

NTP Comments on 1,2,4- and 1,3,5-Trimethylbenzene

This IRIS draft was prepared using a new format that has substantially decreased the unnecessary repetitions. The preamble section is extremely helpful for new readers and even the regulars. However, the formatting changes have also resulted into limited information on the studies that are critical and supportive of the guidance values derived. Therefore it is difficult to fully ascertain the scientific strengths or weaknesses from the summaries of the data presented. Also, the order of the sections in the document does not flow logically. Hopefully, these minor formatting issues would be sorted out with time.

Overall, we find the relevant information on the toxicology of the chemicals very well summarized. We have the following comments for the authors to consider while revising the document:

1. It would be informative if the proportions all three isomers of the commercially available TMB are provided in the document.
2. Table 1 should also have the relevant information on 1,2,3-TMB isomer.
3. On page 21, under Programmatic Interest, please provide the reasons why there is no interest in 1,2,3-TMB.
4. Page 44, if the hypothesized mode of action is relevant to humans, shouldn't that reduce the uncertainty factor for deriving the numbers?
5. Page 84, Is the 1,2,4-TMB PBPK model validated enough to derive RfD from the inhalation studies?
6. We recommend inclusion of EPA recommendations/need for additional studies to reduce the uncertainty associated with the risk assessment of these chemicals or other chemicals assessed in the future by the IRIS program.