DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR RDX

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

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Peer reviewers for the second draft of the Toxicological Profile for RDX were:

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ATSDR would like to thank these scientists for their review of the document. When the reviewer's suggestions were followed, or when other revisions obviated the need to respond, no further response is provided herein. Revisions that may have obviated the need to respond included sections that were rewritten, moved, or deleted. Some of the editorial and format suggestions could not be followed without changing ATSDR established format. Additionally, several stylistic changes that were purely arbitrary were not incorporated. Other suggestions made by the reviewers that ATSDR decided not to follow are discussed below.

Review comments provided by Dr. Kacew

Page 1, line 17: The comment refers to boilerplate text that does not acknowledge the potential for indirect routes of exposure via prenatal or neonatal routes. Dr. Kacew states that these routes need to be included in this paragraph. He also notes that exposure by more than one route is a possibility and needs to be mentioned.

Response: Gestational exposure and exposure via maternal milk are mentioned in Section 1.6. A sentence stating that humans can be exposed by a combination of routes was added to Section 1.3. ATSDR will consider the suggestion of adding information about gestational and lactational exposure in this boilerplate.

Page 1, line 21: Dr. Kacew comments on the use of the term "sex" throughout the profile (i.e., 10/rats/sex/dose or sex-related differences); he believes the term "gender" is more appropriate and should replace "sex".

Response: Either word is correct and they are often used interchangeably. No changes were made.

Page 2, line 3: The comment refers to a sentence in Section 1.2 that states that RDX does not build up in fish or people. Dr. Kacew suggests replacing the terms *build up* with *bioaccumulate/bioconcentrate.*

Response: The terms *build up* are appropriate for the intended reading level of this section. No changes were made.

Page 1, line 22: The comment refers to the following sentence: "You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health." Dr. Kacew states that physiological status, such as pregnancy, should be included in the sentence in question. He also states that kidney function is a factor that needs to be mentioned, as the chemical is eliminated in urine and does not accumulate. Dr. Kacew notes that in the presence of abnormal renal function, adverse effects may be manifested due to higher amounts of the chemical. Thus, inclusion of function of kidneys involved in elimination of these chemicals is important. It is well-established that, in neonates, the function of kidney is not fully developed and thus, this subpopulation may be at higher risk. Although this has not been reported for humans, this needs to be stated with respect to making the public aware.

Response: Dr. Kacew's suggestions will be considered for future profiles.

Page 3, Section 1.5, Laboratory animals: The comment refers to the sentence: "Rats and mice that ate RDX for 3 months or longer had decreased body weights and slight liver and kidney damage (U.S. Army 1980b, 1983a)." Dr. Kacew asks for the biological meaning of the word *slight.*

Response: Slight means *not severe,* or not expected to produce significant dysfunction. The use of terms like this in Chapter 1 is in accordance with guidelines.

Page 44, line 15: The comment refers to the sentence: "In rats receiving a single intraperitoneal dose of RDX, small, but significant, decreases in brain cholinesterase levels were found 1.5, 3, or 6 hours after dosing." Dr. Kacew notes that there are no degrees of significance; therefore, small but significant is simply significant. He suggests deleting *small but.*

Response: The qualifier *small* is intended to convey information regarding the biological significance of the deviation from the norm. Differences between treated and controls groups can be statistically significant without necessarily being biologically (clinically) significant. No changes were made.

Page 28, line 17: The comment refers to the sentence: "No studies were located regarding reproductive effects in humans after oral exposure to RDX." Dr. Kacew suggests inserting the word *adverse* before the word *reproductive.*

Response: The sentence is correct as written since no studies were located that reported *adverse* or *non-adverse* reproductive effects. No changes were made.

Page 28, lines 23 and 31: The comment refers to two places in the text that state that a *nonstatistically significant increase* in testicular degeneration occurred. Dr. Kacew suggests changing *nonstatistically significant* with *quantitative.*

Response: The terms *quantitative decrease* do not convey any information regarding statistical significance. ATSDR is trying to make the point that, although there was an increase relative to controls, the difference was not statistically significant. No changes were made.

Page 56, line 26: The comment refers to the sentence: "A two-generation reproductive study in rats (U.S. Army 1980b) reported nonsignificant decreases in F_0 male fertility." Dr. Kacew suggests replacing the term *nonsignificant* with *quantitative.*

Response: The term *quantitative decrease* does not convey any information regarding statistical significance. ATSDR is trying to make the point that although there was an increase relative to controls, the difference was not statistically significant. No changes were made.

Page 67, line 31: The comment refers to the sentence: "RDX is slightly soluble in methanol, ether..." Dr. Kacew suggests deleting the term *slightly* and state the actual percentage.

Response: The source of the statement does provide an actual percentage; it just uses the word slightly. No change was made.

Page 68, line 26: The comment refers to a sentence stating that RDX is not very lipid soluble. Dr. Kacew suggests removing the word *very* as it has no biological meaning.

Response: The K_{ow} value is provided in the same sentence providing a context for the word *very.* No change was made.

Page 70, line 23: The comment refers to a sentence stating that RDX was shown to degrade very slowly in dark, tea-colored lagoon waters at a Louisiana Army ammunition plant. Dr. Kacew suggests removing the word *very* as it has no biological meaning.

Response: The half-life is given in the text providing a context for the word *very.* No change was made.

Page 86, line 17: The comment refers to the sentence: "Sensitivity for these methods is in the sub- to low-ppm range with good recovery (84–112%) and precision (2.3–24% CV)." Dr. Kacew suggests deleting the word *good* as recovery values are provided.

Response: The values given in the text provide a context for the word good. No change was made.

Page 90, line 2: The comment refers the following boilerplate text in Chapter 8: "MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites." Dr. Kacew suggests inserting the word *adverse* after the word *potential.*

Response: ATSDR will consider the suggestion for future profiles.

All other comments from Dr. Kacew were addressed as suggested.

Review comments provided by Dr. Gong

General Comments

Dr. Gong states that it would be helpful to highlight the updated information added to the profile since the 1995 version was released. Dr. Gong adds that the new lines of evidence should be discussed in a separate chapter or section. Finally, Dr. Gong suggests that the new information should be summarized and presented in an "Update Statement".

Response: Since the profile was released in 1995, 15 years ago, ATSDR felt it was more appropriate to develop a completely new document that incorporated the new data, as well as format changes that ATSDR has introduced over the years.

Specific Comments

Comment regarding the LSE tables: Dr. Gong states that it is inappropriate to categorize toxicological effects into "less serious" and "serious". Because effects are dose-dependent, the higher the dose is, the more severe the toxicity gets. Dr. Gong suggests replacing the "serious LOAEL" with an LD_{50} or LD_{20}. If serious effects occur, an $LD_{50}/_{20}$ can be derived. Otherwise, no $LD_{50}/_{20}$ is available.

Response: As discussed in the second paragraph of Section 3.2, *DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE,* ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are

used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. However, ATSDR will consider Dr. Gong's suggestion.

Comment regarding the acute-duration oral MRL: Dr. Gong notes that the acute MRL was derived on the basis of a 14-day NOAEL of 8.5 mg/kg/day for tremors and convulsions (U.S. Army 2006). However, Figure 3-1 and Table 3-1 clearly show that two other studies reported lower NOAELs of 2 mg/kg/day (U.S. Army 1980b) and 6 mg/kg/day (U.S. Army 1986d) in Sprague-Dawley rats. It is unclear why the U.S. Army (2006) study was selected over the others in the MRL derivation. Dr. Gong states that more explanation is required to justify the selection.

Response: It is standard practice to use the highest NOAEL that is lower than the lowest LOAEL as point of departure for MRL derivation. If no NOAEL can be defined in the database, the lowest LOAEL may be used as point of departure. An MRL based on a NOAEL of 2 or 6 mg/kg/day may be overly conservative.

Comment regarding the intermediate-duration oral MRL: Dr. Gong notes that the derivation of the intermediate MRL is justifiable, but still needs some explanation on why the U.S. Army (2006) study was the sole study selected among all of the available studies.

Response: As indicated on page 14, second paragraph, neurological effects are the critical effects of RDX and the lowest LOAEL was 8 mg/kg/day for tremors and convulsions in rats in the 90-day study by the U.S. Army (2006). The NOAEL in that study was 4 mg/kg/day. This was modern, well-conducted study that evaluated a comprehensive number of end points. For these reasons, it was selected as the basis for the intermediate-duration oral MRL for RDX.

Comment regarding evaluation of the text of Chapter 3: Dr. Gong states that the text does not provide "bottom-line" statements regarding the relevance to human health of the end points summarized.

Response: The relevance of the findings of animal studies to human health is discussed in Chapter 2, *RELEVANCE TO PUBLIC HEALTH.*

Comment regarding analytical methods: Dr. Gong states that it is unclear whether the methods discussed can be used to measure RDX metabolites and no methods specifically for measuring key metabolites (e.g., MNX, DNX, and TNX) have been included.

Response: It is beyond the scope of this toxicological profile to discuss the analytical methods available for measuring RDX metabolites.

All other comments from Dr. Gong were addressed as suggested.

Review comments provided by Dr. Meyer

Page 47, line 6: The comment refers to the following sentence that appears at the end of Section 3.6, *TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS*: "*No in vitro studies were located regarding endocrine disruption of RDX.*" Dr. Meyer asks why only *in vitro* studies are mentioned here and not studies reporting testicular effects in animals mentioned in Section 3.2.2.5, Reproductive Effects.

Response: This section is intended to summarize effects produced by an action of the chemical via the neuroendocrine axis. The text was revised to indicate that there is no evidence that the reproductive or developmental alterations summarized in Sections 3.2.2.5 and 3.2.2.6 are the consequence of RDX-induced alterations in the neuroendocrine axis.

All other comments from Dr. Meyer were addressed as suggested.