Charge

Charge to external panel review

1. Overall document quality: in your comments, address the overall quality of the documents and provide advice on approaches to improve the assessment from both technical and communication standpoints, and advice on the integration of data into an overall characterization of hazard.

   a) How well are the data from individual studies characterized?

   b) Comment on the conclusions that are drawn from each study.

   c) How well are the data integrated into an overall conclusion and characterization of hazard as presented in the Toxicological Review for Dichlorobenzenes?

2. RfD derivation

   a) The RfD for 1,2-DCB is based on a 2-year and a 13 week rat gavage study for liver necrosis. These studies examine the effect of 1,2-DCB on various organs. Evaluations included clinical signs, body weight, and necropsy and histology on all tested animals. Reviewers have to consider if this RfD is protective of adverse health effects in the general population and in the sensitive sub-population such as children (growth and development) and pregnant women (developmental effects in fetus and neonates). The Benchmark Dose Model (BMD) applied to the sub-chronic study revealed that the BMDLs were much lower than the chronic NOAEL used in the RfD derivation. Given the Agency's preference in using the BMDL to derive an RfD, the reviewers need to evaluate the RfD calculation and comment on whether or not it is appropriately derived. Comments should be made regarding the use of the NOAEL for RfD vs. use of BMDL for RfD derivation.

   b) The RfD for 1,3-DCB is based on a 90-day rat gavage study using a $BMDL_{10}$. The study examined the effect of 1,3-DCB on various organs and evaluations included clinical signs and mortality (observed daily), body weight (measured weekly), and food and water consumption (measured weekly). Reviewers have to consider if this RfD will be protective of adverse health effects in the general population and in the sensitive sub-population such as children (growth and development) and pregnant women (developmental effects in fetus and neonates).

   c) Are the methods of analysis and the Benchmark dose (BMD) methodology/calculations that were used to evaluate dose-response data for 1,3-DCB appropriate?

   d) The RfD for 1,4-DCB is based on a chronic beagle dog study using a BMDL10. Chronic and sub-chronic studies on 1,4-DCB have indicated the liver and kidney to be the most sensitive organs with developmental and gestational effects occurring at higher

doses. These results indicate that liver is the most sensitive endpoint for oral exposure to 1,4-dichlorobenzene and is the best basis for RfD derivation. Consider whether this RfD will be protective of adverse health effects in children (growth and development) and pregnant women (developmental effects in fetus and neonates)? Is the beagle dog study well conducted (include study size and duration) and is it the best study for the derivation of an RfD? If this is not the case, what other study should be used for the derivation of an RfD?

e) Are the methods of analysis and the Benchmark dose (BMD) methodology/calculations that were used to evaluate dose-response data for 1,4-DCB appropriate?

In addition to questions listed above, the reviewers will also consider these related questions:

a) Consider the choice of critical effect and principal study
b) Identification of effect level-including choice of NOAEL vs. BMDL
c) Uncertainty Factors
- Interspecies-Animal to Human
- Intraspecies
- LOAEL to NOAEL (where relevant)
- Subchronic to chronic (where relevant)
- Database adequacy (where relevant)

3. RfC derivation

a) Data for 1,2- DCB is considered inadequate for derivation of RfC. Is this agreeable?

b) Data for 1,3-DCB is considered inadequate for derivation of RfC. Is this agreeable?

With reference to the two above questions, please also consider whether or not the data are adequate for derivation of an RfC. If reviewers conclude that data are adequate, what would be recommended as the principal study, critical effect, and uncertainty factors?

c) The RfC for 1,4-DCB is based on rat 2-generation study using a $BMCL_5$. The RfC is based on an inhalation study causing toxicity in adult animals, including signs of neurotoxicity and eye and nasal irritation, as well as postnatal developmental toxicity in their pups. The most serious effect in the study was reduced postnatal survival in the pups.

In considering the RfC derivation for 1,4-DCB is protective of the general population and sensitive subpopulations, please consider whether the following were appropriate:

a) Choice of critical effect and principal study
b) Identification of effect level-BMC or LOAEL/NOAEL
c) Uncertainty factors
- Interspecies-Animal to human

Intraspecies
LOAEL to NOAEL (where relevant)
Subchronic to Chronic (where relevant)
Database (where relevant)

4. Cancer Weight-of-Evidence Classification and Quantitative Assessment.

a) The weight of evidence classification and quantitative estimation (both oral slope factor and inhalation unit risk) for 1,2-, 1,3-,and 1,4- DCBs have been discussed in Sections 4.6 and 5.3 of the Toxicological Review document and have also been discussed to a limited extent in the three IRIS summary documents. Have appropriate criteria been applied from the EPA 1999 draft cancer guidelines for Carcinogen Risk Assessment?

b) Based on the 1999 draft cancer guidelines, should a linear and non-linear approach be presented for 1,4-DCB cancer assessment or is a linear approach sufficient?

c) Is the evidence of the a-2m-globulin protein in male F344 rat nephropathy sufficiently presented? The NTP and other studies indicate that no hepatotoxicity is evidenced in F344 rats. Is this well supported in the document? The review panel shall provide specific comments related to the role of a-2m-globulin protein in male F344 rat nephropathy and bring to attention literature that indicates otherwise. They will also bring to attention literature supporting hepatoxicity in male rats caused due to exposure to 1,4-DCB.

5. Has the issue of knowledge/data gaps been handled appropriately?

6. In addition to addressing the issues above, provide other comments and recommendations you think are important to this assessment.

7. Please comment on the totality of information provided in the Metabolism/Mode-of-Action sections of the document.

(a) Is the information complete and correctly assembled?

(b) Are the conclusions drawn from the metabolism/MOA data appropriate and justified? Are they relevant to human exposure? Are they applicable to the derivation of human health toxicity values?

(c) Has the issue of data gaps been handled appropriately?

(d) Consider the data on MOA of 1,4-DCB Should both a linear and nonlinear method be presented for carcinogenicity assessment based on the 1999 revised cancer guidelines?

In considering the questions related to carcinogenicity assessment, please consider the following as well:

Mode of action assessment
Weight of evidence narrative statement

Determination of linear vs. nonlinear assessment
Quantitative-if none, why not?
Oral quantitation, were the study, endpoint, species, value calculated, and method used appropriate?

8. In addition to addressing the issues above, provide other comments and recommendations you think are important to this assessment.