

**Brief Response to Denka July 23, 2018 Request for
Reconsideration #17002 Chloroprene.**

Denka's request for reconsideration (RFR) does not provide sufficient basis for finding significant omissions or errors on the part of EPA, related to EPA's denial of the Denka RFC. The RFR takes statements from external peer review comments out of context and uses them to misrepresent the sentiments of the external peer reviewers with regard to the toxicological review, and is devoid of any legitimate criticism of the science at issue in the denial of the original Denka request for correction (RFC). Further, the RFR is untimely, having been submitted approximately two weeks after the expiration of the original RFR deadline.

General comments

Denka's RFR rehashes scientific data which was already thoroughly reviewed by EPA, such as the well-studied "healthy worker effect" comparing worker morbidity rates to those of the general population (which includes the very young, the very old, and the chronically ill). As added examples of rehashing settled science, Denka objects to the use of animal models in the denial of the request for correction (RFC). Denka also objects to EPA's rounding up at two stages of EPA's calculations. These issues were all considered in the RFC process, and rejected as not material to the original toxicological review of chloroprene.

In fact EPA did revise its 2010 Chloroprene toxicological review document after peer review. Denka objects that the revised post-peer review document was not itself peer reviewed. Denka is objecting to a practice that is academically and scientifically accepted and standard in the peer review process. The document was appropriately revised to address issues revealed in the peer review process. Specifically, the editors and authors correct any

Marco Kaltofen, PhD., PE (WPI) – Keeve Nachman, PhD (JHU) deficiencies according to the comments given by the reviewers. Returning to the review step initiates the potential for an “infinite loop” process.

Denka improperly reserves the right to make untimely supplements to the RFR, based on outstanding FOIA requests; one of which was not made until after the expiration of the original RFR deadline (FOIA dated May 9, 2018 vs. the original RFR unextended deadline of April 25, 2018).

Denka attempts to further extend the process by requesting that EPA participate directly with Ramboll (Denka’s consultant) in a new PBPK model workplan. Despite the expiration of the original and extended due dates in the RFR, Denka attempts to gain a further extension by requesting the EPA await the completion of Denka’s own PBPK model.

The bulk of Denka’s RFR consists of cherry-picking peer reviewers comments to present a distorted and false picture of “harsh” peer review comments. In effect, Denka highlights a reviewer’s minor or inconsequential comment, while ignoring the commenter’s overall agreement with EPA’s work product. These objections are addressed in the following section; where the dissonance between commenters’ intent and what the RFR cherry-picks is detailed.

Peer reviewer comments

Denka’s RFR misrepresents the opinions of the peer reviewers it cites. The specific comments from Denka’s RFR are given below, followed by additional comments from the cited peer reviewers, including the first line of each reviewers’ general impressions of EPA’s response document. Systematically showing the reviewers’ first lines effectively prevents the kind of cherry-picking found in Denka’s RFR.

Denka RFR: Peer reviewer Dr. Herman J. Gibb is cited in the RFR saying, EPA had “grossly misrepresented” the epidemiological data on chloroprene exposure.

Dr. Gibb's first sentence: "In general, the document lays out its arguments well."

Followed by: "The descriptor of 'likely to be carcinogenic to humans' is justified based on the animal and genotoxicity information, but the document overstates the human evidence."

Denka RFR: Peer reviewer Dr. John B. Morris is cited in the RFR as questioning the appropriateness of mouse data as a predictor of human responses to chloroprene.

Dr. Morris' first sentence: "From my perspective as an inhalation toxicologist with expertise in rodent studies, the Toxicological Review of Chloroprene provides an in depth review of the toxicological literature on this compound."

Followed by: "In many ways it is quite clear and thorough. The available database appears to be presented accurately and objectively. The overall conclusion, that chloroprene is an animal carcinogen whose mechanism(s) may include genotoxicity and mutagenesis, appears well founded."

Dr. Morris does indeed suggest that EPA consider interspecies differences, but ultimately Dr. Morris concludes the fundamental "conclusions appear sound".

Denka RFR: Dr. R. L. Melnick and D. Hattis suggested that the body of evidence presented by EPA was sufficient to change the chloroprene cancer descriptor to "carcinogenic to humans". Denka demands that the denial of the RFC be overturned because EPA "misstates" that these two reviewers based their decision on the epidemiological evidence.

Dr. Melnick's first sentence: "The draft document is a well-written, comprehensive review and assessment of published studies on the health effects of chloroprene in humans and in experimental animals."

Followed by: “The information is clearly presented and the conclusions are generally scientifically justified and consistent with EPA policy”; and, “Based on the animal data, mechanistic findings, and ‘the reasonably consistent’ evidence of increased risk of liver cancer mortality ‘among workers exposed to chloroprene in different cohorts in different continents,’ it is not clear why consideration was not given to the conclusion that chloroprene is ‘carcinogenic to humans.’”

Dr. Hattis’ first sentence: “Overall, the judgments made in the draft IRIS document for chloroprene are sound.”

Followed by: [EPA - Has the scientific justification for not deriving an RfD been clearly described in the document?] “Yes. But such a derivation would be possible if the PBPK model (or some suitable range of models derived from sensitivity analyses) were used. The principal study selected for analysis is fine.

Both reviewers’ asserted an opinion that the underlying evidence supported a “carcinogenic to humans” classification for chloroprene. General comments by both reviewers supported the underlying evidence that led to the denial of the RFC. Despite how EPA characterized the arguments of Melnick and Hattis, EPA retained the “likely carcinogenic to humans” status for chloroprene, rendering the point in the Denka RFR moot.

Denka RFR: Dr. Schlesinger suggested that EPA might want to consider a rat model.

Dr. Schlesinger’s first sentence: “The background information that is provided to support the selection of the key studies is clearly and accurately presented.” Even with his suggestion that a rat model may be worth considering, he still finds that “the overall conclusions appear to be sound.”

Denka RFR: Dr. Ruder assumed that the mouse model was appropriate, but did not see data to document this.

Dr. Ruder is identified in the peer review reports as an occupational epidemiologist, and it is clear that EPA is reliant on his expertise in that domain. The validity of the mouse model does not rest solely on the opinion of Dr. Ruder, as the opinions of multiple other peer reviewers with animal toxicological experience formed the basis of EPA's support for this choice.

In addition to the carefully-picked quotes of reviewers, Denka's RFR also had specific objections that are addressed below.

Denka RFR: Dr. Morris had specific questions regarding use of the mouse model, including the existence of species less sensitive to chloroprene-induced tumor formation.

By Dr. Morris: I am aware of no additional toxicity studies relative to chloroprene. The mouse bronchiolar airway lesions are reminiscent of those induced by naphthalene and styrene.

Denka RFR: Dr. Hattis indicated that the dosimetry could be informed by the application of a preliminary PBPK model.

This point is correct, but its framing as a problem with the assessment is misleading. It is clear from Dr. Hattis's comments that the suggestion was not intended to undermine EPA's choice. As stated by Dr. Hattis, "The PBPK model may well be considered not sufficiently tested against human data for un-caveated application to human risk projection, but I think its implications should at least be explored for sensitivity analyses."

Denka RFR: Dr. Morris and Dr. Gibb speculate on the usefulness of relying on a subset of human worker exposure data.

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By Dr. Morris: “The selection of the NTP inhalation study as the principal study is scientifically justified. It was well conducted and subject to peer review.”

By Dr. Gibb: “I am not aware of any additional original studies or reports that should be considered.”

Denka RFR: Dr. Marsh, cited by EPA, describes limitations in the IRIS 2010 Review that were already examined and discussed in the RFC and that represent well-known limitations of epidemiology that are not at issue in the denial of the RFC.

This objection to the denial of the RFC fails the test of relevance to the RFR.

Denka RFR: Denka objects to definitions of cancer descriptors used by EPA, however these are not at issue in this denial of the RFC.

Denka asserts that it believes the cancer descriptor should be downgraded in light of the evidence. In contrast, multiple peer reviewers suggested upgrading the cancer descriptor to “carcinogenic to humans” (and none suggested downgrading the descriptor); EPA ultimately chose to retain the descriptor of “likely carcinogenic to humans”, which is justified in light of the evidence and the support of the peer review comments.

This objection to the denial of the RFC fails the test of relevance to the RFR.

Denka RFR: Denka objects that EPA did not alter its conclusions despite “harsh” peer review comments.

The peer review comments do not provide a substantive basis for EPA to alter its conclusions. The RFR presents selected peer review comments, often taken out of context, in an attempt to mischaracterize and distort the opinions of the peer reviewers.

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A more accurate characterization of the chloroprene peer review is that the reviewers are generally in agreement with the 2010 IRIS assessment. The actual peer review comments themselves broadly and directly support EPA's toxicological review of chloroprene.

Signed:

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9/14/18



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