

TCE Meeting Presentation Supporting Material for P. Casano

Paul Dugard

to:

Marc Rigas

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Please respond to Paul Dugard

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Dear Dr Rigas:

Please find attached material upon which Ms. Casano's presentation on May 10 will be based. This material is the set of slides used by Dr R. Canady during his presentation at EPA's "listening session" for the TCE IRIS draft. Many important issues were raised by Dr Canady during his presentation and Ms. Casano will address several of these topics.

Thank you.

Paul Dugard



# Comments to listening session for EPA's IRIS assessment of Trichloroethylene (TCE)

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# TCE is a flagship EPA regulatory toxicity assessment

The assessment is considered “flagship” in the sense that it presents cutting edge approaches to regulatory risk assessment and policy.

However,

- It is a complex mix of new data and policy that are difficult to tease apart.
- It takes on too much at once and, therefore, it may not stand the test of time.
- Specific changes are needed to make it last.



# Goal for the assessment

To develop a stable assessment of the toxicology for TCE in “regulatory risk assessment policy” terms that are useful in a risk management decision context.

# Goal for this listening session

- To point out any issues that may cause the final TCE assessment to be successfully challenged and, therefore, to be not as useful as it could be.
- To ask for serious consideration of changes so that the assessment can provide a sound and lasting basis for TCE decisions.

# New findings: EPA is saying that...

- ... TCE carcinogenicity in humans is no longer uncertain and its regulatory dose-response is driven by kidney tumors not liver tumors.
- ... Cancer potency for use in regulatory decisions is probably less than previously thought.
- ... The comparison values for the most sensitive noncancer endpoints for regulatory decision making for air exposures are lower and are now based on kidney, developmental heart defects, and immune effects.
  - *based on new PbPk modeling*

## New policy: EPA is...

- ... Lowering the bar on what may be considered “known human.”
  - The evidence for TCE is not in the same league as plutonium and asbestos.
  - TCE would be the new floor to the “known human carcinogen” group in terms of supporting evidence.
- ... Using PbPk modeling so extensively has the effect of new policy by the sheer magnitude of its influence in the assessment.
- ... Using a new approach of deriving multiple RfDs and RfCs that mixes toxicology with policy.

# Main messages: Cancer findings

- The data do not support “known” carcinogen under the 2005 EPA Cancer Guidelines.
  - New policy interpretation on cancer classification pushes the data too far and sets an unevaluated precedent for lower weight of evidence.
  - Charbotel et al 2006 found that consideration of cutting oil exposures removed the association between TCE and kidney cancer.
  - To be lasting the TCE assessment should be reviewed as carefully as EPA policy in a policy-review setting.
- Give risk managers a more complete description of the weight of evidence, not less, and not a bump up to a higher category.

## Quote from Charbotel et al 2006

“The results of the present study do not agree with the negative results obtained by a number of large cohort studies.

...

Although this study shows a possible link between high levels of exposure to TCE and increased risk of RCC, further epidemiological studies are necessary to assess the effect of lower levels of exposure.”



## Data support nonlinear dose-response for cancer, at least in part of the dose-response range

- The argument for linear is not strong enough to support it being the only model presented.
- The 2005 EPA Cancer Guidelines say that both models should be presented, or a dual model used in a case like this.
- Again, give risk managers more of the science and show the whole dose-response and the effects of considering both modes of action.

## Main messages: Non-cancer findings

- The new inhalation reference concentrations depend too heavily on assumptions in the PbPk and dose-response modeling
- Assuming higher human production of DCVC is a critical part of the complicated analysis of RfC, RfD, and cancer dose response
  - It is disputed science and EPA's analysis appears to show that it does not fit the modeling well
- The standard and well-tested approach for deriving RfCs directly from the study data should still be presented and preferred for now



## EPA does not use the entire database in its assessment of heart defects

- Animal studies are severely limited methodologically and in the reporting of data.
- Human data suffers from inadequate exposure definition and inconsistent findings.
- Mechanistic argument needs better support than seemingly irrelevant *in vitro* data and flawed *in vivo* data.
- Data are seemingly ignored from well-conducted studies that show no increase in heart defects.

*EPA should not say that heart defects may occur at environmentally relevant TCE doses in humans.*

*A full weight of evidence evaluation (not a strength of evidence argument) should be provided for risk managers.*



## EPA needs to show the effect of their assumptions and modeling choices

- The inter-related PbPk and dose-response modeling for multiple endpoints and dose metrics is so complex that even experts have trouble sifting through it.
- The support for multiple dose metrics and route-to-route extrapolation requires a very complex set of weight of evidence evaluations for modes of action.
- Even a simple narrative of the most influential assumptions and data sets (and their support) would be helpful.
  - The narrative does not have to be exhaustive and time consuming.
  - Scientists at EPA may already know the most sensitive parameters.

# Please...

## to make this assessment a lasting one

- ... Give the SAB ample time to hear and consider *science comments from experts*.
  - Five minutes per expert is not enough for a sufficient and transparent review of something this complex.
- ... Help SAB sort through the complexity. Provide a road map that identifies influential data and model assumptions that drive the conclusions.
- ... Clearly separate the review of science by scientists from the review of new policy in this assessment.
- ... For transparency and to prevent process objections:
  - Show how last year's interagency science comments were addressed.
  - Let the National Academy of Sciences' National Research Council committee respond to EPA's response to their 2006 report.



extra slides



## Quote from 2005 EPA Cancer Guidelines on presenting nonlinear and linear models

“If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur. Modeling to a low response level can be useful for estimating the response at doses where the high-dose mode of action would be less important.”

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