# 2. RELEVANCE TO PUBLIC HEALTH

## 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO RDX IN THE UNITED STATES

RDX is a military explosive produced by the nitrolysis of hexamine with nitric acid. It is a synthetic compound that does not occur naturally in the environment. Effluents and emissions from Army ammunition plants and many current and former military installations are responsible for the release of RDX into the environment. RDX can enter the air, water, and soil as a consequence of these releases. RDX is expected to exist as a particulate in the atmosphere. RDX has low water solubility and is subject to photolysis (half-life of 9–13 hours). RDX undergoes biodegradation in water and soil under anaerobic conditions to form several biodegradation products. RDX is mobile in soil and can leach into groundwater, and can be transported from soils or water to terrestrial and aquatic plants. RDX is not very lipid soluble, and therefore, has a low potential for bioaccumulation in aquatic species.

RDX has been identified in environmental samples, primarily near army munitions depots. Indoor air samples collected at ammunition plants were found to contain RDX in concentrations ranging from 0.032 to 60 $mg/m^3$. In water, RDX has been identified in a variety of groundwater samples from ammunition plants in the United States (<20–43,200 μg/L) and Germany (21–3,800 μg/L). Sediment samples from Army depots have been found to contain RDX in concentrations ranging from <0.1 to 3,574 mg/kg and in composts prepared from contaminated sediments (>2.9–896 mg/kg). Additionally, RDX was identified in plant species irrigated with or grown in contaminated water (<20–3,196 μg/L).

For the general population, including children, exposure to RDX is limited to areas around Army ammunition plants where it is manufactured, used in munitions, packed, loaded, or released through the demilitarization of antiquated munitions. The most likely route of exposure is ingestion of contaminated drinking water or agricultural crops irrigated with contaminated water. Exposure can also occur though dermal contact with soil containing RDX or by inhaling contaminated particulate matter produced during incineration of RDX-containing waste material. Children playing in contaminated water or soil may also be exposed via ingestion. Children can also be exposed if workers inadvertently bring home RDX adhered to shoes or clothing.

Occupational exposure to RDX can occur when workers handle RDX at Army ammunition plants. Under these conditions, exposure can occur as a result of release of dust into the workroom air, principally

during dumping of dried RDX powder, screening and blending, and clean-up of spilled material. Exposure to RDX can also occur through dermal contact during manufacture, handling, and clean-up of RDX. RDX was detected at a concentration of 0.052 mg/m$^3$ (0.47 ppm) in the particulate fraction of only one of eight indoor air samples taken from the incorporation area of Holston Army Ammunition Plant in Tennessee in 1986. Based on the observed concentration, the potential for exposure to RDX is considered to be negligible.

## 2.2 SUMMARY OF HEALTH EFFECTS

There is limited information on the toxicity of RDX in humans; the database consists of studies of workers exposed to RDX dust, soldiers using C-4 (a plasticized explosive containing 91% RDX) as a cooking fuel, and case reports of individuals ingesting RDX. Most of these studies involve acute exposure to RDX and provide limited exposure information. Neurologic dysfunction, primarily seizures and convulsions, was the most commonly reported effect. The seizures/convulsions typically occurred within several hours of exposure, and in some cases, convulsions were noted for several days after exposure. Other neurological symptoms that have been observed in humans include disorientation, lethargy, muscle twitching, and marked hyperirritability.

Studies in laboratory animals support neurological effects as a sensitive end point of RDX. Seizures, convulsions, and tremors have been reported in rats, deer mice, dogs, and monkeys orally exposed to RDX for acute, intermediate, or chronic durations. As with human exposure, the clonic-tonic convulsions and seizures are often observed shortly after exposure; however, a study in monkeys did not report seizures in some of the animals until after 34–57 doses of 10 mg/kg/day. In acute-exposure studies, the lowest adverse effect level for seizures and convulsions was 17 mg/kg/day, with no seizures at 12.5 mg/kg/day. In addition to these neurological effects, decreases in motor activity and impaired learning were observed in rats following administration of a single gavage dose of 12.5 mg/kg/day; however, no alterations in motor activity were observed in rats administered 10 mg/kg/day for 16 or 30 days. A lower adverse effect level (8 mg/kg/day) was reported in an intermediate-duration study, with a no-observed-adverse-effect level (NOAEL) of 4 mg/kg/day. At higher doses (≥40 mg/kg/day), hyperactivity, hyperirritability, hyperreactivity, and increased fighting have been observed in rats. Although the database is mostly comprised of studies in rats, intermediate-duration studies in monkeys and dogs do not suggest species differences in RDX-induced seizures/convulsions. In chronic-duration oral studies, seizures and convulsions were observed at 40 mg/kg/day; this dose was also associated with 88% lethality. No neurological effects were observed in rats chronically exposed to 8 or 10 mg/kg/day.

The animal data suggest that there may be other targets of RDX toxicity, including the hematological system and liver following oral exposure. Small, although significant, decreases in hemoglobin and erythrocyte levels were observed following intermediate-duration exposure, but this was not consistently found in other intermediate or chronic studies. Several studies found minor changes in serum chemistry parameters suggestive of a slight impairment of liver function. These alterations include decreases in alanine aminotransferase and in serum triglyceride and/or cholesterol levels and increases in serum cholesterol levels. A decrease in blood glucose levels observed in one study of rats may also be related to impaired liver function. Hepatomegaly and hepatocellular vacuolization have been reported in rats; however, most studies did not report histological alterations in the liver. An intermediate-duration study in monkeys reported an increase in vomiting following gavage administration of 10 mg/kg/day RDX; the occurrence of vomiting at 0.1 or 1 mg/kg/day was similar to controls.

There is limited information to suggest that RDX is a reproductive toxicant following oral exposure. An increased incidence of spermatic granuloma in the prostate was observed in rats following exposure to 40 mg/kg/day for 6 months; however, this effect was not observed at longer durations (1 or 2 years) in the same study. A nonsignificant increase in testicular degeneration was also observed in this study in rats exposed for 6 months to 40 mg/kg/day, but testicular effects were not observed in another study of rats exposed to 100 mg/kg/day for 13 weeks. Adverse developmental effects have been observed in rats, particularly at maternally toxic doses. Decreases in pup survival and increases in the occurrence of stillbirths were observed at 50 mg/kg/day; this dose also resulted in maternal deaths. A decrease in pup body weight and an increase in the incidence of renal cysts were observed in $F_2$ pups at 16 mg/kg/day in a two-generation study of rats and a decrease in fetal body weight and length were observed in the offspring of rats administered 20 mg/kg/day on gestation days 6–15. No adverse developmental (or maternal) effects were observed in rabbits.

The carcinogenic potential of RDX was evaluated in orally exposed rats and mice; no evidence of carcinogenicity was observed in two rat studies. In mice, an increase in the combined incidence of hepatocellular adenomas and carcinomas was observed in females only. However, a re-evaluation of these data using current diagnostic criteria resulted in a reclassification of some hepatocellular adenomas as foci of cytoplasmic alterations. As a result of the re-analysis, the combined incidence was significantly higher than concurrent controls at 35 mg/kg/day, but not at 100 mg/kg/day and the incidence in the 35 mg/kg/day group was within the range of historical control data. The investigators suggested that the study provided equivocal evidence of carcinogenicity. The International Agency for Research on Cancer

(IARC) and the Department of Health and Human Services (DHHS) have not classified the carcinogenicity of RDX. EPA classified RDX as a group C carcinogen, possibly carcinogenic to humans; however, this evaluation was done prior to the re-evaluation of mouse tumor data. EPA is currently re-evaluating RDX.

## 2.3 MINIMAL RISK LEVELS (MRLs)

ATSDR has made estimates of exposure levels posing minimal risk to humans (MRLs) for RDX. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous adverse health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive levels posing minimal risks to humans (Barnes and Dourson 1988; EPA 1990b), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for adverse health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

### *Inhalation MRLs*

ATSDR has not derived inhalation MRLs due to the limited data available on the toxicity of RDX following inhalation exposure. Several studies reported convulsions in humans acutely exposed to unspecified amounts of RDX (Hollander and Colbach 1969; Kaplan et al. 1965; Testud et al. 1996a). Nausea and vomiting have also been reported in humans (Hollander and Colbach 1969; Ketel and Hughes 1972); however, these individuals may have been exposed to RDX via inhalation and ingestion. Deaths due to bronchopneumonia, pneumonia, or pulmonary congestion were observed in rabbits and guinea pigs exposed to an unspecified concentration of RDX (Sunderman 1944). The lack of dose-response data for the human and animal studies precludes derivation of inhalation MRLs.

***Oral MRLs***

***Acute-Duration***

- ATSDR has derived an MRL of 0.2 mg/kg/day for acute-duration oral exposure (14 days or less) to RDX. This MRL is based on a NOAEL of 8.5 mg/kg/day and LOAEL of 17 mg/kg/day for convulsions/seizures observed in rats administered RDX via gavage 7 days/week for 14 days (U.S. Army 2006). A PBPK model was used to predict peak brain concentrations in the rat and to estimate human equivalent doses (HEDs). The $NOAEL_{HED}$ of 6.45 mg/kg/day was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

The acute toxicity database consists of several human exposure studies reporting convulsions and seizures following oral exposure to RDX (Hollander and Colbach 1969; Kasuske et al. 2009; Ketel and Hughes 1972; Küçükardalĩ et al. 2003; Merrill 1968; Stone et al. 1969; Woody et al. 1986). Although some studies provide exposure estimates, these values are not considered reliable. Animal studies have also identified convulsions and seizures as the most sensitive effect following acute-duration oral exposure (Burdette et al. 1988; Meyer et al. 2005; Schneider et al. 1977; U.S. Army 1980b, 1986d, 2006). The lowest adverse effect level for convulsions/seizures was 17 mg/kg/day in rats administered RDX via gavage for 14 days (U.S. Army 2006); an increase in the incidence of mortality was also observed at this dose level (U.S. Army 2006). Several other studies have identified similar lowest-observed-adverse-effect levels (LOAELs); convulsions were observed in rat dams administered via gavage 20 mg/kg/day on gestation days 6–15 or 19 (U.S. Army 1980b, 1986d) and seizures were observed in rats administered a single gavage dose of 25 mg/kg (Burdette et al. 1988). The dose-response curve for seizures/convulsions appears to be fairly steep, with no effects at 8.5 (U.S. Army 2006) or 12.5 (U.S. Army 1985b) mg/kg/day and seizures at 17 mg/kg/day (U.S. Army 2006). Additionally, decreases in motor activity and learning were observed at a lower dose (12.5 mg/kg/day) in rats receiving a single gavage dose (U.S. Army 1985b).

There are limited data on the non-neurological toxicity of RDX following acute-duration exposure. U.S. Army (2006) monitored body weight, hematological parameters, clinical chemistry parameters, and organ weight in male and female rats administered gavage doses of 2–17 mg/kg/day for 14 days. No biologically relevant alterations in these systemic toxicity end points were observed. Decreases in fetal weight and length were observed in the offspring of rats administered 20 mg/kg/day on gestation days 6–15 (U.S. Army 1986d); however, this exposure was associated with maternal convulsions/seizures and death.

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Based on the available data, impaired neurological function was identified as the critical effect for derivation of an acute-duration oral MRL. Although the acute database lacks studies adequately assessing systemic toxicity, intermediate-duration studies have found no systemic effects at doses lower than those affecting the nervous system. The lowest adverse effect level for neurological effects is 12.5 mg/kg/day for decreases in motor activity and learning in rats following a single gavage dose (U.S. Army 1985b); this study did not identify a NOAEL. In a repeated exposure study by this group (U.S. Army 1985b), no significant alterations in motor activity were observed in rats following 15 or 30 days of exposure to doses as high as 10 mg/kg/day. At a slightly higher dose (17 mg/kg/day), convulsions and tremors were observed in rats administered RDX for 14 days (U.S. Army 2006); no neurological effects were observed at 8.5 mg/kg/day. The U.S. Army (2006) study was selected as the principal study because it identified a NOAEL and involved repeated exposure, and it is likely that an MRL based on this study would be protective for the neurobehavioural effects observed at 12.5 mg/kg/day in the U.S. Army (1985b) study. In the U.S. Army (2006) study, groups of 6 male and 6 female Sprague-Dawley rats were administered via gavage 0, 2.125, 4.25, 8.5, 17.00, 25.50, 34.00, or 42.5 mg/kg/day as a suspension of RDX/1% methylcellulose/0.2% Tween 80 in distilled water 7 days/week for 14 days. Rats were monitored daily for toxic signs and morbidity. Body weights and feed consumption were measured on days 0, 1, 3, 7, and 14. Additional parameters used to assess toxicity included clinical chemistry and hematology values, organ weights, and gross necropsies. A significant increase in early deaths was observed at ≥25.5 mg/kg/day. Tremors and convulsions were observed in rats exposed to ≥17 mg/kg/day. In the males exposed to ≥17 mg/kg/day, blood stains around the mouth and nose and low arousal were also observed. Increased arousal, blood around the mouth and nose, barbering, and lacrimation were observed in females exposed to ≥17 mg/kg/day. No signs of neurological alterations were observed in rats exposed to ≤8.5 mg/kg/day. Significant decreases in body weight were observed in male rats exposed to ≥17 mg/kg/day on days 1 and 7, but there were no significant alterations in male body weight at termination. In female rats, significant decreases in body weight gain were observed at ≥34 mg/kg/day on day 1 and in the 8.5 mg/kg/day group on day 14; however, the magnitude of the decreased body weight was <10% and no significant alterations were observed at higher dose levels. Significant decreases in food consumption were also observed during the first 7 days of exposure in males and females exposed to ≥8.5 mg/kg/day. Significant decreases in absolute liver weights and liver-to-brain weights and increases in blood cholesterol levels were observed in females exposed to 8.5 mg/kg/day; these effects were not observed at higher dose levels or in males. Due to the lack of dose-response relationships for the alterations in liver weight and blood cholesterol levels, these changes observed in the 8.5 mg/kg/day

female group were not considered biologically relevant. No significant alterations in hematological parameters or other clinical chemistry parameters or organ weights were observed.

The acute-duration oral MRL was derived using the NOAEL/LOAEL approach; the lack of incidence data for the neurological effects precluded using a benchmark dose approach. The MRL is based on the NOAEL of 8.5 mg/kg/day and a LOAEL of 17 mg/kg/day identified in the U.S. Army (2006) study. The available mode of action data suggest that the induction of seizures and/or convulsions is likely associated with the binding of RDX to GABA receptors in the brain and the onset of seizures is directly related to the levels of RDX in the brain (Gust et al. 2009; Williams et al. 2011). A physiologically based pharmacokinetic (PBPK) model (Sweeney et al. 2012) was used to predict peak brain RDX concentration and mean brain RDX concentration for each administered dose in the U.S. Army (2006) study. Based on a comparison of predicted brain RDX concentrations to the NOAEL and LOAEL values for seizures/convulsions observed in intermediate and chronic studies, ATSDR determined that peak brain RDX concentration was a more appropriate internal dose metric for derivation of the MRL than mean brain RDX concentration. To determine the point of departure for the MRL, the PBPK model was used to predict HEDs from peak brain concentration data. Detailed discussions of the PBPK model and support for using peak brain concentration as the internal dose metric are presented in Appendix A. The PBPK model predicted a peak brain concentration of 6.19 mg/L in rats administered 8.5 mg/kg/day 7 days/week for 14 days and a HED of 6.455 mg/kg/day. The MRL of 0.2 mg/kg/day was calculated by dividing the $NOAEL_{HED}$ of 6.45 mg/kg/day for neurological effects (U.S. Army 2006) by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

***Intermediate-Duration***

- ATSDR has derived an MRL of 0.1 mg/kg/day for intermediate-duration oral exposure (15–364 days) to RDX. The MRL is based on a 90-day study which identified a NOAEL of 4 mg/kg/day and LOAEL of 8 mg/kg/day for seizures/convulsions in rats receiving gavage doses of RDX 7 days/week (U.S. Army 2006). ATSDR derived the MRL using benchmark dose modeling of seizure/convulsion incidence data and PBPK modeling to predict peak brain concentrations in the rat and to estimate HEDs. The $BMCL_{HED}$ of 4.13 mg/kg/day was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

No human studies have examined the toxicity of RDX following intermediate-duration exposure. Data from laboratory animal studies suggest that the nervous system is the most sensitive target of RDX toxicity. Convulsions, seizures, and/or tremors have been observed in rats at doses of ≥8 mg/kg/day (U.S.

Army 1983a, 2006; von Oettingen et al. 1949), monkeys at 10 mg/kg/day (U.S. Navy 1974b), and dogs at 50 mg/kg/day (von Oettingen et al. 1949). In addition, hyperactivity was noted in rats exposed to 100 mg/kg/day (Levine et al. 1981, 1990). The results of the U.S. Army (2006) study suggest that there is a steep dose-response curve for seizure induction. The occurrences of seizures were 0% at 4 mg/kg/day, 20–30% at 8 mg/kg/day, 45–50% at 10 mg/kg/day, and 80–90% at 12 or 15 mg/kg/day. An increase in mortality was often reported at the lowest doses associated with seizures. Less serious adverse health effects have been observed at similar or higher dose levels. Several studies have found changes in serum chemistry parameters suggestive of impaired liver function, although histological alterations were not generally found in the liver. Decreases in serum cholesterol and/or triglycerides were observed at ≥8 mg/kg/day (U.S. Army 1983a, 2006; Levine et al. 1981) and decreases in serum alanine aminotransferase activity levels were observed at 28 mg/kg/day (U.S. Army 1980b). The magnitude of these alterations was small and not likely to be biologically significant. Small, although significant, decreases in erythrocyte and hemoglobin levels were also observed in rats exposed to 40 mg/kg/day (U.S. Army 1983a) and mice exposed to 160 mg/kg/day (U.S. Army 1980b), but this finding has not been consistently found in intermediate-duration studies (U.S. Army 1980b, 2006; von Oettingen et al. 1949). Emesis was observed in monkeys administered via gavage 10 mg/kg/day for 90 days (U.S. Navy 1974b); the incidence in monkeys administered 1 mg/kg/day was not considered to be different from the controls. There is limited evidence that RDX is a reproductive toxicant. An increased incidence of spermatic granuloma was observed in the prostate of rats exposed to 40 mg/kg/day for 6 months (U.S. Army 1983a). In a two-generation study in rats, decreases in $F_2$ pup body weight and increases in the incidence of renal cysts were observed at 16 mg/kg/day and increases in the number of stillbirths and decreases in pup survival were observed in the $F_1$ generation exposed to 50 mg/kg/day (U.S. Army 1980b).

Impaired neurological function was identified as the critical effect for derivation of an intermediate-duration oral MRL. The lowest adverse effect level for this end point is 8 mg/kg/day with a NOAEL of 4 mg/kg/day (U.S. Army 2006). A slightly higher LOAEL of 10 mg/kg/day was identified in monkeys (U.S. Navy 1974b); a NOAEL was not identified in this study. The rat study (U.S. Army 2006) was selected as the principal study. In this study, groups of 10 male and 10 female F344 rats were administered via gavage 0, 4, 8, 10, 12, or 15 mg/kg/day as a suspension of RDX/1% methylcellulose/ 0.2% Tween 80 in distilled water 7 days/week for 90 days. Rats were monitored weekly for toxic signs and functional observational battery (FOB) observations (home-cage, hand held, and open arena observations), and body weights and feed consumption were measured weekly. Additional parameters used to assess toxicity included neurobehavioral tests after week 11 (motor activity, grip strength, and sensory reactivity to different types of stimuli), ophthalmic examination, urinalysis, clinical chemistry,

hematology, coagulation, organ weights, gross necropsies, and histopathological examination of major tissues and organs from rats exposed to 0 or 15 mg/kg/day. Significant increases in mortality rates were observed at ≥10 mg/kg/day. Convulsions were observed in most animals dying early. Transient clinical signs included changes in arousal, inflammation of eyelash follicles, increased salivation, blood stains around mouth and nose, rough haircoat, tremors, and convulsions; the incidence and severity increased with dose. The incidences of convulsions were 0/20, 0/20, 3/20, 6/20, 13/20, and 12/20 in rats exposed to 0, 4, 8, 10, 12, and 15 mg/kg/day, respectively. Although the incidence of convulsions was not statistically significant at 8 mg/kg/day, the increased incidence of seizures was considered biologically significant and the 8 mg/kg/day dose level was considered a LOAEL. The tremors/convulsions were observed within the first week of exposure in the 12 or 15 mg/kg/day groups and persisted throughout the study. No significant RDX-related alterations in foot splay, front limb grip strength, or response to stimuli were found. Hematological tests showed significant increases in erythrocyte mean cell volume at 8 (males only), 10, and 12 mg/kg/day and significant decrease in serum cholesterol in males exposed to ≥8 mg/kg/day. No significant increases in the incidence of histopathological alterations were observed.

The intermediate-duration oral MRL was derived using benchmark dose modeling and PBPK modeling. As discussed for the acute-duration oral MRL, a PBPK model (Sweeney et al. 2012) was used to predict peak and mean brain RDX concentrations. Comparisons with empirical seizure data following intermediate- or chronic-duration exposure with predicted brain RDX levels provided support for using peak brain concentration as the internal dose metric for the MRL derivation. The incidence data for convulsions in rats were fit to several dichotomous models using a benchmark response (BMR) of 10% and the internal dose metric of peak brain concentration. Detailed discussion of the benchmark dose modeling, the PBPK model, and support for the selection of the internal dose metric are presented in Appendix A. The log-probit model provided the best fit to the data and was used to estimate a 95% lower confidence limit on the benchmark dose ($BMDL_{10}$) of 3.9624 mg/L. Using PBPK modeling, a HED of 4.1308 mg/kg/day was predicted from the $BMDL_{10}$. The MRL of 0.1 mg/kg/day was calculated by dividing the $BMDL_{HED}$ of 4.1308 mg/kg/day for neurological effects by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

***Chronic-Duration***

- ATSDR has derived an MRL of 0.1 mg/kg/day for chronic-duration oral exposure (≥365 days) to RDX. This MRL is based on a NOAEL of 8 mg/kg/day and LOAEL of 40 mg/kg/day for convulsions/seizures observed in rats exposed to RDX in the diet for 2 years (U.S. Army 1983a). A PBPK model was used to predict peak brain concentrations in the rat and to estimate HEDs.

The $NOAEL_{HED}$ of 4.223 mg/kg/day was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

The chronic oral toxicity of RDX has been evaluated in two rat studies (U.S. Army 1983a; U.S. Navy 1976) and a mouse study (U.S. Army 1984c). A number of adverse health effects have been observed in rats exposed to 40 mg/kg/day including tremors, convulsions, and hyperresponsiveness; decreased hematocrit, hemoglobin, and erythrocyte levels; hepatomegaly and decreased serum cholesterol and triglycerides; renal papillary necrosis and increased blood urea nitrogen levels; testicular degeneration; and cataracts (females only) (U.S. Army 1983a); no adverse effects were observed in rats exposed to 8 mg/kg/day. The 40 mg/kg/day dose was also associated with an 88% mortality rate. In addition to these effects, significant increases in the incidence of suppurative inflammation were observed in the prostate of rats exposed to ≥1.5 mg/kg/day (U.S. Army 1983a). U.S. Army (2006) noted that inflammation of the prostate gland is a common condition in older rodents and is generally not due to toxicity; additionally, the prostate effects in the U.S. Army (1983a) study were predominantly found in rats dying early.

In the U.S. Navy (1976) rat study, no adverse effects were observed at doses as high as 10 mg/kg/day. This study did not include a histological examination of the prostate and the animals were monitored weekly for overt signs of toxicity. In mice, increases in serum cholesterol levels were observed in females exposed to 35 mg/kg/day and increased relative kidney weights and cytoplasmic vacuolization in the kidney were observed at 100 mg/kg/day (U.S. Army 1984c). The toxicological significance of the increased serum cholesterol level in the absence of other indications of hepatic damage is not known.

The lowest LOAEL identified in chronic-duration studies is 1.5 mg/kg/day for prostate inflammation; the NOAEL for this effect is 0.3 mg/kg/day. However, U.S. Army (1983a) suggested that this effect is likely secondary to a bacterial infection in older rats dying early; thus, it was not considered an appropriate basis of a chronic-duration MRL. The effects observed in rats (including convulsions/tremors, hematological alterations, impaired hepatic function, and renal lesions) exposed to 40 mg/kg/day (NOAEL of 8 mg/kg/day) were considered as the basis of a chronic-duration MRL. Based on a comparison of the effects observed in rats exposed to 40 mg/kg/day and those observed in mice exposed to 35 mg/kg/day, rats appear to be more sensitive to the toxicity of RDX than mice; thus, the mouse study was not considered for MRL derivation.

In the U.S. Army (1983a) study, groups of male and female Fischer 344 rats (75/sex/group) were exposed to 0, 0.3, 1.5, 8.0, or 40.0 mg/kg/day RDX in the diet for 2 years. The following parameters were used to assess toxicity: daily observations, ophthalmic examinations, hematology, clinical chemistry, organ weights, and complete histopathology of major tissues and organs of rats in the 0 or 40.0 mg/kg/day groups, and histopathological examination of the brain, gonads, heart, liver, kidneys, spleen, and spinal cord of rats in the 0.3, 1.5, and 8.0 mg/kg/day groups. Actual RDX doses were within 3% of the intended dose. Deaths were observed at 40 mg/kg/day; 88% of males and 41% of females died by week 88. The mean survival time for the 40 mg/kg/day males was 14.6 months compared with 22.3 months for the control males. A 20.6 month survival time was seen for the 40 mg/kg/day females vs. 22.0 months for the control females at 40 mg/kg/day. A significant decrease in survival time was also observed in the males exposed to 1.5 mg/kg/day (21.0 months); however, no alterations in survival time was observed in the females exposed to 1.5 mg/kg/day (22.2 months) or in the males (22.2 months) or females (22.4 months) exposed to 8 mg/kg/day. Additionally, there were no significant differences in mortality incidence in the 1.5 or 8 mg/kg/day groups, as compared to controls. Statistically decreased body weight gain was observed in males (20–30%) and females (10–15%) exposed to 40.0 mg/kg/day; statistically significant decreases in body weight gain were also observed at 8.0 mg/kg/day, but the body weight was within 10% of controls. Tremors and convulsions were observed prior to death at 40 mg/kg/day; the animals were hyperactive to approach and had increased fighting. No adverse clinical signs were noted for the lower dose groups. Significant decreases in hemoglobin and erythrocyte counts were observed in the 40 mg/kg/day group beginning at week 26; the study investigators noted that the anemic state was considered slight and there was no evidence of physiologic compensatory responses. Thrombocytosis was observed in rats exposed to 40 mg/kg/day and elevated platelet counts were observed in 8 mg/kg/day males during weeks 13 and 26. Significant decreases in blood glucose, total cholesterol, and triglyceride levels were observed in the 40 mg/kg/day group starting at week 13. Significant decreases in serum alanine aminotransferase levels were observed in males exposed to 8 or 40 mg/kg/day at weeks 26 and 52 and in females at 40 mg/kg/day at week 26. Other clinical chemistry alterations included decreases in globulin and albumin levels at weeks 52 and 78 and increases in serum potassium levels at weeks 26, 52, and 78. A significant increase in the incidence of cataracts was observed in females in the 40 mg/kg/day group during weeks 78 and 104. Histological alterations observed after 2 years of exposure included suppurative inflammation of the prostate in the 1.5, 8, and 40 mg/kg/day groups; renal medullary papillar necrosis, renal pyelitis, and urinary bladder luminal distension and cystitis in males exposed to 40 mg/kg/day; splenic extramedullary hematopoiesis in female rats exposed to 40 mg/kg/day; and hemosiderin-like pigment in males exposed to 1.5, 8, or 40 mg/kg/day. In the absence of altered hematological parameters or other effects on the spleen, the increased pigment levels observed at 1.5 or 8 mg/kg/day were not considered adverse.

The U.S. Army (1983a) study identified a NOAEL of 8 mg/kg/day and a LOAEL of 40 mg/kg/day for tremors and convulsions in rats exposed to RDX in the diet for 2 years. ATSDR derived a chronic-duration oral MRL using the NOAEL/LOAEL approach; benchmark dose modeling could not be utilized because the investigators did not report incidence data for neurological signs. As discussed for the acute-duration oral MRL, a PBPK model (Sweeney et al. 2012) was used to predict peak and mean brain RDX concentrations. Comparisons with empirical seizure data following intermediate- or chronic-duration exposure with predicted brain RDX levels provided support for using peak brain concentration as the internal dose metric for the MRL derivation. To determine the point of departure for the MRL, the PBPK model was also used to predict the HED for a given rat peak brain RDX concentration; detailed discussions of the PBPK model and support for selecting peak brain RDX concentration as the internal dose metric are presented in Appendix A. The NOAEL from the U.S. Army (1983a) study corresponds to peak brain concentrations of 4.051 mg/L and a HED of 4.223 mg/kg/day. The MRL of 0.1 mg/kg/day was calculated by dividing the $NOAEL_{HED}$ of 4.223 mg/kg/day by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).