Reevaluation of the toxicity and carcinogenicity of RDX within the guidelines of modern risk assessment

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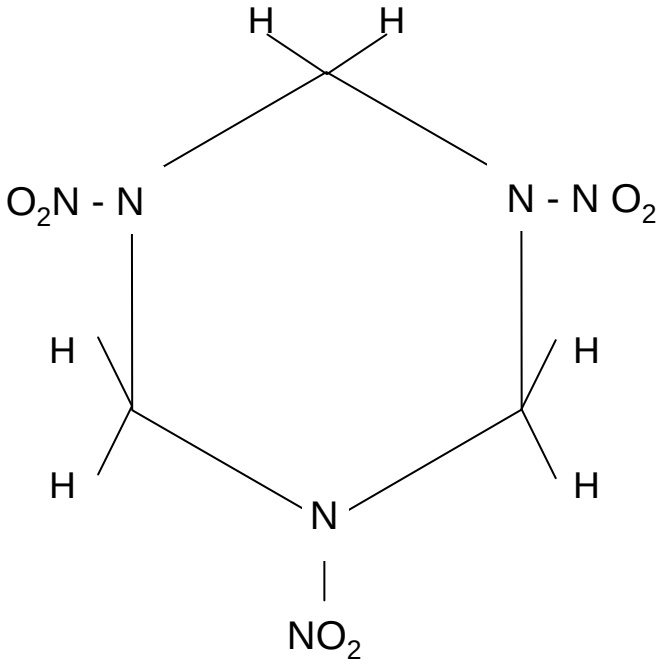


CHEMICAL:

RDX

- **Synonyms**
  Cyclonite, Hexolite, Hexogen, T4, PBX (AF) 108
  Cyclotrimethylenetrinitramine,
  Hexahydro–1,3,5–trinitro-1,3,5-triazine

- **CAS No. 121-82-4**
- **Molecular Weight: 222.26**
- **Molecular Formula: C3H6N6O6**
- **Physical Form – White Crystalline Solid**
- **Specific Gravity – 1.816 @ 20#C**

Tiered Approach for Reevaluation

- Check validity of cancer findings.
- Complete the genotoxicity assessment.
- Determine the metabolites in mammals.

  If a threshold approach is appropriate.
- Check quality of NOEL and redo if necessary
- Consult with EPA's IRIS group to determine UF applied.
- Do appropriate research to address UF, publish and send data to IRIS group.

Summary of RDX Pathology Findings

- The cancer potency of RDX was overestimated by about 5 fold. The finding of RDX as a carcinogen now rests on equivocal findings in one dose group of one gender of one species and only if the statistics are calculated using the combined incidence of carcinoma and adenoma and only if the calculations are performed using the remarkably low incidence of lesions in the concurrent controls.

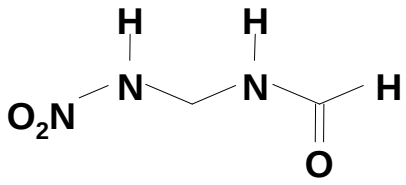
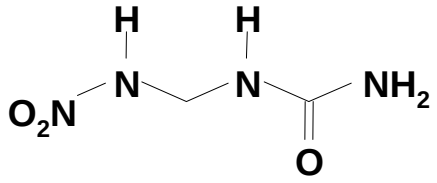
Importance of Genotoxicity Assessment

- Genotoxic assessments work under the assumption that one molecule of the carcinogen could potentially produce a mutation that would cause cancer. Because of this, these assessments are done by extrapolating the dose to 0.
- Usually produce more conservative MCLs and cleanup decisions and more costly remedies.
- Carcinogens are assumed to be genotoxic unless shown to be otherwise.
- If there is a CSF in the IRIS data base many states are required to use it in calculation of cleanup values.

Genotoxicity Summary

- Ames – Negative
- Mouse Lymphoma Test – Negative
- Mouse Micronucleus Test – Negative
- Unscheduled DNA Synthesis – Negative
- Dominant lethal assay F344 Rats - Negative

Table Urine metabolites of RDX

Sample Origin	Retention Time (Minutes)	$[M-H]^-$	Proposed Metabolite Identification	Characteristics Product Ions (m/z)
Urine peak 1 M1	2.35	118		61, 46, 44.
Urine peak 2 M2	2.26	133		61, 59, 46.

Non-Linear Toxicity

- If a compound is not genotoxic it is appropriate to assess risk by using threshold type assessments.
- Threshold type, suggestive carcinogens and non-carcinogenic toxicants.
- Reference dose (RfD) values are derived for noncancer endpoints. Experimental NOEL or LOEL are converted to RfD values by application of UFs.

Development of a Reference Dose

- Based on a sub-chronic or a chronic study done under the strictures of GLP in rodents or higher species. The longer the duration and the higher the species the more favorably the data is viewed.
- Uncertainty factors (UFs) are used to derive RfD from animal dose/response data.
- Common to have UFs for interspecies, intraspecies, duration (if subchronic data is used) and sometimes for data quality.
- Additional specialized testing can reduce or eliminate uncertainty factors.

PUBLICATIONS	Data Complete	In Draft	Submitted	Accepted
Cancer Reassessment	X	X	X	X
PBPK Model	X	X		
New Subchronic Study	X	X		
Metabolite Study	X	X	X	X
Genotoxicity Assessment	X	X	X	X
Toxicodynamics	-			
Relative Source Term	X	X		
Toxicogenomic Study	X			
Oral Bioavailability RDX	X	X	X	
Dermal Absorption RDX	X	X	X	