistically significant increase in locomotor activity was observed in F1 males at postnatal day (PND) 61; no other effects were observed in any of the neurobehavioral evaluations. The study authors concluded that the increases in motor activity "were not conclusive evidence of a change in CNS status."

AMEC presented the results of further investigations they undertook to assess the significance of the locomotor activity and thyroid hyperplasia. The literature shows that neurotoxicologists consider motor activity tests to be reliable screening tools, but a single measure of activity is not considered sufficient evidence for neurotoxicity. AMEC noted that although the pairwise comparisons of motor activity were statistically significant, the significance was caused by one or two outliers. Regression analysis demonstrated the lack of a clear dose-related effect. Therefore, AMEC concluded that it agreed with WIL (2003) that resorcinol in drinking water at the doses tested did not cause neurotoxic effects.

AMEC conducted additional statistical analysis to determine whether a dose-dependent trend in thyroid hyperplasia might exist. Odds ratios indicated there were no significant differences between individual dose groups and controls. When all animals (interim sacrifice and terminal males, and females) were grouped to increase statistical power, the high dose group of 360 mg/L was statistically significantly different from control.

AMEC determined that WIL (2003) was the most appropriate choice of critical study because resorcinol was administered via drinking water, the most relevant route of exposure, and because it measured multiple endpoints, including a comprehensive evaluation of the thyroid. Average daily doses (ADD) were calculated over the course of the study for males and females in the high dose group of 360 mg/L, and an animal-weighted average ADD of the two male groups and the female group was selected as the point of departure. Therefore, a point of departure of 47.7 mg/kg-day was used; this dose could be considered either a NOAEL or a LOAEL depending on the interpretation of the extra statistical analysis. A composite uncertainty factor of 30-100 was applied. This factor consisted of a 1 for extrapolation from an animal study, a 3 to account for human variability, a 3 to account for use of a subchronic study, a 1 (or a 3 if the high dose is considered to be a LOAEL), and a 3 to account for database deficiencies (a two-generation study is not yet completed). The resulting RfD ranges from 0.5 to 2 mg/kg-day, depending on the selection of the UF_L uncertainty factor.

The Resorcinol Task Force has been sponsoring research about resorcinol, including the WIL (2003) study. The Manager of the RTF gave a short presentation about the RTF members and the research on resorcinol that has been conducted to date (see slides in Appendix C). The presentation also reinforced that the WIL (2003) study was designed to define the appropriate range of doses for the two-generation study. As such, the emphasis of the study was not to define a LOAEL or NOAEL. The RTF noted that the WIL (2003) study indicated that higher dose levels were necessary. The final dose levels selected for the guideline-compliant two-generation study were 120, 360, 1080, and 3000 mg/L. This two-generation study was started in December 2003 and the in-life phase ended in late September 2004. Although the full QA procedures associated with GLP studies were yet to be finalized, the preliminary results were indicating that there are no effects of resorcinol at even the highest dose tested. Accordingly, RTF believed the designation of 360 mg/L in WIL (2003) as a LOAEL to be highly conservative. The final report for the two-generation study is anticipated for the Spring of 2005.

5.0 Clarifying Questions

One panel member asked if the RTF could describe the exposure of the animals in the WIL study relative to necropsy. The RTF replied that, for the animals scheduled for thyroid analysis, exposure continued until the morning of sacrifice when blood was drawn, and that the sacrifice was random across dose groups. Another panel member asked the RTF to clarify the statement that the F1 animals did not have a separate exposure in drinking water and to explain that decision. The RTF indicated that most of the F1 animals were not exposed following weaning at PND 21 because the goal of the study was to evaluate prenatal effects of resorcinol in drinking water. He did note that a small group of F1 animals did receive drinking water exposure from PND 21 to 28, but these were the animals scheduled for thyroid analysis, not the behavioral tests. The purpose of extending the dosing for this group of animals was to maximize the possibility of detecting a change in thyroid chemistry.

Another panel member asked whether there was a blind pathology review. An RTF representative indicated that two different WIL pathologists looked at the slides, but there had not been an outside review to date. One panel member asked the Authors to further explain their statistical analysis of the thyroid. The Author replied that AMEC wanted to determine whether the increase in incidence would become statistically significant if the power was increased by combining the groups. One panel member asked the RTF to clarify the scheduled times for necropsy of the males. The RTF replied that half the males were sacrificed at 48 days and that the remainder of the males were sacrificed at 87 days.

The panel also asked some clarifying questions in response to the presentation by RTF. One panel member asked if the WIL (2003) study conducted morphometric measurements of the thyroid and brain. RTF indicated that no detailed measurements of brain had been done but that the study was conducted following guidelines for developmental neurotoxicity studies. This had involved light microscopy on brain regions where earlier studies with thyroid active positive control chemicals had found differences compared to controls. This panel member then asked about the basis for the determination of maximum tolerated dose in the study. The RTF indicated that the MTD was based on palatability, not on a biological effect and would better be described as a Maximum Palatable Dose. One panel member asked if the F2 generation in the ongoing two-generation study will be dosed in the same way as the F1. The RTF indicated that for F1 animals not selected as parents for the F2 generation, dosing stopped at PND 21, when the animals were weaned. Another person wanted to know if the two-generation study will look at thyroid peroxidase activity or methemoglobin formation. The RTF indicated that it would not. Finally, a different panel member asked about the ways that the two-generation study varied from the dose-range finding study (WIL, 2003). The RTF indicated that the full two-generation study uses higher doses than WIL (2003) and that it does not contain any evaluation of developmental neurotoxicity endpoints.

6.0 Discussion of Charge Questions

The panel discussed the resorcinol RfD document, focusing on issues highlighted by the Charge to Reviewers that was distributed to the panel before the meeting. The Charge is presented in Appendix D.

6.1 Charge Question 1:

> *A summary of the key recommendations from the 2003 peer review is attached. Has the document adequately addressed these issues? If not, please discuss areas that require additional work.*

The panel complimented the Sponsors and Authors on the excellent job they did in revising the document. The panel reached unanimous consensus that the Authors adequately addressed and responded to all recommendations made by the panel in 2003, and the panel recognized the significant additional work incorporated into the updated risk assessment.

One panel member indicated that the use of the word "continuous" to describe drinking water exposure was incorrect. Another panel member agreed, noting that, although drinking water is continuously available to rats, the rats only drink after dark. This is much different from the human studies that report effects of resorcinol following use of topical salves, which represent a true continuous exposure. AMEC said that the word "continuous" was used in the document to indicate that exposure was not by gavage. Panel members responded that this would be clear by using the description "drinking water exposure."

Therefore, the panel unanimously recommended that the word "continuous" should be removed from the resorcinol RfD document when referring to drinking water exposures.

6.2 Charge Question 2:

> *Is the design and conduct of the subchronic study conducted as part of the range-finding study for reproductive toxicity by WIL Laboratories (2003) adequate to evaluate resorcinol toxicity, particularly thyroid toxicity?*

One panel member began the discussion by stating that the WIL (2003) study is a well-conducted study; although, it is clearly a dose-range finding study with a primary purpose of identifying appropriate doses for the full two-generation study. This study addresses the question "does dosing through weaning result in irreversible effects on the brain?" However, since exposure was stopped before the behavioral tests were performed, there was a recovery period and so the study would not have detected any reversible changes. Generally, this panel member agreed that the study found no treatment-related effects of resorcinol following drinking water exposure at the doses tested. However, this panel member noted that in Table 101 of the WIL (2003) study the data presented show a statistically significant decrease in brain width in F1 females. WIL (2003) indicated this effect was not treatment related; however, this panel member indicated that there is no support for this statement. This panel member noted that it is important to determine whether this brain effect is real and

to provide supporting information to the conclusion that it is not treatment-related. Finally, this effect may suggest the need for additional developmental neurotoxicity (DNT) studies.

AMEC pointed out that neither brain weight nor length changed, so they agreed with WIL (2003) that the change in brain width was not a real effect.

The panel discussed the statistical test used to evaluate the brain width data. One panel member noted that, looking at the individual animal data, there do not appear to be any outliers. The panel decided that the statistical tests were adequate and the brain width effect is statistically significant. The panel then discussed whether the effect was treatment-related or biologically significant. The panel also discussed the biological significance of the brain width effect while evaluating whether the point-of-departure should be characterized as a NOAEL or LOAEL in response to charge question 4. For clarity in this report, the entire discussion on the biological significance of this effect is presented in Section 6.4.

The panel unanimously concluded that the WIL (2003) study was generally appropriately designed to evaluate resorcinol toxicity. In particular, the study design was adequate to evaluate the potential for direct thyroid toxicity (thyroid hormone changes and thyroid histopathology) in adult male and pregnant female animals exposed to resorcinol via drinking water and in neonates potentially exposed to resorcinol *in utero* and during lactation and in some cases through their drinking water. The WIL (2003) study design was not adequate to evaluate the link between thyroid toxicity and possible neurodevelopmental effects in offspring exposed after postnatal day (PND) 21 because the F1 generation animals undergoing behavioral tests up to PND 61 were not exposed to resorcinol after PND 21.

6.3 Charge Question 3:

> *Evaluate the biological and statistical significance of the thyroid effects in WIL (2003). Does the addition of the WIL (2003) study change the conclusion of the previous panel that thyroid toxicity is the critical effect for resorcinol? If so, what is the appropriate critical effect? If not, is WIL (2003) the appropriate choice of critical study?*

One panel member began the discussion by explaining that the following dose-response related thyroid effects can result from resorcinol exposure (from lowest dose to highest): inhibition of thyroid peroxidase, alteration of hormones including increase of serum TSH and decrease of serum T3 and T4, increased incidence of thyroid hypertrophy and hyperplasia, and finally, developmental neurotoxicity effects. Panelists concluded that the resorcinol-related adverse effects to avoid are the neurodevelopmental effects that result from a decrease of thyroid hormones either in the dam, fetus, or neonate. The presumed MOA is through thyroid peroxidase and it appears that the WIL (2003) study was designed following this presumption. The F0 generation was exposed to resorcinol in drinking water and was evaluated for the appropriate thyroid variables. All of the F1 animals were exposed *in utero* and through nursing[1]. For F1 animals undergoing thyroid evaluation, exposure continued in

[1] This exposure is assumed. There are no data available to show whether or not resorcinol crosses the placenta or was excreted in breast milk in this study.

drinking water from weaning (PND 21) to PND 28. For F1 animals undergoing behavioral evaluation, exposure stopped at the time of weaning. Based on a review of the WIL (2003) study, this panel member concluded that no effects were observed.

Another panel member said that the effects on thyroid histopathology were minimal. Key indicators of thyroid toxicity are thyroid colloid depletion, hypertrophy, and hyperplasia, which were diagnosed separately in the WIL (2003) study. Although, no colloid depletion and hypertrophy were observed in any dose group, minimal thyroid hyperplasia (not statistically significant) was observed in the high dose groups. This panel member indicated that because the thyroid hyperplasia was not preceded by observations of colloid depletion and hypertrophy, the effect was likely to be random and not treatment related. Therefore, this panel member agreed that the WIL (2003) study did not result in any effects on thyroid histopathology or hormones following drinking water exposure to resorcinol at the doses tested. This conclusion also applies to the F1 animals, which were exposed to resorcinol until PND 28 and for which no effects on any thyroid parameter evaluated were reported. One panel member asked if the incidence of hyperplasia (3/7) in the controls is common. Another panelist replied that this incidence is typical if the slides are read blind. A different panel member asked if the power of the study was adequate to detect changes in thyroid histopathology. Again, a panel member replied yes; with small numbers of animals, there is a tendency is to over interpret rather than under interpret the findings, which gives confidence that the study was adequately sensitive. Another panel member noted that it would be possible to design a study that found thyroid effects by increasing the dose above those used in the WIL (2003) study, using an exposure route that delivers a continuous dose, and sacrificing during exposure. However, the WIL (2003) study is appropriate for assessing resorcinol effects following a realistic environmental exposure. Another panel member agreed and suggested that this point should be stressed in the resorcinol RfD document.

Another panel member noted that for some of the measured endpoints, a certain amount of time had passed between the end of exposure and the evaluation of the endpoint. This panel member asked if this aspect of the study design was sufficient to allow observation of adverse effects. Other panel members replied that for the F0 and for the pups evaluated at PND 4 and 28, the time between exposure and sacrifice was short enough to allow for observation of potential thyroid effects. For the F1 animals that were evaluated for behavioral effects, the amount of time for recovery was too great. However, one panel member pointed out that the culled pups evaluated at PND 4 were from the litters that went on to behavioral evaluations. Therefore, the thyroid effects in these PND 4 pups does give a picture of what happened to the F1 animals that went on to behavioral testing right after birth. Another panel member noted that there was a wide range of actual doses in the individual dams, so it is really not possible to estimate what exposure the PND 4 pups actually received.

The panel then discussed the statistical approach AMEC used to evaluate the significance of the thyroid histopathology. One panel member commended AMEC for their effort in exploring all possible approaches to conducting a conservative, health protective risk assessment. However, this panel member indicated that combining the interim males, the terminal males, and the females for statistical analysis was not appropriate. Other panel

members agreed, noting that there is no biological justification for combining these diverse groups.

Another panel member described the behavioral data gathered from the F1 animals. The tests involved included tests of learning and memory, locomotor activity, and acoustic startle (reaction to noise). The acoustic startle response is known to be a very sensitive indicator of thyroid-related effects during development. WIL (2003) did not report effects in either acoustic startle or the learning/memory tests. This panelist agreed with AMEC's analysis of the locomotor activity results and concluded that the developmental neurotoxicity tests in the WIL (2003) study were all negative.

One panel member asked what would be the critical effect if the WIL (2003) study had identified no effects. Another panelist replied that thyroid toxicity is still a fair statement of critical effect and that neurodevelopmental effects that result from a decrease of thyroid hormones either in the dam, fetus, or neonate are the most significant adverse effect. Another panel member indicated that, in spite of the lack of effects, the WIL study does not change the conclusion of the 2003 panel that thyroid effects are the critical effect. In addition, WIL (2003) is clearly the best critical study.

The panel unanimously concluded that, as designed and conducted, the WIL (2003) study would have detected any adverse thyroid effects at the doses tested. No adverse effects of any kind were detected in adults or offspring at the time periods and doses evaluated. The panel reached this conclusion after careful review of the original data in the WIL study regarding thyroid hormone levels and histopathology in adults and neonates and neurodevelopmental endpoints in the F1 generation, including locomotor activity. In addition, the panel unanimously concluded that, on the basis of clinical reports and some experimental data from *in vitro* and *in vivo* studies, the WIL (2003) study, although negative, does not change the conclusion that thyroid toxicity is the critical effect for resorcinol. The panel determined that the WIL (2003) study is the most appropriate choice of critical study.

In addition, the panel unanimously recommended the following revisions to the resorcinol RfD document:

- Address the implications of the differences between the time at which the F1 animals in the WIL (2003) study were dosed and when they were evaluated for developmental toxicity.

- Expand the discussion of the thyroid histopathology observations from the WIL (2003) study. In particular, the resorcinol RfD document should describe the lack of effects on colloid depletion and thyroid follicular cell hypertrophy and discuss the relevance of this observation for interpreting the hyperplasia data.

- The resorcinol RfD document should include only a discussion of standard, appropriate statistical approaches. For example, when evaluating thyroid hyperplasia, do not combine gender and time points and only compare each group to its concurrent control.

6.4 Charge Question 4:

> *What is the appropriate point-of-departure (POD) for a resorcinol RfD? Has the document used an appropriate approach for estimating average daily dose and for determining which average daily dose from the WIL (2003) study should be used as the POD? Is another method or choice for POD more appropriate?*

One panel member lead the discussion by noting that, since it is not appropriate to combine the male and female groups for statistical analysis, it is also not appropriate to use an animal-weighted average daily dose as the point of departure. This panel member indicated that the population of concern is the F1. Therefore, it is inappropriate to use the male average daily dose at all. In the absence of data on exposure of the F1 pups, the average daily dose of the dams is the most appropriate point-of-departure, as a surrogate for the dose to the pups. In addition, this panel member noted that the point-of-departure should only have one significant figure. Therefore, the point-of-departure for a resorcinol RfD would be 60 mg/kg-day, the average daily dose for the female rats in the WIL study. Other panel members agreed. However, one reviewer noted that the doses to the dams were highly variable and that AMEC should carefully check its calculation of ADD before making a final determination of the point-of-departure.

The panel then discussed whether the point-of-departure should be considered a NOAEL or LOAEL. The panel had already concluded that the thyroid histopathology and the locomotor activity were not real, treatment-related effects in the WIL (2003) study. Therefore, the discussion centered on whether the decreased brain width in the F1 females was a treatment-related, adverse effect. One panel member asked if the brain width measurements were made on fresh tissue. The RTF replied that they were. In response to a panelist question, RTF representatives also stated that the brain width was measured on brains that had been removed from the skull, a process that can result in small changes in brain dimensions, including width.

The panel consulted with EPA's Guidelines for Neurotoxicity Risk Assessment (US EPA, 1998) and located the following statements that pertained to the discussion of brain width effects:

> "Alterations in the structure of the nervous system (i.e., neuronopathy, axonopathy, myelinopathy, terminal degeneration) are regarded as evidence of a neurotoxic effect….
>
> Changes in brain weight are a more reliable indicator of alteration in brain structure than are measurements of length or width in fresh brain, because there is little historical data in the toxicology literature."

One panel member asked if the study (WIL, 2003) had included a histopathological assessment of several structures of the brain. The RTF indicated brains were examined in the F1 animals on PND 30 and that no abnormal histopathology was observed. A different panel member noted that the standard methods used in a basic toxicological evaluation would not detect brain changes that occurred in response to changes in thyroid hormone levels.

Therefore, one cannot conclude from the WIL study (2003) that these effects did not occur. So, this study only answers the question "are there irreversible changes" but does not answer the question "are there any changes".

One panel member noted that the assumed mode of action (MOA) for resorcinol involves inhibition of thyroid peroxidase (TPO) resulting in changes in levels of TSH and thyroid hormones followed by neurodevelopmental effects. It was also noted that in order for resorcinol to be acting through TPO, the receptor needs to be continuously bound. In addition, early events in this MOA are rapidly reversible, which explains why the dosing schedule in WIL (2003) study affects the interpretation of the developmental toxicity analyses. Given this MOA, one would not expect that the brain width effect is treatment related because there were no effects on thyroid hormones in the study. Another panel member noted that it is possible that resorcinol does have other MOAs since it also interferes with oxygen metabolism. In response to a question from the panel, AMEC noted that there are only some *in vitro* data measuring thyroid peroxidase inhibition by resorcinol and agrees that other MOAs could be operative.

One panel member asked whether it would be possible to look at individual animal data and compare thyroid hormone data and brain width data to see if there was a correlation. Another panel member replied that thyroid hormone analysis and brain measurements were not done on the same set of animals, and that the two sets of data were collected at different times. However, this panel member agreed that this type of analysis is needed to support the statement that the brain width effect is not treatment related. For example, it might be possible to evaluate the thyroid effects in dams, individually, to see if thyroid changes in an individual dam could be correlated to a brain width effect in her pups. A different panel member acknowledged that the decreased brain width is probably not an effect of treatment. However, the resorcinol RfD document should discuss and analyze the decreased brain width in more depth and the conclusion that it is not treatment related should be explained and supported. Other panel members agreed.

An observer asked if there was any relationship between the locomotor activity and the brain width effects. A panel member answered that both behavioral effects and histopathological changes are often observed in the same studies but these effects do not necessarily predict each other and it is not possible to do a direct correlation between the effects. Another panel member acknowledged that this is generally true, but also mentioned that there are some changes in specific brain areas that can be correlated with functional behavioral changes. However, the brain width measurements are crude measurements for the way science is practiced today and a decrease in the measurement does not carry much weight and should be cross validated with other more reliable measures of morphometry, such as measuring the volume of a structure. This panel member reinforced that the locomotor activity changes were meaningless. The first panel member agreed, noting that in order to have confidence that a chemical exposure resulted in significant neurotoxicity effects one would expect to see multiple changes in multiple neurological endpoints.

Overall, the panel concluded that the high dose is a NOAEL since no adverse effects were observed at this dose. With this conclusion, the panel agreed that is was not appropriate to conduct benchmark dose analysis of these data.

The panel unanimously concluded that the point-of-departure is most appropriately based on exposure of the F1 pups; the average daily dose to the dams best represents this point-of-departure. Therefore, an average daily dose of approximately 60 mg/kg-day, based on the average daily dose to the dams across all exposure periods, is the point-of-departure. However, the panel recommended that AMEC carefully check this ADD calculation before selecting the final value for the point of departure. The panel unanimously concluded that this dose level is a NOAEL.

In addition, the panel unanimously recommended that the resorcinol RfD document must describe the observation of statistically significantly decreased brain width in the F1 female pups. It is likely that the effect is not associated with resorcinol treatment, but the supporting evidence for this conclusion must be discussed.

6.5 Charge Question 5:

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?

The panel discussed the data supporting each of the different uncertainty factors individually, and then discussed the appropriate composite uncertainty factor.

6.5.1 UF_L – extrapolation from LOAEL to NOAEL

The panel reached unanimous consensus that since the point of departure for the RfD was a NOAEL, the appropriate value for this uncertainty factor is 1.

6.5.2 UF_S – extrapolation from a subchronic study

It was noted that the resorcinol RfD document recommended a value of three for this factor. One panel member noted that sufficient data are available on chronic exposure, for example the NTP (1992) study, to warrant a value of 1. However, another panel member indicated that the chronic studies are not by the drinking water route of exposure. Because of the pharmacokinetic issues related to the differences in drinking water compared to gavage exposure, this panel member was not comfortable reducing this factor to 1. The first panel member acknowledged this issue, but indicated that the issue could be addressed by using a value of 10 for UF_D. This panel member further noted that the same composite uncertainty factor would result if one used a 1 and 10 or a 3 and a 3 for UF_S and UF_D, respectively. The panel concluded that the value of UF_S could range from 1 to 3, although there was not unanimous consensus on the value.

6.5.3 UF_D – database deficiencies

It was noted that the resorcinol RfD document recommended a value of 3 for this factor. One panel member indicated that this chemical has a strong database compared to many chemicals. There are no large gaps in the database, and therefore a full 10 is not appropriate. This panel member agreed that a value of 3 was appropriate. Another panel member, while agreeing with this conclusion, noted that there are still some deficiencies in the developmental toxicity studies that have not been eliminated by the ongoing two-generation study. In addition, it was noted that reports of methemoglobin arising following continuous exposure in humans is rare, but that there are no animal studies that evaluated hematology using the appropriate route of exposure. Another panel member noted that there are still some deficiencies in the database regarding the developmental neurotoxicity endpoints. The panel reached unanimous consensus that a value of 3 was adequate to address database deficiencies.

6.5.4 UF_H – variability in human populations

It was noted that the resorcinol RfD document recommends a value of 3 for this factor. One panel member opened this discussion by noting that this factor is considered to be composed of subfactors to address both kinetic and dynamic variability. This panel member noted that the document gives a good summary of kinetic variability; although, it should also discuss variability at the tails of the distribution curve. Other panel members agreed with this. However, the document did not discuss the dynamic variability regarding the formation of methemoglobin and developmental neurotoxicity effects or the sensitivity of children. Another panel member indicated that 3 was an appropriate value for this factor since there were still concerns about methemoglobin formation following drinking water exposure. A different panel member disagreed about the concern for methemoglobinemia following drinking water exposure, but still agreed that 3 was an appropriate value for this factor because the focus of RfD is the F1 generation, which is the most sensitive population. Other panel members agreed, noting that basing the RfD on the F1 as a sensitive population addresses the issue of dynamics. In addition, panel members noted that the new WIL (2003) study, which looks at a sensitive endpoint and an appropriate exposure route, increases the confidence in using a 3 for the UF_H factor. One panel member noted that the kinetics should be consistent among humans, so a value of 1 for the kinetic subfactor is appropriate. This person noted that some uncertainty in human dynamics remained, since there are no data to address the sensitivity of neonates in the response to resorcinol. Therefore, a value of 3 for the dynamic subfactor is appropriate.

A different panel member suggested that a full value of 10 may be appropriate since there are no data addressing kinetics in the developing fetus, and insufficient data addressing dynamics in humans. On page 60, Section 6.2.2, of the resorcinol RfD document is a statement that there are no data addressing the dynamics of resorcinol. Therefore, this panel member said that a value of 3 of the dynamic subfactor is appropriate. This same section of the document describes kinetics data for average neonates, not sensitive neonates. This panel member reinforced the idea that the uncertainty factor analysis should consider the ends of the distribution curve. Therefore, since the dynamic data are incomplete, a value of 3 is

appropriate for the dynamic subfactor and a 10 is appropriate for UF_H. This panel member indicated that the Section 6.2.2 was well written, but that it presents arguments why the value of this factor should be 10, rather than 3.

Another panel member agreed, stating that even though the default value of 10 seems high given the existing data, there are really not any data addressing human kinetics and dynamics that can justify dropping the default. One panel member asked if there were data describing the total human variability in glucuronidation. The first panel member indicated there was about a 10-fold variation. However, it was noted that the better focus for humans is total clearance. Since the target tissue concentration is due to both absorption and removal, which is due to both metabolism and excretion, then total clearance is a better measure for overall human variability. One panel member asked whether the Dorne et al. (2001) study, described in Section 6.2.2 of the document, provides any additional information regarding variability in total clearance. The Authors reported that the study presented data on Clearance AUC and C_{max}, so it does have a measure of variability in parameters related to tissue dose. Another panel member asked at what age glucuronidation starts in neonates. The Authors cited Ginsberg et al. (2002) as reporting the ratio of the average child half-life to the average adult half-life for glucuronidation substrates in their database was 3 for neonates, 2 for infants 1 week to 2 months of age, 0.90 for infants 2-6 months of age, 1.1 for children 6-24 months of age and 1.2 for children 2-12 years of age, and indicated that at that age, neonates could be exposed to resorcinol in water used to make up formula.

Therefore, the panel reached unanimous consensus that this factor ranged between 3 and 10. However, the panel could not agree on a single value.

6.5.5 UF_A – variability between animals and humans

It was noted that the resorcinol RfD document recommended a value of 1 for this factor. One panel member opened this discussion by indicating that there is no uncertainty regarding extrapolating from the average animal to the average human. The appropriate value for the kinetic subfactor (A to H_K) is 1 and the appropriate value for the dynamic subfactor (A to H_D) is less than one. Therefore, a value of 1 is appropriate for UF_A. Several panel members agreed with this analysis, indicating that the developing rat is a sensitive indicator of resorcinol effects and that rats are clearly more kinetically sensitive to resorcinol's thyroid effects. One panel member indicated that sufficient data exist to indicate that metabolism of phenolic compounds in animals and humans is qualitatively and quantitatively the same. Another panel member asked whether oral absorption is the same in rats and humans. The first panel member indicated that there are only data on dermal absorption, not oral. The panel reached unanimous consensus that a value of 1 was appropriate for UF_A.

6.5.6 Composite Factor

Given the range of opinions on the individual factors, the panel then discussed the appropriate value of the composite factor (i.e., the combination of the individual uncertainty factors). Given the individual UF values the panel just discussed (UF_S of 1 to 3, UF_A of 1, UF_H of 3 to 10, UF_D of 3), the composite uncertainty factor would range from 10 to 100. One

panel member noted that after the 2003 meeting, the composite factor was 100-300. Now that the point of departure is better defined and additional data have reduced the uncertainty, the composite factor should be lower. Another reviewer noted that a composite factor of 30 was appropriate and could be supported by choosing a value of 3 to represent both UF_S and UF_D. However, another panel member stated that there was limited purpose in recommending a single number for the composite uncertainty factor. The most critical part of the risk assessment is to define well the point of departure, which has been done for resorcinol. By expressing the composite factor as a range, and describing the ranges for the UF_S and UF_H factors, the document would identify the areas of uncertainty that are lacking data and would change if more data became available.

However, the Sponsors and an Observer from the Pennsylvania Department of Environmental Protection (PADEP) indicated that the preferred approach would be to have the panel recommend a single value for the composite uncertainty factor. Given this request, the panel reached unanimous consensus that a composite uncertainty factor of 30 would be appropriate. The panel agreed that the Chair will prepare text supporting a composite factor of 30 that should be used in the final resorcinol RfD document. However, the panel also reached unanimous consensus that the resorcinol RfD document should present and discuss the composite uncertainty factor as a range, before presenting a single value.

6.6 Charge Question 6:

Are there any other issues that should be discussed? What specific recommendations would you make to help the authors improve the RfD for resorcinol?

The panel had comments on Table 3 of the resorcinol RfD document. While appreciating the addition of this table to the revised document, several panel members said that the table conveyed too much information and was confusing. One panel member suggested creating two tables – one that compares the different studies and one that evaluates the dose-response for the various endpoints. Another panel member suggested grouping the data by type of exposure and then by endpoint to facilitate comparison among studies. A third panel member suggested grouping the data by duration of exposure. Finally, other panel members suggested creating graphs similar to those found in ATSDR's Toxicological Profiles to help readers better evaluate the data.

The panel unanimously concluded that the resorcinol RfD can be loaded onto *TERA*'s ITER database[2], after the Sponsors make the few revisions recommended by the panel in Section 8.0. The panel agreed that the Chair shall review the final document to ensure that the revisions are satisfactory and that the Chair shall only forward the document to the panel if she has questions for the panel.

[2] International Toxicity Estimates for Risk (ITER) is a database of international toxicity values that have undergone peer review. *TERA* developed this database, which can be viewed at www.tera.org/ITER or on the National Library of Medicine's Toxnet.

7.0 Conclusions

These conclusions were reached by unanimous consensus of the panel as a whole. Unanimous consensus means that everyone agrees, or can "live with" the decision.

- The panel complimented the Sponsors and Authors on the excellent job they did revising the document. The panel concluded that the Authors adequately addressed and responded to all recommendations made by the panel in 2003 and recognized the significant additional work incorporated into the updated risk assessment.

- Generally, the WIL (2003) study was appropriately designed to evaluate resorcinol toxicity. In particular, the study design was adequate to evaluate the potential for direct thyroid toxicity (thyroid hormone changes and thyroid histopathology) in adult male and pregnant female animals exposed to resorcinol via drinking water and in neonates potentially exposed to resorcinol in utero and during lactation and in some cases through their drinking water. The WIL (2003) study design was not adequate to evaluate the link between thyroid toxicity and possible neurodevelopmental effects in offspring exposed after postnatal day (PND) 21 because the F1 generation animals undergoing behavioral tests up to PND 61 were not exposed to resorcinol after PND 21.

- As designed and conducted, the WIL (2003) study would have detected any adverse thyroid effects at the doses tested. No adverse effects of any kind were detected in adults or offspring at the time periods and doses evaluated. The panel reached this conclusion after careful review of the original data in the WIL study regarding thyroid hormone levels and histopathology in adults and neonates and neurodevelopmental endpoints in the F1 generation, including locomotor activity.

- On the basis of clinical reports and some experimental data from *in vitro* and *in vivo* studies, the WIL (2003) study, although negative, does not change the conclusion that thyroid toxicity is the critical effect for resorcinol. The panel determined that the WIL (2003) study is the most appropriate choice of critical study.

- The point-of-departure is most appropriately based on exposure of the F1 pups; the average daily dose to the dams best represents this point-of-departure. Therefore, an average daily dose of approximately 60 mg/kg-day is the point-of-departure. The panel determined that this dose level is a NOAEL.

- The appropriate values for the uncertainty factors UF_A, UF_L, and UF_D are 1, 1, and 3, respectively. The value of UF_H ranges from 3-10; the value of UF_S ranges from 1-3. The resulting composite uncertainty factor ranges from 10-100. This range adequately describes the variability and uncertainty associated with data available for resorcinol. If a single value within this range is required, a composite uncertainty factor of 30 is most appropriate.

- Based on a point-of-departure of 60 mg/kg-day and a composite uncertainty factor of 30, a RfD of 2 mg/kg-day is appropriate for resorcinol.

8.0 Recommendations

These recommendations were reached by unanimous consensus of the panel as a whole. Unanimous consensus means that everyone agrees, or can "live with" the decision.

- The word "continuous" should be removed from the resorcinol RfD document when referring to drinking water exposures.

- The resorcinol RfD document should address the implications of the differences between the time at which the F1 animals in the WIL (2003) study were dosed and when they were evaluated for developmental toxicity.

- Expand the discussion of the thyroid histopathology observations from the WIL (2003) study. In particular, the resorcinol RfD document should describe the lack of effects on colloid depletion and thyroid follicular cell hypertrophy and discuss the relevance of this observation for interpreting the hyperplasia data.

- The resorcinol RfD document should include only a discussion of standard, appropriate statistical approaches. For example, when evaluating thyroid hyperplasia, do not combine gender and time points and only compare each group to its concurrent control.

- The Authors should carefully check the average daily dose calculations for dams.

- The resorcinol RfD document must describe the observation of statistically significantly decreased brain width in the F1 female pups. It is likely that the effect is not associated with resorcinol treatment, but the supporting evidence for this conclusion must be discussed.

- The uncertainty factor discussion should present and discuss the composite uncertainty factor as a range of values before selecting a single value to carry forward to the RfD calculation. The panel will provide text that supports a presents an argument for the composite uncertainty value of 30; it is recommended that this text should be incorporated into the final risk assessment document.

9.0 References

Dorne, J.L., Walton, K., and Renwick, A.G. 2001. Human variability in glucuronidation in relation to uncertainty factors for risk assessment. Food Chem Toxicol. 39:1153-1173.

Ginsberg, G., Hattis, D., Sonawane, B., Russ, A., Banati, P., Kozlak, M., Smolenski, S., and Goble, R. 2002. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci. 66:185-200.

NTP (National Toxicology Program). 1992. Toxicology and Carcinogenesis Studies of Resorcinol (CAS No. 108-46-3) in F344N/ Rats and B6C3F1 Mice (Gavage Studies). NTP Technical Report 403. July.

US EPA (U.S. Environmental Protection Agency). 1998. Guidelines for Neurotoxicity Risk Assessment. Risk Assessment Forum, Washington, DC. April. EPA/630/R-95/001F.

WIL Research Laboratories, Inc . 2003. A drinking water dose range-finding reproductive toxicity study of resorcinol in rats. Study Number WIL-455002. Final Report, 2419 pages.

APPENDIX A
Panel Biography and
Conflict of Interest Disclosures

Panel Biography and Conflict of Interest Disclosures

Peer Review of
"Description of a Proposed Reference Dose for Resorcinol"
November 17 and 18, 2004

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. The panel selected for this follow-up review of the resorcinol document is the same panel that conducted the initial peer review in March 2003. Prior to selecting the panel in 2003, *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. In 2003, each panel member was asked to complete a questionnaire to determine whether his/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. Prior to confirming the participation of individuals on the 2004 panel, each member was asked to describe in writing any issues of potential conflict or bias that had arisen since the March 2003 review.

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 are asked to objectively evaluate the materials for this review, along with their personal knowledge and expertise, to independently reach conclusions on this document. If a panel member feels at any time that another member is 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 will be discussed by the panel at the beginning of the meeting and panel members will be asked whether they have any additional information to add. The final outcome of this COI discussion will be included in the final meeting notes.

The peer reviewers have donated their time and talents to this effort. They are 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 are 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 is 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 the phenol assessment for U.S. EPA) and served on several peer review panels, including the panel that reviewed the dichlorobenzenes risk assessment for U.S. EPA. She is also certified as a Diplomate of the American Board of Toxicology. 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 have the same metabolism issues). Prior to the 2003 review meeting, the panel discussed a potential corporate conflict of interest, in that different *TERA* employees had reviewed an earlier version of the document. The panel concluded that appropriate steps were taken to manage the conflict and that Dr. Haber should participate as the meeting Chair. Dr. Haber indicated that she has no new COI or bias issues since the 2003 review meeting.

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 is not ongoing, is not related to resorcinol, and is not related to the BCAS, *TERA* determined that this activity does not constitute a conflict. However, this information was disclosed at the 2003 meeting. Dr. Kamrin indicated that he has no new COI or bias issues since the 2003 review 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. Kenyon indicated that she has no new COI or bias issues since the 2003 review meeting.

Dr. Steven Lamm. Consultants in Environmental and Occupational Health. Dr. Lamm is the President of CEOH. 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 was an occupational health consultant to Kopper's from about 1978 until Beazer took them over. In 2000-2001, he was an expert witness for Beazer in a Coal Tar Plant case. *TERA* determined that these activities are not a conflict because they are not currently ongoing. Dr. Lamm indicated that he has no new COI or bias issues since the 2003 review meeting.

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. Manning indicated that he has no new COI or bias issues since the 2003 review meeting.

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 2003 panel, which determined that this is not a conflict that would prevent Dr. McGinnis from participating on the panel. Dr. McGinnis indicated that she has no new COI or bias issues since the 2003 review meeting.

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. Dr. Pleus indicated that he has no new COI or bias issues since the 2003 review meeting.

Dr. Allan Susten. Agency for Toxic Substances and Disease Registry, Retired. Since the 2003 meeting Dr. Susten has retired as 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. Dr. Susten indicated that he has no new COI or bias issues since the 2003 review meeting.

Dr. Douglas Wolf. U.S. Environmental Protection Agency. Dr. Wolf is a research scientist 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. Dr. Wolf indicated that he has no new COI or bias issues since the 2003 review meeting.

APPENDIX B
Sponsor Presentation

Resorcinol Peer Review Panel

Toxicology Excellence for Risk Assessment

Brian Magee, Ph.D.

November 17-18, 2004

AMEC Earth & Environmental, Inc.

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Resorcinol Reference Dose Chronology

- TERA Independent Review Panel - March 2003
- TERA Panel conclusions – July 2003
  - Thyroid = critical effect
  - Panel made various recommendations to expand and clarify RfD document
- AMEC charged to revise document
- Meanwhile, new data released from study better suited for reference dose derivation

Responses to TERA's July 2003 Recommendations

- More completely and thoroughly review all pertinent studies in the database
  - conducted comprehensive literature search for all citations containing the word resorcinol – search results described in Section 1
  - approximately 100 of 600 citations contained information on resorcinol in context of human or animal toxicity
  - additional studies are discussed in RfD document

Responses to TERA's July 2003 Recommendations (cont'd)

- Review all primary studies, particularly key studies on toxicity
  - key studies were reviewed, including a new study made available to AMEC subsequent to TERA meeting (WIL, 2003)
- Add more data on mode-of-action & mechanism of resorcinol toxicity
  - literature consulted concludes that resorcinol affects the thyroid by thyroid peroxidase inhibition
  - statements on mode-of-action were added to RfD document in (Section 6.1)

Responses to TERA's July 2003 Recommendations (cont'd)

- Provide more information about other target organs in humans
  - expanded discussion on association of resorcinol exposure from use of topical products on ulcerated skin with hypothyroidism (Section 5.1.3)
  - added discussion on resorcinol exposure and methemoglobinemia (Section 5.1.1)
  - calculated dose estimates when sufficient data were provided in case studies
  - expanded discussion on resorcinol exposure and contact dermatitis (Section 5.1.2)

Responses to TERA's July 2003 Recommendations (cont'd)

- Include discussion on the remaining two TOMA (1978, 1982) studies
  - acquired and reviewed the TOMA studies
  - Section 5.1.3 discusses all four TOMA studies as well as other occupational studies (Roberts et al., 1990; West and Stafford, 1997)
- Include table that identifies the NOAEL or LOAEL for each study/endpoint
  - Table 3 summarizes animal studies and identifies the NOAEL or LOAEL, including the multiple endpoints in NTP studies

Responses to TERA's July 2003 Recommendations (cont'd)

- Review Gatgounis and Walton (1962)
  - study details appear in Section 5.2.1.2
- Strengthen the discussion of thyroid toxicity as critical effect
  - strengthened the discussion, principally with addition of the WIL (2003) dose range finding study
  - WIL (2003) study is discussed in Section 5.2.2.2
  - selection of WIL (2003) as key study is discussed in Section 6.1

Responses to TERA's July 2003 Recommendations (cont'd)

- Include a more critical evaluation of design of developmental toxicity studies
  - acknowledged that some studies may have missed periods of thyroid development that might be affected by resorcinol (Section 5.2.4)
  - acknowledged Hazelton rabbit study sensitivity might be questionable due to 50% pregnancy rate and low malformation rate among positive controls (Section 5.2.4)
  - excluded discussion of Burnett and Goldenthal (1988) because rats were exposed to complex mixtures, not resorcinol only (Section 5.2.4)

Responses to TERA's July 2003 Recommendations (cont'd)

- Acknowledge data gaps for reproductive and developmental toxicity
  - WIL (2003) dose range finding study filled several data gaps, including reproductive performance, late gestational and early neonatal toxicity, and developmental neurotoxicity (Section 5.2.2.1)
  - acknowledged that uncertainty might still exist concerning adequacy of multigenerational studies (Section 6.2.5)

Responses to TERA's July 2003 Recommendations (cont'd)

- Expand point-of-departure (POD) discussion
  - WIL (2003) dose range finding study selected as key study for thyrotoxicity
  - POD selected from WIL (2003)
  - detailed discussion of key study and POD selections in Section 6.1
- Expand discussion of uncertainty factors
  - Selection of uncertainty factors revised
  - Rationale for new factors in Section 6.2

Resorcinol Task Force

- Resorcinol Task Force (Resorcinol Manufacturers) interested in filling reproductive toxicity data gap
- Scheduled full two-generation drinking water study
- Three phases
  - 14-day palatability study (completed in 2002)
  - comprehensive dose range finding study (completed in winter 2003)
  - guideline compliant two-generation study with full thyroid histopathology (currently underway)
- Dose range finding study available to AMEC

WIL (2003) Dose Range Finding Study

- Groups of 14 rats/sex exposed to resorcinol in drinking water at 0, 10, 40, 120 and 360 mg/L
- Females dosed for an average of 75 days (prior to mating, during mating, gestation, and lactation)
- Interim-study males dosed for 48 days; males scheduled for necropsy dosed for 87 days

WIL (2003) Dose Range Finding Study (cont'd)

- Multiple endpoints evaluated
  - reproductive performance
  - mortality, body weight and organ weight changes
  - thyroid
    - thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3)
    - microscopic examination of thyroid
  - developmental neurobehavioral battery – F1 pups

Results of WIL (2003) Dose Range Finding Study

- No impact on reproductive performance, mortality, body weight or organ weight
- Thyroid results
  - non-statistically significant increases in TSH levels reported for interim males; increases not sustained at scheduled necropsy
  - T_3 and thyroxine levels not affected in males; T_3 levels increased in 360 mg/L females, thyroxine and TSH levels not affected
  - minimal microscopic changes characterized as follicular hyperplasia reported
  - incidence of follicular hyperplasia was not statistically significant between individual dose groups and controls

Results of WIL (2003) Dose Range Finding Study (cont'd)

- Developmental neurobehavioral battery results
  - no difference from controls for the functional observational battery evaluations, acoustic startle response and Biel maze
  - statistically significant increase in locomotor activity in males at PND 61
  - locomotor activity not significantly increased in females at PND 61 or in males and females at PND 21

Results of WIL (2003) Dose Range Finding Study (cont'd)

- WIL (2003) concluded "in the context of a dose range-finding study of limited power, the numerical increases in motor activity were not considered as conclusive evidence of a change in CNS status."

Further Investigation of Locomotor and Hyperplasia Results

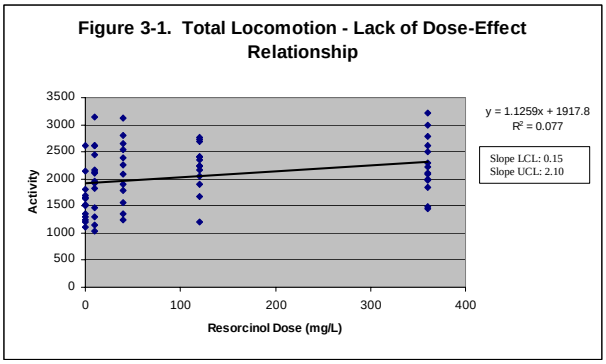
- AMEC conducted further investigation of locomotor and hyperplasia results
  - biological significance of locomotor activity test
  - additional statistical analyses on the locomotor and hyperplasia data

Further Investigation of Locomotor and Hyperplasia Results (cont'd)

- Biological significance of locomotor activity in absence of other CNS findings
  - literature search identified over 30 citations related to motor activity endpoint in neurotoxicity testing
  - determined that motor activity tests are reliable screening tools, but a single measure of activity is not considered sufficient evidence for neurotoxicity by many toxicologists and regulatory agencies

Additional Statistical Analyses

- Locomotor activity
  - additional statistical analyses confirmed the statistically significant difference across dose groups
  - regression analysis demonstrated the lack of a clear dose-effect



Additional Statistical Analyses (cont'd)

- Thyroid Follicular Cell Hyperplasia
  - additional statistical analyses to determine whether a dose-dependent trend in hyperplasia incidence might exist
  - Odds Ratio indicated no significant differences between individual dose groups and controls
  - all animals (interim and scheduled sacrifice males and females) grouped to increase statistical power
  - a LOAEL (360 mg/L) and dose-dependent trend were potentially indicated when animals were grouped

Conclusions of Additional Analyses

- AMEC agrees with WIL's (2003) conclusion that resorcinol in this study did not cause neurotoxic effects
  - no clear dose-response relationship for increase in locomotor activity
  - statistical significance of motor activity caused by one or two outliers
  - locomotor activity was the only neurobehavioral endpoint recorded as statistically significant
  - no locomotor activity changes seen in females or male animals of younger age

Conclusions of Additional Analyses (cont'd)

- AMEC's thyroid follicular cell hyperplasia analysis indicates high dose level could be considered either a NOAEL or a LOAEL depending on the statistical approach followed
  - uncertainty associated with merging data from male and female animals because of the potential gender specificity of resorcinol's effects on the thyroid
  - AMEC believes that the consensus of the toxicology community would be to conclude that 360 mg/L is a NOAEL for thyrotoxicity

Revised Reference Dose for Resorcinol

- Selection of key study
- Selection of point-of-departure
- Selection of uncertainty factors
- Revised reference dose for resorcinol

Selection of Key Study

- Human case studies inappropriate for RfD derivation
- No suitable epidemiology studies available for RfD derivation
- Acute and subacute animal studies are inappropriate
- Studies under consideration for key study
  - Cooksey et al. (1985)
  - Seffner et al. (1995)
  - NTP (1992)
  - WIL (2003)

Selection of Key Study (cont'd)

- Cooksey et al. (1985) and Seffner et al. (1995) – subchronic drinking water studies
  - no information on concentration of resorcinol in water or dose information
  - only a single drinking water concentration tested
  - no measurement of overt pathology or thyroid hormone levels

Selection of Key Study (cont'd)

- NTP (1992) – subchronic and chronic gavage studies
  - administration of resorcinol by gavage bolus, not continuous drinking water route
  - circulating thyroid hormone levels only measured in 13-week study
  - only T3 and thyroxine measured, not TSH

Selection of Key Study (cont'd)

- WIL (2003) – subchronic drinking water study
  - measured multiple endpoints, including thyroid weight, circulating T3, thyroxine, TSH levels and thyroid histopathology
  - administration of resorcinol via continuous drinking water route
  - selected as key study
- No effects reported for any endpoint at any dose
- Highest dose (360 mg/L) designated a NOAEL for thyroid effects, i.e., hyperplasia of follicular cells
- Highest dose could be designated a LOAEL under advanced statistical techniques when all animals merged to increase power

Selection of Point of Departure

- Average Daily Doses (ADDs) calculated over the course of study for males and females
- Animal-weighted average ADD of two male groups and females best represents study
  - POD = 360 mg/L = 47.7 mg/kg/day
  - POD as a NOAEL or LOAEL

Uncertainty Factors

- Animal to Human Extrapolation (UF_A)
  - $UF_A = 1$
  - pharmacokinetics similar between species
  - critical endpoint is thyroid toxicity
  - rat more sensitive than humans to disruption in thyroid function
  - resorcinol administered in drinking water, optimal for characterization of human exposure

Uncertainty Factors (cont'd)

- Human Sensitivity (Intraspecies) Extrapolation (UF_H)
  - $UF_H = 3$
  - increased sensitivity might be anticipated based on reduced clearance
  - based on clearance rate ratios, default uncertainty factor of 3 adequately protects neonates, infants, children, elderly, and people with liver or kidney disease

Uncertainty Factors (cont'd)

- LOAEL to NOAEL Extrapolation (UF_L)
  - UF_L = 1 when POD considered NOAEL
  - UF_L = 3 when POD considered very conservative LOAEL
- Subchronic to Chronic Extrapolation (UF_S)
  - UF_S = 3
  - resorcinol is cleared quickly
  - chronic studies show no progression of effects

Uncertainty Factors (cont'd)

- Database (UF_D)
  - UF_D = 3
  - existing toxicological database contains four of the five required studies
  - account for uncertainty that might still exist regarding lack of full two-generation study
- High Dose Can be Designated a NOAEL for Thyroid Effects; It Can Also be Conservatively Designated a LOAEL for Thyroid Effects
- 360 mg/L = 47.7 mg/kg/day
- Point of Departure for RfD = 47.7 mg/kg/day as a NOAEL or LOAEL

Revised Reference Dose

- RfD = 2 mg/kg/day
  - Composite UF = 30
  - POD of 47.7 mg/kg/day = NOAEL
- RfD= 0.5 mg/kg/day
  - Composite UF = 100
  - POD of 47.7 mg/kg/day = LOAEL

APPENDIX C
Resorcinol Task Force Presentation

Resorcinol Task Force

Contribution to the Resorcinol Panel Meeting
TERA

Wednesday 17th/Thursday 18th November 2004

Input from the Resorcinol Task Force

by

Paul Ashford – Manager, Resorcinol Task Force

Resorcinol Task Force (RTF)

- Formed in 1998 to fulfill several parallel objectives:
  - *To provide information on the uses of resorcinol and any likely health and environmental issues arising*
  - *To seek to fill any potential data gaps in the toxicological and epidemiological data sets (esp. for HPV and ICCA)*
  - *To assist regulators in assessing the overall risks to human health and the environment posed by resorcinol*

RTF - Membership

- The three major global producers:
  - ***INDSPEC (United States)***
  - ***Sumitomo (Japan)***
  - ***Mitsui (Japan)***
- Liaison with other significant users:
  - ***Tyre industries in the United States (RMA) and in Europe (BLIC)***
  - ***European Phenolic Resins Association (a CEFIC Affiliate)***
  - ***Hair colouring industry in Europe (HCTS)***
  - ***Pharmaceutical industry in Europe (EFPIA)***
  - ***Wood adhesives industry via CASCO***
- Facilitated by:
  - ***Caleb Management Services Ltd, UK – Project management services***
  - ***Orbitox – Toxicological services (Frank Welsch, Study Director)***

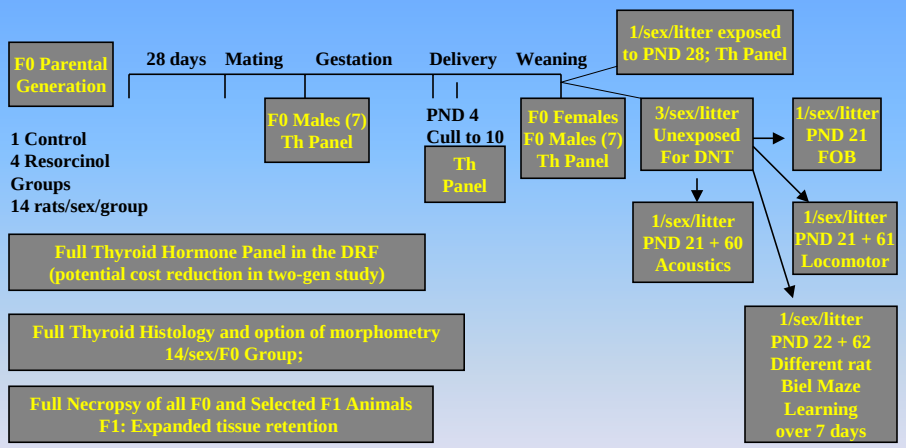
RESORCINOL TASK FORCE

RTF – Deliverables to date

- Carried out an initial and rapid in vitro screening study on wider endocrine effects (non GLP) *(August 1999)*
- Developed a Basic Resorcinol Status Report *(July 2000)*.
- Commissioned a full, independent Literature Review with CANTOX *(August 2000) – summary published as Lynch 2002 [Regulatory Toxicology & Pharmacology Oct;36(2):198-210],*
- Carried out an initial environmental emissions review *(June 2002)*
- Carried out a review of data gaps and commissioned a compliant two generation drinking water study with WIL Research in July 2002 *(Est. spend $750k - $1million)*

RESORCINOL TASK FORCE

RTF – DRF Study Outline



RESORCINOL TASK FORCE

RTF – DRF Study Observations

- Although GLP, the DRF was never intended as a stand alone Study
- RTF recognizes the value of such a study in the absence of more definitive work
- Some colloidal changes in thyroid observed at 360 mg/l, but no related changes in hormone levels
- LOAEL or NOAEL debate was a moot point for the Task Force
- Higher dosage levels were seen as necessary
- Final dose levels selected were 120, 360, 1080, 3000 mg/l
- Definitive two-gen study commenced in December 2003 and completed its in-life phase in late September
- Initial results suggest that AMEC's interpretation as a LOAEL is very conservative and a reasonable basis on which to proceed
- Report to follow in late Q1/early Q2 2005

RESORCINOL TASK FORCE

APPENDIX D
Follow-up Peer Review of a Proposed Reference Dose for Resorcinol
Charge to Peer Reviewers

Follow-up Peer Review of a Proposed Reference Dose for Resorcinol
Charge to Peer Reviewers

Background

In 2003, 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. The panel reached consensus that clearly enough data exist on resorcinol to develop a RfD; however, more of that data need 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.

Since the original peer review, a new subchronic dose range finding study of resorcinol has become available. The Sponsors and Authors have revised the original document to incorporate both the new study and additional work done in response to the panel's original comments. This follow up peer review has two purposes. The first is to evaluate the new study and its impact on the resorcinol RfD. The second is to evaluate how well the revised document addresses the recommendations made by the panel at the 2003 meeting. The follow-up peer review will not reopen discussion on issues that had resolution following the 2003 meeting and are not affected by the new study.

Charge Questions

1. A summary of the key recommendations from the 2003 peer review is attached. Has the document adequately addressed these issues? If not, please discuss areas that require additional work.

2. Is the design and conduct of the subchronic study conducted as part of the range-finding study for reproductive toxicity by WIL Laboratories (2003) adequate to evaluate resorcinol toxicity, particularly thyroid toxicity?

3. Evaluate the biological and statistical significance of the thyroid effects in WIL (2003). Does the addition of the WIL (2003) study change the conclusion of the previous panel that thyroid toxicity is the critical effect for resorcinol? If so, what is the appropriate critical effect? If not, is WIL (2003) the appropriate choice of critical study?

4. What is the appropriate point-of-departure (POD) for a resorcinol RfD?
    - Has the document used an appropriate approach for estimating average daily dose and for determining which average daily dose from the WIL (2003) study should be used as the POD? Is another method or choice for POD more appropriate?
    - Should this POD be considered a NOAEL or a LOAEL?
    - Are the data amenable to modeling with benchmark dose software in order to estimate a POD?
    - What should the final POD be?

5. 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?

6. Is the final RfD (proposed by the authors as a range of 0.5 to 2 mg/kg-day) consistent with the doses at which effects were observed in other human and animal studies? Will a RfD in this range protect sensitive individuals?

7. Are there any other issues that should be discussed? What specific recommendations would you make to help the authors improve the RfD for resorcinol?

Summary of 2003 Panel Recommendations

1. The panel recommended that if the remaining two TOMA (1978, 1982) studies could be obtained, they should be reviewed in the document.

2. 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.

3. The panel recommended that the document authors review the Gatgonis and Walton (1962) study in detail to provide additional information about the potential for CNS effects.

4. 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.

5. 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.

6. The panel recommended that the document expand on the discussion of rationale behind the choice of uncertainty factors.

7. The panel recommended 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.

8. 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.