May 9, 2016

Docket ID No. EPA-HQ-ORD-2013-0430

Dr. Marry Ross
Deputy Director, National Center for Environmental Assessment
US Environmental Protection Agency
Washington, DC

Dear Dr. Ross:

I am submitting these comments because I was surprised and shocked when I read EPA's cancer weight-of-evidence (WOE) conclusion for hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). It is obvious to me that the WOE determination for RDX is inconsistent with both the data that are summarized in the IRIS Draft Toxicological Review of RDX (EPA/635/R-15/034a) and with the cancer descriptors provided in EPA's 2005 Guidelines for Carcinogen Risk Assessment.

The Executive Summary of the IRIS draft review of RDX concludes "results from animal studies provide *suggestive evidence* of carcinogenic potential for RDX based on positive trends in liver and lung tumor incidence in experimental animals." This statement is incomplete since there are significant increases in tumor incidence in addition to the positive trends in RDX exposed animals. In addition, while acknowledging two separate organ sites for tumor induction by RDX, the statement neglects to note that carcinogenic effects were observed in two species. As indicated on page 1-73 of Section 1, the data for RDX matches the descriptor *likely to be carcinogenic to humans* because it "induced dose-related increases in tumors in two species (mouse and rat), in both sexes, and at two sites (liver and lung)." In recognizing the multiple site carcinogenicity of RDX, the dose-response data for liver and lung tumors in female B6C3F1 mice from the study by Lish et al. (1984) were considered to be reliable for estimating carcinogenic risk from oral exposure to RDX (see Section 2.3, pages 1-25 to 1-31); furthermore, no uncertainties were listed for the reported liver or lung tumor responses that were used to derive the cancer risk value (see Table 2.8).

Regarding the liver tumor effects of RDX, the draft document notes that "an increased incidence of liver tumors was observed in one chronic mouse study (Lish et al., 1984) and one of two chronic rat studies (Levine et al., 1983b)." In female mice from the Lish et al. study there were significant increases in the trend and incidences of hepatocellular adenomas or carcinomas, while in male mice the incidence of hepatocellular adenomas or carcinomas was higher in the two high dose groups (42.4% and 48.1%) compared to controls (31.7%). These findings show consistency for the liver tumor response in male and female mice. After the reanalysis of the liver lesions in female mice (Parker et al., 2006), the trend was still significant. The RDX draft document failed to note in the text or in Table 1-13 that the incidence of hepatocellular adenomas or carcinomas was also significantly increased in the two high dose groups of female mice compared to controls (controls: 1.5% vs 15.6%, and 12.9% in the higher dose groups) after the reanalysis. In

male rats, there was a significant positive trend for hepatocellular carcinomas, and the incidence of liver carcinomas in the two highest RDX treatment groups (3.6% and 6.5%) exceeded the National Toxicology Program's (NTP) historical control range for this rare tumor in F344 rats (0-2%) from studies conducted during that same time period. To evaluate the occurrence of rare tumors in a carcinogenicity study for a possible chemical-related effect, it is important to compare incidence values with historical control rates. Using NTP historical control data, the trend for liver carcinomas in RDX-treated F344 rats is highly significant ($p = 0.003$).

Regarding lung tumors, the incidence of alveolar/bronchiolar (A/B) carcinomas and the combined incidence of A/B adenomas and carcinomas in the Lish et al. (1984) study showed a significant positive trend in female mice. The incidence of A/B carcinomas in male mice also showed a significant positive trend. The draft RDX document should also have noted that the increased incidence of A/B carcinomas in the high dose group of male mice appears to be significant (18.5% vs 4.8% in controls) and should list the *p value* for this increase. The above findings provide consistency for the lung tumor response in male and female mice.

Based on the analysis of the liver and lung tumor responses observed in mice or rats exposed to RDX, it is not clear why the cancer WOE categorization for RDX was reported in the draft document as *suggestive evidence of carcinogenic potential* when the tumor data for RDX clearly meet EPA's criteria for the descriptor *likely to be carcinogenic to humans*: According to EPA's 2005 Guidelines for Carcinogen Risk Assessment, supporting data for the descriptor "likely to be carcinogenic to humans" may include "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, OR exposure route, with or without evidence of carcinogenicity in humans." The tumor data on RDX certainly meets the criteria covered by this descriptor and is much stronger than all of the criteria listed in EPA's cancer guidelines for *suggestive evidence of carcinogenicity*.

In attempting to justify the lower cancer WOE category, the report gives a misdirected emphasizes the number of hepatocellular carcinomas in male F344 rats (two in the 8 and 40 mg/kg groups and one in the controls). However, in doing so, the statement neglects to note that the denominator values were different between the control group (55) and the 40 mg/kg group (31). With proper adjustment for differences in the denominators, incidence values are 1.8% and 6.5%, respectively. As noted above, the latter value exceeds NTP's historical control rate for this tumor. Surely the EPA staff and managers know that it is inappropriate to highlight tumor numbers that are not adjusted for differences in the number of animals at risk. Misleading information should not be used to justify the lower cancer WOE descriptor.

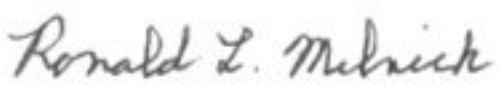
The *suggestive evidence of carcinogenic potential* descriptor is also promoted in the draft report by the claim that "RDX did not increase the incidence of carcinomas at any other site in F344 or Sprague-Dawley rats." However, in earlier text (pages 1-60 to 1-63), it was noted that "interpretation of results from this study [Hart, 1976 in Sprague-Dawley rats] is limited by the comparatively lower doses employed in the study, and the recording of effects only at the control and high dose groups" and "the lack of characterization of the test material." These omissions in the draft document on RDX result in a misleading

justification for the selection of the descriptor *suggestive evidence of carcinogenic potential.*

In its role of protecting people from toxic agents in the environment, it is EPA's obligation to promote policies that reduce human exposures to adverse environmental agents. The faulty cancer evaluation of RDX will result in risk management decisions that protect polluters rather than protecting US citizens who are exposed to this cancer-causing chemical.

The RDX document does a poor job of explaining how or why EPA opted for the *suggestive evidence* WOE descriptor. I urge the EPA to correct the serious defects in this IRIS assessment in a timely and transparent fashion because the inappropriate application of the cancer descriptor differs markedly from evaluations of animal cancer data performed by the NTP, by the International Agency for Research on Cancer, and previously by EPA; and most importantly, it sets a bad precedent for future assessments of environmental carcinogens.

Sincerely,



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