U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM) "white paper" on RDX, submitted to MA DEP by Robert L. Muhly Army REC, Regions I&II. Dr. Mick Major is the primary CHPPM toxicologist responsible for putting this paper together. December 2001.

SUBJECT: Update on the Reevaluation of the Carcinogenic Potential of RDX

## Background

Because of the presence of RDX in the environment and its potential to migrate to groundwater, the health effects of this compound are of great concern to the Army. In 1988, the Environmental Protection Agency (EPA) in collaboration with the Army, published a Health Advisory (HA) document for RDX. The HA provided a review of the toxicity and health related information for RDX and recommended safe drinking water levels for various exposure durations. For exposures over an entire lifetime, the recommended HA is 2 ppb. This level is based on non-cancer toxic effects seen in rats exposed for 2 years to RDX. In a very similar 2-year study, female mice exhibited a weak carcinogenic response. These data will be discussed in more detail below. Because of this finding in the female mice, the EPA classified RDX as a possible human carcinogen. Lifetime HA recommendations for these compounds are based on non-cancer endpoints with an additional 10 fold uncertainty factor to provide an additional margin of safety.

Approximately 2 years ago, Toxicologists from the Army's Center for Health Promotion and Preventive Medicine (CHPPM) held preliminary discussions with the EPA to re-evaluate the toxicity information on RDX and the EPA published their intent to conduct a review in the Federal Register. The EPA Headquarters personnel involved with this reevaluation were Dr. D. Singh, Dr. Vincent Cogliano, and Dr. Harlal Choudhury. Dr Cogliano is the Chief of the EPA's National Center for Environmental Assessment and an expert on cancer studies who has the EPA lead in development of cancer risk assessment guidance. Dr. Choudhury is director of the EPA Superfund Health Risk Technical Support Center in Cincinnati and the Army's primary point of contact on this evaluation. Dr. Singh is an EPA pathologist who has made a specialty of cancer research and is used as a technical authority in this area by the EPA.

Because of the potential long-term exposure of populations to low concentrations of RDX in drinking water, initial priority was given to the carcinogenic effects. There have been several studies of the cancer effects of RDX, including feeding studies in rodents (mice

and rats) and epidemiological studies in exposed workers. All studies were negative for the cancer endpoint with the exception of a single rodent study. The study that produced positive findings was done on a type of hybrid mouse (B6C3F1) in which liver cancer is easily induced by chemical and physical stimuli. In this study, the female animals showed a correlation between the administered dose levels and lesions in liver tissue. It is important to note, that the response was weak and was not statistically significant for definitive carcinomas. However, when the incidence of liver cancer was combined with the incidence of adenomas (a type of non-cancerous lesions that sometimes become cancerous) the results for the female mice were significant. On the weight of this evidence the EPA classified RDX as a possible human carcinogen.

**Work to date**

The reevaluation, of the toxicity and carcinogenicity of RDX is currently in progress. Due to improvements in the manner in which data is assessed statistically it was determined to start this reevaluation by recalculating the dose response curve for the existing data using the EPA's benchmark dose analysis program. Because benchmark methods of data analysis fit an equation to the entire data set, these methods usually provide a more reliable assessment of data than older methods that placed greatest reliance on toxic responses at the lower (most uncertain) portion of the dose/response curve. It is often difficult or impossible to fit experimental data to a Benchmark equation because of the limited number of dose groups in many of the early studies. However, the study in question was designed with a control and 4 dose groups and the data set has proven ideal for the use of Benchmark procedures. Upon completion of these analyses we forwarded our calculations of Benchmark EC10 and calculation of a new cancer slope factor to Dr. Jim Cogliano of the EPA.

Because of numerous reports in the literature on the excessive hepatocellular sensitivity of the B6C3F1 hybrid mouse used in the positive study and it was determined that the validity of the original pathological findings should also be reassessed. Scientific understanding of the carcinogenic process has improved greatly since this study was completed (1984) and it is now understood that some lesions that were formerly classified as carcinomas and adenomas may have been misidentified. Reevaluation of the

pathology slides from the original study, by an expert in rodent pathology, produced findings with a lower incidence of adenoma and carcinoma than the earlier findings. Because of the differences in findings between the earlier and later pathological evaluations, the Directorate of Toxicology arranged for the National Institute of Environmental Health Sciences (NIEHS) to conduct a Pathology Working Group (PWG). The NIEHS was selected to empanel this group because they are the acknowledged leader in such assessments. The PWG met on the 5th of June 2001 and reviewed the findings in question. The findings of the PWG agreed with the findings of the reevaluation pathologist (the lower incidence of adenoma and carcinoma). A comparison of the incidence of carcinoma and adenoma in the original findings and the reevaluation is shown in Table 1 and the findings of the PWG are included as Attachment 1.

Table 1. Comparison of Pathological findings for hepatocellular adenomas or carcinomas.

| Dose | Old Findings | New Findings |
|---|---|---|
| 0.0 | 1 (1.5%) | 1 (1.5%) |
| 1.5 | 5 (8.1%) | 4 (6.4%) |
| 7.0 | 9 (14.1%) | 5 (7.8%) |
| 35.0 | 12 (18.8%) | 10 (15.6%) |
| 100 | 6 (19.4%) | 4 (12.9%) |
| Historic (1984) Controls (8.3%) | | |

The results of the new pathology findings of the PWG were conveyed to Drs. Cogliano and Choudhury. Due to the very low incidence of cancer in the control animals as compared to historical averages for the B6C3F1 mouse, we determined the statistical relevance of this new data set using both the concurrent control and a 1984 average historical value for the incidence of adenoma and carcinoma in control populations of the female B6C3F1 mouse. Statistical analysis of these findings using historical controls does not show a statistically significant relationship between dose and response. In short, they do not indicate that RDX is a carcinogen. Calculation using concurrent controls indicates that the combined incidence of hepatocellular adenoma and carcinoma in the lower dose groups also do not differ statistically from the incidence in the controls. However, the

incidence of adenoma and carcinoma the highest two dose groups are statistically different from the controls (Table 2) and a positive finding for carcinogenicity is implied.

Table 2. **Statistical Analysis Using Concurrent Controls**
A trend test was used to compare all groups and test for the increasing percentage of tumors with increasing dose. A significant trend was observed, $p<0.01$. Therefore a Fisher's exact test was used to compare each dose group to the control group, to determine significance from the control group. The 35 and 100 mg/Kg/day groups were significantly different from the control group in the percentage of tumors observed, $p<0.01$ and $p<0.05$ respectively.

**Statistical Analysis Using Historical (1984) Controls**
A Binomial test was used to compare the percent of tumors for each dose group to the historical control tumor percentage, 8.3% provided by the EPA. None of the RDX groups were statistically significantly different from the historical control.

The results from the reevaluation were statistically evaluated using version 3.1 of the EPA's benchmark dose program and, for purposes of consistency, the original pathologist's findings were also redone using the new 3.1 version (Appendix 2). The EC10 values produced using the data from the reevaluation was 5 times higher than that produced from the original pathology findings (4.02 with the old data and 20.45 with the new data). Because the EC10 point is used as the point of departure for the linear extrapolation of the dose/response curve to the 0/0 point, this value ultimately determines the cancer slope. Thus, the 5-fold increase in the EC10 in the reevaluated data set decreases the cancer slope factor by 5 fold.

**New Cancer Studies:**

Due to the implications of these findings a meeting was held with the EPA. The discussions between the EPA and the UACHPPM covered the studies done to date and new work that will be needed for reevaluation of the carcinogenic status of RDX. The following points were discussed and agreed upon.

a. The chronic studies performed thus far have produced only equivocal results. Because of the equivocal results produced in the first two chronic rodent studies, performance of additional 2-year rodent studies would probably provide little new information and is not warranted at this time.

b. New studies should be designed with the goal to better understand the toxicity of RDX at the molecular level. Additional studies are required to better determine the mixture of metabolites formed from oral doses of RDX and these studies should be done in both a large and a small animal species. If a similar mixture of metabolites is generated in replicate studies and between species, it is assumed that the mixture of metabolites can be predicted reliably, and that mixture should be assessed (as a mixture) for its genotoxic properties. If similar compounds are not generated in all studies and the mixture of metabolites can't be predicted reliably in different species, each individual metabolite that is identified should be assessed for genotoxicity.

c. Studies to determine the maximum tolerated dose (MTD) should be repeated because the original chronic studies suffered from uncertainty in this area. This study would be best done as a subchronic, mechanistic study that would address the pre-cancerous conditions that give rise to hepatocellular neoplasms. This is especially important because recent work has shown that some conditions that give rise to adenoma and carcinoma in rodents (such as peroxisome proliferation) do not occur in humans.

d. Due to the extreme underweight condition of the female mice in the 100 mg/kg-day dose group it should be determined if this concentration was above the maximum tolerated dose. Subsequent examination of the food consumption data indicated that the female animals in the 100 mg/kg-day group were 20% underweight despite consumption of feed at levels identical with those of the lower dose groups and controls (Figure 1). Thus, the female B6C3F1 mice in the highest dose group were chronically exposed to RDX at levels in excess of the MTD and as a result of this, data from these animals should not be used in the evaluation of carcinogenicity.

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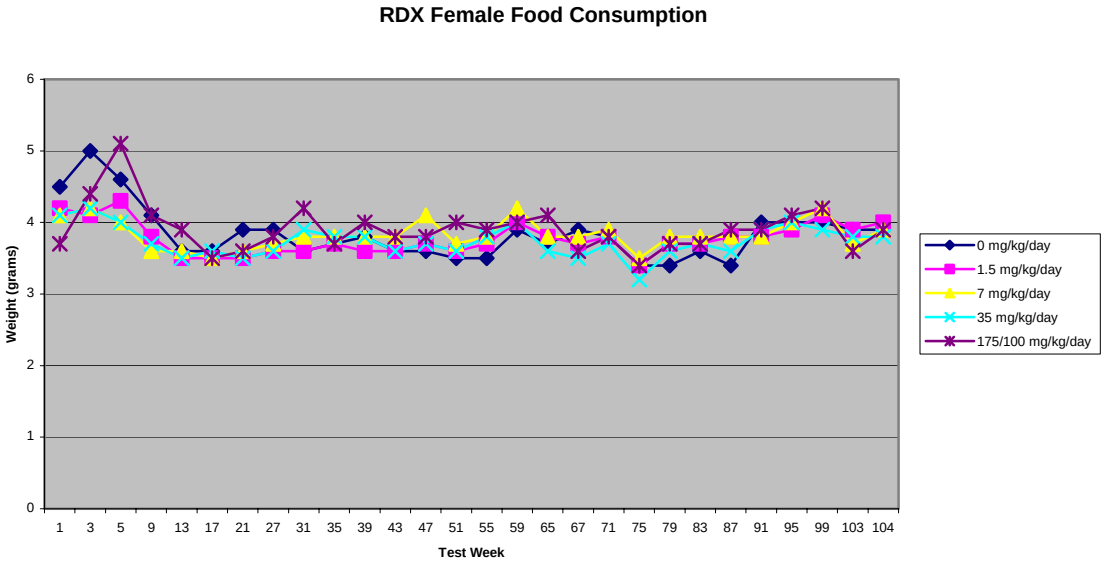


Summary of the reevaluation of the carcinogenicity of RDX:

The reevaluation of the carcinogenicity has demonstrated that the carcinogenic potency of RDX was not as great as originally estimated. Removal of the highest (100 mg/Kg day) treatment level from consideration (because it is above the MTD) leaves only one dose level (35 mg/Kg day) that is statistically different from the concurrently run controls. Therefore the finding of RDX as a possible human carcinogen is now based on the findings in one dose group in one gender of one species and then, only if the incidence of carcinoma and adenoma are combined and the statistics calculated using the remarkably low incidence of adenoma and carcinoma found in the concurrent controls. Due to the equivocal nature of the carcinogenic response shown in previous studies it is unlikely that running another chronic study in rodents would affect the current classification of RDX as a possible human carcinogen. It is possible however that studies that detail the metabolism and mode of toxicity of RDX could affect this classification by removing the uncertainty now associated with the mode of action of this toxicant.

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**ATTACHMENT 1**
**PATHOLOGY WORKING GROUP**
**CHAIRPERSON'S REPORT**

# REEVALUATION: TWENTY-FOUR MONTH CHRONIC TOXICITY/CARCINOGENICITY STUDY OF HEXAHYDRO-1,3,5-TRINITRO-1,3.5-TRIAZINE (RDX) IN THE B6C3F1 HYBRID MOUSE

DATE OF PWG: June 5, 2001

LOCATION OF PWG: NIEHS, Research Triangle Park, NC

PARTICIPANTS: Drs. G. Boorman (NIEHS), R. Herbert (NIEHS), J. Hailey (NIEHS), A.Nyska (NIEHS), G. Parker (Biotechnics, PWG Chairperson), D. Wolf (EPA), R. Baumgartner (CHPPM, observer) and M. Major (CHPPM, observer). A signature record of the participants is included as part of this report.

## SUMMARY OF FINDINGS FROM PWG

The PWG was convened to review selected H & E-stained liver sections from a two-year chronic study of hexahydro-1,3,5-trinitro-1,3.5-triazine (RDX) administered in the diet.. The following is a summary of review findings.

- **A number of liver lesions were downgraded from tumor to non-tumor status. As a result of these changes there are four less hepatocellular tumors in Group 3, two less hepatocellular tumors in Group 4, and two less hepatocellular tumors in Group 5.**

- **A number of lesions were downgraded from malignant to benign status. As a result of these changes there are three less hepatocellular carcinomas in Group 2, three less hepatocellular carcinomas in Group 4, and one less hepatocellular carcinomas in Group 5.**

- **Two new non-tumor diagnoses were added. As a result of these changes there are two additional non-tumor hepatocellular lesions in Group 2.**

- **The PWG review altered the numerical incidence of hepatocellular lesions in all dose groups except the controls. The general incidence pattern persisted in Groups 1 through 4, but the previously noted linear increase in liver tumor incidence in all treated groups was no longer evident in Group 5.**

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INTRODUCTION

Hexahydro-1,3,5-trinitro-1,3.5-triazine (RDX) is an explosive that is widely used in munitions that are used by the U.S.Army. This study was performed during the early 1980s (protocol signature date 17 March 1981; report date April 1984). There is recent evidence of RDX contamination of ground water near U.S. Army installations. This reevaluation was performed to confirm or refute the original histopathologic findings and interpretations in female mice. Microslides from female mice on the study were retrieved from the archives of the original contract laboratory (IIT Research Institute, Chicago, IL) and a second examination was performed by the PWG Chairperson.

**STUDY DESIGN**

Groups of 85 each male and female B6C3F1 mice were given RDX in the feed at dosage levels of 0, 1.5, 7, 35, or 175 mg/kg/day. The dosage level in the high dose group was reduced to 100 mg/kg/day at Study Week 11 due to excess mortality in that group. Ten mice/sex/dose were sacrificed at 6 and 12 months. The remaining surviving mice were sacrificed by carbon dioxide anesthesia and exsanguination at study termination at 24 months. The study was conducted at IIT Research Institute, Chicago, IL. The Study Pathologist (SP) was Dr. J. Sagartz, a consulting pathologist. The Reviewing Pathologist (RP) was Dr. G. Parker of Biotechnics, Inc.

**STUDY RESULTS**

Survival: By study week 10 there was reduced survival of males in the 175 mg/kg/day group. Following reduction of the dosage level to 100 mg/kg/day the survival of the high dose males was similar to that of controls. Survival of treated females and lower dose group males was similar to that of controls.

Clinical observations: Males in the 175/100 mg/kg/day group exhibited aggressive behavior that included fighting, which resulted in numerous skin wounds.

Body weights: Body weights of males from the 175/100 mg/kg/day group were significantly less than control values on weeks 95, 101, 103 and 104. Body weights of 175/100 mg/kg/day males on weeks 95, 101, 103, and 104 were 95.6%, 95.0%, 95.0%, and 95.0% of control values, respectively. Body weights of females from the 175/100 mg/kg/day group were significantly less than control values beginning on week 10, remained lower than control values through the remainder of the study. Body weights of 175/100 mg/kg/day females on weeks 10, 51, 69, 101, and 104 were 95.0%, 90.0%, 88.5%, 82.3%, and 80.8% of control values at those time points.

Feed consumption: There was no alteration in food consumption that would explain the altered body weights.

Necropsy: Thirty male and 36 female mice from the 175/100 mg/kg/day group that died during

the first six months of the study commonly had dark red mottled lungs, dark red spleen, and dark red liver. Unscheduled death males from that group commonly had urinary bladders distended with red, yellow, or brown fluid. Terminal kill female mice from all treated groups had an increased incidence of hepatic masses and nodules as compared to controls. The gross necropsy observations are tabulated as the number of animals with masses or nodules rather than the total number of nodules, therefore the tables presented in the initial report do not indicate the total number of masses/nodules.

Histopathology: Male mice from all dosage groups that died spontaneously or were sacrificed for humane reasons prior to the scheduled six-month sacrifice had cytoplasmic vacuolization of renal tubular epithelial cells. Renal lesions were not observed in male mice from the 12- or 24-month sacrifices. Lungs of the unscheduled death mice commonly had histologic evidence of congestion. There were no histologic correlates of the gross necropsy observations in the spleen, liver and urinary bladder of the unscheduled death mice. At the 24-month sacrifice, male mice from the 35 and 175/100 mg/kg/day group had testicular changes consisting of necrosis of germinal epithelium, interstitial fibrosis, and aspermia. At the 24-month sacrifice there was a statistically significant increase in the incidence of hepatocellular adenoma/carcinoma in female mice from the 7, 35, and 175/100 mg/kg/day group.

CONDUCT OF THE PWG

In preparation for the PWG, the PWG Chairperson reviewed the study pathology tables, the study Final Report that included the pathology narrative, and H & E-stained slides of all tissues from female mice. The Chairperson then selected slides for review by the PWG. The selected slides included all liver lesions in which SP or RP recorded hepatocellular neoplasms and selected lesions that had some histologic similarity to hepatocellular neoplasms. The PWG reviewed slides without knowledge of the dose groups.

PWG RESULTS

**Liver**

The diagnosis of the PWG participants regarding each reviewed lesion was recorded on the Pathology Working Group Diagnosis worksheet (attached) and the numerically predominant diagnosis was considered to be the final PWG consensus diagnosis. The PWG consensus diagnosis regarding each reviewed lesion is recorded on the Pathology Working Group Chairperson's Report (attached). The PWG consensus diagnoses were entered in the Starpath database that was prepared by the RP prior to the PWG. The lesion tables included with the final report by the RP include the consensus PWG diagnoses, as do the text tables included in the narrative portion of that report.

The incidence of hepatocellular proliferative lesions as recorded by the study pathologist (SP), reviewing pathologist, (RP) and Pathology Working Group (PWG) are presented in Text Table 1.

**TEXT TABLE 1**
**INCIDENCE OF HEPATOCELLULAR NEOPLASMS AS RECORDED BY STUDY PATHOLOGIST AND PATHOLOGY WORKING GROUP**

| GROUPS | 0 mg/kg/day | 1.5 mg/kg/day | 7 mg/kg/day | 35 mg/kg/day | 175/100 mg/kg/day |
|---|---|---|---|---|---|
| Animals per group | 67 | 62 | 63 | 64 | 31 |
| **STUDY PATHOLOGIST** | | | | | |
| Hepatocellular adenoma | 1 | 0 | 6 | 6 | 3 |
| Hepatocellular carcinoma | 0 | 4 | 3 | 6 | 3 |
| Hepatocellular adenoma and carcinoma combined | 1 (1.49%) | 5 (8.06%) | 9 (14.29%) | 12 (18.75%) | 6 (19.35%) |
| **PATHOLOGY WORKING GROUP** | | | | | |
| Hepatocellular adenoma | 1 | 3 | 2 | 8 | 2 |
| Hepatocellular carcinoma | 0 | 1 | 3 | 2 | 2 |
| Hepatocellular adenoma and carcinoma combined | 1 (1.49%) | 4 (6.45%) | 5 (7.94%) | 10 (15.63%) | 4 (12.9%) |

SP's impression of a treatment-related increase in the incidence of hepatocellular neoplasms in all RDX-treated groups was supported by PWG consensus diagnoses, but the magnitude of the treatment-related effect was reduced by reclassification of a small number of hepatocellular lesions.

SP's initial diagnoses recorded a combined incidence of hepatocellular adenomas/carcinomas as 1.49%, 8.06%, 14.29%, 18.75%, and 19.35% for Groups 1-5, respectively. The PWG consensus diagnoses of hepatocellular adenomas/carcinomas combined were 1.49%, 6.45%, 7.95%, 15.63%, and 12.9% for Groups 1-5, respectively. Thus, in addition to the reduction in the overall incidence of hepatocellular neoplasms, the PWG consensus diagnoses altered the linear increase in incidence of hepatocellular neoplasms that was associated with increasing dose of RDX. The altered linearity of the response applied only to the 175/100 mg/kg/day group, which had markedly fewer animals due to treatment-related mortality in this dosage group. Statistical analysis was not performed as part of this review.

PWG attendees made a number of comments regarding interpretation of the liver lesions, as follows:

1. Absence of necropsy and histology processing records made it impossible to determine whether all grossly noted liver lesions were represented in the histologic sections.

2. The control females had an unusually low incidence of hepatocellular neoplasms. Experience with similar situations in other studies has indicated the necessity of reviewing the fixed tissue remnants to determine whether all liver lesions were included in the histologic sections. This review cannot be performed on the present study, as fixed tissue remnants are not available. There are no available laboratory records to indicate that a fixed tissue review took place soon after completion of the study. As stated above, there are no available laboratory records to indicate that grossly observed liver lesions were tracked through histology and included in the final histologic sections.

3. The following comments were made regarding the liver sections.

a. The liver sections were smaller than typical for a carcinogenesis study.

b. Only one liver section was present in most animals, as opposed to the minimum of two sections that are present in many studies of this type.

c. The sections did not appear to be taken uniformly from the same area of the liver of all animals.

d. That there was some variation in the number of liver sections taken from individual animals.

It was suggested that the PWG Chairperson review the liver sections and determine whether there was any group-related bias in the number of liver sections. That action has been completed as a post-PWG action and is reported below under that heading.

4. Though the purpose of this PWG review was solely to determine the accuracy of the pathology data, a number of attendees commented on the weak nature of the evidence supporting RDX-associated carcinogenicity. Factors mentioned included the single species involved, the single sex involved, the absence of treatment-related precursor lesions such as foci of cytoplasmic alteration, and the unusually low incidence of hepatocellular neoplasms in the control females.

5. A number of PWG attendees commented on the use of historical control data in interpretation of tumor incidence, and the risks inherent in the use of historical control data. The concurrent controls in a study provide the best estimate of “background” lesion incidence. Tumor incidence in control groups in other studies performed concurrently by the same laboratory may also be useful in interpreting tumor incidence in a particular study. Published historical control values from multiple laboratories on studies that were conducted during the same time frame as the study of interest are of less value than concurrent controls within a single laboratory. Published historical control values from multiple laboratories involving studies

conducted during a different time frame than the study of interest are of least value in interpreting tumor incidence rates.

POST-PWG ACTION

The PWG Chairperson reviewed the liver sections from all females and tabulated the number of liver sections present for each animal. Two liver sections were prepared for five females from Group 1, nine females from Group 3, three females from Group 4, and two females from Group 5. Four liver sections were prepared from one female from Group 4 (#81-1019). Remaining females had only one liver section per animal. The increased number of liver sections appeared to be related to gross necropsy observations, as the additional section typically contained a neoplasm that was large enough to be seen at necropsy. As stated above, absence of necropsy records and histology processing records hindered this evaluation. There was no overt evidence of group-related bias in preparing liver sections.

**SUMMARY**

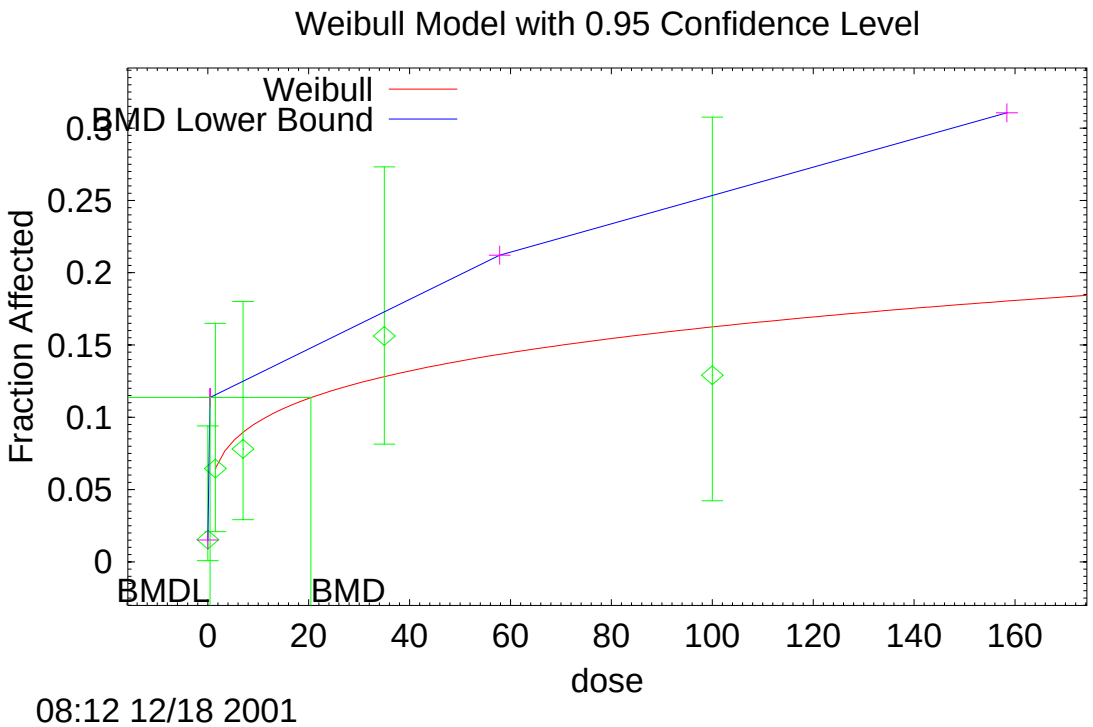
There was generally good agreement between the Study Pathologist and the Pathology Working Group in the diagnostic terminology applied to lesions recorded in the study. The increased incidence of hepatocellular neoplasms in female B6C3F1 mice given hexahydro-1,3.5-trinitro-1,3.5-triazine (RDX) in the diet, as noted by the study pathologist, was supported by the Pathology Working Group but reclassification of a number of lesions resulted in a reduction in the magnitude of the treatment-related alteration in liver tumor incidence.

**George A. Parker, D.V.M., Ph.D.** **Date**
**Dipl. ACVP, ABT**
**PWG Chairperson**

**Attachments:**
**NTP Pathology Working Group signature record**
**Pathology Working Group Chairperson's Report**

ATTACHMENT 2

RDX Benchmark Dose: New Data Set

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Weibull Model $Revision: 1.1 $ $Date: 2005/10/07 15:20:31 $
Input Data File: C:\BMDS\NEW_RDX_CANCER_SET.(d)
Gnuplot Plotting File: C:\BMDS\NEW_RDX_CANCER_SET.plt

==========

BMDS MODEL RUN

~~~~~~~~~~

The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Dependent variable = Column2
Independent variable = COLUMN2
Power parameter is not restricted

Total number of observations = 5
Total number of records with missing values = 0
~~~~~~~~~~

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values

Background = 0.0227273
Slope = 0.0331354
Power = 0.294408

Asymptotic Correlation Matrix of Parameter Estimates

| | Background | Slope | Power |
|---|---|---|---|
| Background | 1 | -0.45 | 0.24 |
| Slope | -0.45 | 1 | -0.89 |
| Power | 0.24 | -0.89 | 1 |

Parameter Estimates

| Variable | Estimate | Std. Err. |
|---|---|---|
| Background | 0.0151575 | 0.0149821 |
| Slope | 0.0463378 | 0.0294318 |
| Power | 0.272184 | 0.176979 |

Analysis of Deviance Table

| Model | Log(likelihood) | Deviance | Test DF | P-value |
|---|---|---|---|---|
| Full model | -77.2031 | | | |
| Fitted model | -77.607 | 0.807827 | 2 | 0.6677 |
| Reduced model | -82.4341 | 10.462 | 4 | 0.03332 |

AIC: 161.214

Goodness of Fit

Scaled

| Dose | Est._Prob. | Expected | Observed | Size | Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.0152 | 0.985 | 1 | 65 | 0.01498 |
| 1.5000 | 0.0648 | 4.019 | 4 | 62 | -0.009775 |
| 7.0000 | 0.0897 | 5.740 | 5 | 64 | -0.3238 |
| 35.0000 | 0.1282 | 8.207 | 10 | 64 | 0.6704 |
| 100.0000 | 0.1627 | 5.044 | 4 | 31 | -0.5078 |

Chi-square = 0.81 DF = 2 P-value = 0.6661

BMDL curve computation failed for BMR = 0.050000 .
The BMDL curve appearing in the graph may not be accurate.

Benchmark Dose Computation

Specified effect = 0.1

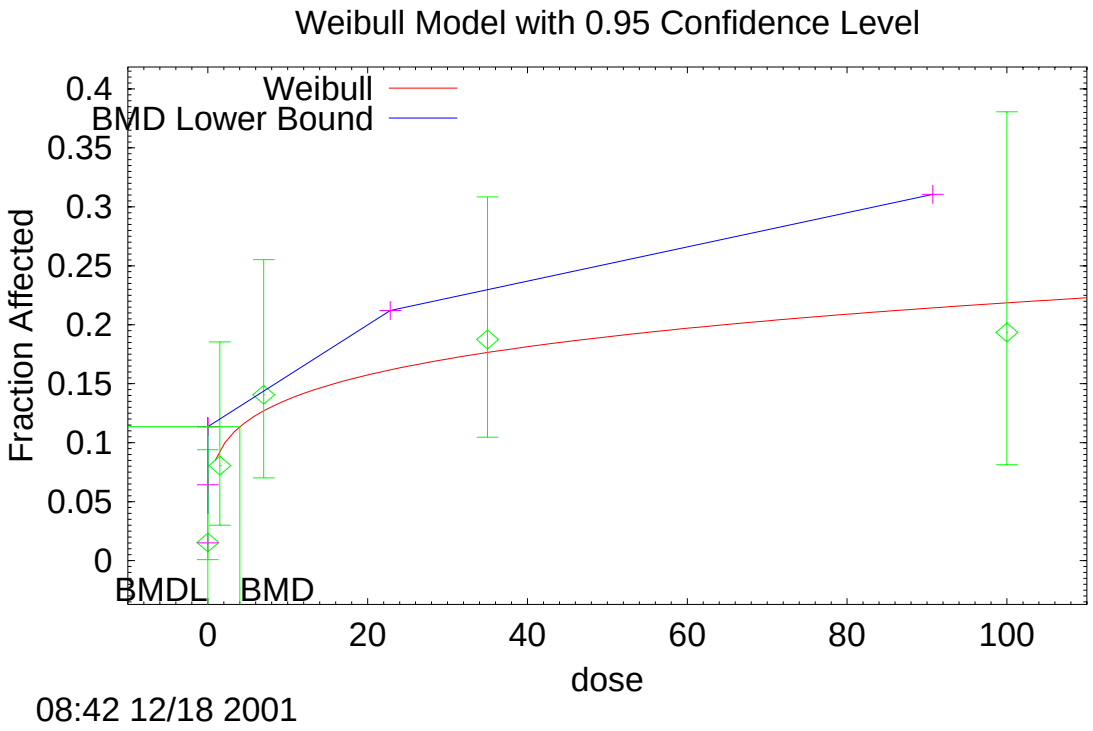
Risk Type = Extra risk

Confidence level = 0.95

BMD = 20.4487

BMDL = 0.459087

RDX Benchmark Dose: Old Data Set

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Weibull Model $Revision: 1.1 $ $Date: 2005/10/07 15:20:31 $
Input Data File: C:\BMDS\OLD_RDX_CANCER_SET.(d)
Gnuplot Plotting File: C:\BMDS\OLD_RDX_CANCER_SET.plt

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BMDS MODEL RUN

~~~~~~~~~~

The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Dependent variable = Column2
Independent variable = COLUMN2
Power parameter is not restricted
~~~~~~~~~~

Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values
Background = 0.0227273
Slope = 0.0624676
Power = 0.25706

Asymptotic Correlation Matrix of Parameter Estimates

| | Background | Slope | Power |
|---|---|---|---|
| Background | 1 | -0.37 | 0.18 |
| Slope | -0.37 | 1 | -0.88 |
| Power | 0.18 | -0.88 | 1 |

Parameter Estimates

| Variable | Estimate | Std. Err. |
|---|---|---|
| Background | 0.0150925 | 0.0149426 |
| Slope | 0.0749198 | 0.0355542 |
| Power | 0.245219 | 0.1383 |

Analysis of Deviance Table

| Model | Log(likelihood) | Deviance | Test DF | P-value |
|---|---|---|---|---|
| Full model | -94.6542 | | | |
| Fitted model | -94.8521 | 0.395948 | 2 | 0.8204 |
| Reduced model | -102.281 | 15.2544 | 4 | 0.004202 |

AIC: 195.704

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Scaled Size | Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.0151 | 0.981 | 1 | 65 | 0.01932 |
| 1.5000 | 0.0933 | 5.785 | 5 | 62 | -0.343 |
| 7.0000 | 0.1271 | 8.135 | 9 | 64 | 0.3247 |
| 35.0000 | 0.1766 | 11.305 | 12 | 64 | 0.2278 |
| 100.0000 | 0.2188 | 6.784 | 6 | 31 | -0.3405 |

Chi-square = 0.39 DF = 2 P-value = 0.8223

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 4.01675

BMDL = 7.30108e-005