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IRIS SUMMARY

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Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetr... (HMX) (CASRN 2691-41-0)

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Reference Dose for Chronic Oral Exposure (RfD)



0311

Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetr... (HMX); CASRN 2691-41-0

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR HMX

File First On-Line 09/26/1988

| Category (section) | Status | Last Revised |
|----------------------------------|---------|--------------|
| Oral RfD Assessment (I.A.) | on-line | 02/01/1993 |
| Inhalation RfC Assessment (I.B.) | no data | |
| Carcinogenicity Assessment (II.) | on-line | 02/01/1993 |

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name -- Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX)
 CASRN -- 2691-41-0
 Last Revised -- 02/01/1993

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

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__I.A.1. Oral RfD Summary

| Critical Effect | Experimental Doses* | UF | MF | RfD |
|---------------------------|----------------------|------|----|----------------|
| Hepatic lesions | NOAEL: 50 mg/kg/day | 1000 | 1 | 5E-2 mg/kg/day |
| 13-Week Rat Feeding Study | LOAEL: 150 mg/kg/day | | | |
| U.S. DOD, 1985a | | | | |

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*Conversion Factors: None

__I.A.2. Principal and Supporting Studies (Oral RfD)

U.S. Department of Defense. 1985a. AD-A171 601. Available from Defense Technical Information Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

The subchronic (13-week) toxicity of HMX has been studied in Fischer 344 rats (U.S. DOD, 1985a). HMX was incorporated into the daily diet of 20 rats/sex/dose for 13 weeks at the following levels: 0, 50, 150, 450, 1350, and 4000 mg/kg/day for males and 0, 50, 115, 270, 620, and 1500 mg/kg/day for females. Three deaths occurred during the course of the study; the study authors considered none to be treatment-related. One male receiving 150 mg/kg/day died during week 9; a female receiving 1500 mg/kg/day died during week 1, and a control female died at blood sampling in week 13. No treatment-related clinical signs of toxicity were observed in the HMX-treated animals. All HMX-treated animals exhibited significant ($p < 0.001$ to $p < 0.05$) dose-related reductions in mean body weight gain with concomitant reductions in food consumption in the early part of the study. By week 5, only animals in the two highest dose groups continued to have significantly depressed weight gains until study termination.

Histopathological examination revealed a significant incidence of toxic liver changes occurring almost exclusively in males at 4000, 1350, and 450 mg/kg/day (the three highest dose levels) and some changes at 150 mg/kg/day. These liver changes were characterized by enlarged centrilobular cells with pale nuclei and dark cytoplasm, dilation of sinusoids, and necrosis. Tubular kidney changes characterized by focal atrophy and dilation were observed almost exclusively in females at the three highest doses. These changes seemed to correlate with some of the clinical pathology changes observed, i.e., increased AP activity and altered indicators of renal function (BUN, albumin, and total protein and urine changes). Thus, it would appear that there are sexual differences in the target organ response of rats to HMX.

The following changes were observed in clinical pathology parameters in the high-dose animals (clinical pathology was not conducted in the lower doses). Hemoglobin and hematocrit were decreased in high-dose males and females at week 5 and in high-dose females at week 12. Red blood cell counts were also significantly decreased in high-dose females at week 12 when compared with controls. There was a significant ($p < 0.001$) increase in serum alkaline phosphatase (AP) in high-dose males at 12 weeks and a marginal increase in high-dose females when compared with controls. The level of alkaline phosphatase in male controls was, however, lower than normal at 12 weeks; therefore, the toxicologic importance of the increase is not clear. There was a slight increase in albumin in high-dose males, but the values were within the normal range. Blood urea nitrogen (BUN) was slightly increased in females receiving 1500 mg/kg/day ($p < 0.05$ at week 5 and $p < 0.001$ at week 12) when compared with controls. There was an increase in urine volume and lowered pH and specific gravity in high-dose females at 12 weeks, but no urinary effects were observed in males.

There were several organ weight changes in dosed animals, although they were difficult to interpret because many reflected the overall decrease in body weight. An increase in absolute brain weight was seen in females receiving all but the lowest dose level, and an increase in brain-to-body weight ratio was increased in males receiving

1350 and 4000 mg/kg/day. Liver-to-body weight ratios, but not absolute liver weights, were increased in females receiving 620 and 1500 mg/kg/day. Kidney weights tended to be decreased in dosed males; the kidney-to-body weight ratios were increased in females at all but the lowest dose level. Adrenal weights and adrenal-to-body weight ratios were decreased in all dosed males; spleen-to-body weight ratios were decreased in all dosed females. It was reported that small changes in spleen, adrenal, testes, and ovary weights were of questionable toxicologic significance.

Based on the results of this study, a NOAEL of 50 mg/kg/day for males and 115 mg/kg/day for females can be estimated, together with a LOAEL of 150 mg/kg/day for toxic liver effects in males and 270 mg/kg/day for toxic renal effects in females.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF -- The UF of 1000 allows for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10A), uncertainty in the threshold for sensitive humans (10H), and uncertainty in the effect of duration when extrapolating from subchronic to chronic exposure (10S).

MF -- None

I.A.4. Additional Studies/Comments (Oral RfD)

In a subchronic (14 day) study commissioned by the U.S. DOD (1985b) in B6C3F1 mice, five groups of 20 mice/sex/dose were administered HMX in the diet at the following concentrations: 0, 5, 12, 30, 75, and 200 mg/kg/day (males) and 0, 10, 30, 90, 250, and 750 mg/kg/day (females). Mortality in males was 0/20, 0/20, 0/20, 1/20, 2/20, and 13/20 for the 0-, 5-, 12-, 30-, 75-, and 200- mg/kg/day groups, respectively, and mortality in females was 1/20, 0/20, 1/20, 0/20, 12/20, and 20/20 for the 0-, 10-, 30-, 90-, 250-, and 750-mg/kg/day groups, respectively. The deaths that occurred in both sexes at 30 mg/kg/day were not thought to be related to HMX, but no reason was given for this conclusion. Despite the seemingly high mortality rates in the high-dose groups of both sexes, no treatment-related clinical signs of toxicity were noted. Similarly, no significant changes in body weight or clinical chemistry were observed in the treated mice. Except for slight increases in brain weight seen in both males receiving 200 mg/kg/day and females receiving 250 mg/kg/day that are of questionable significance, no remarkable treatment-related changes were noted at necropsy or upon histologic examination. However, only liver, kidney, spleen, and brain were examined in high-dose males and females. Dark red lungs were observed grossly, but were not examined histologically. It is therefore difficult to estimate a NOAEL or LOAEL from this study because of the lack of obvious treatment-related toxicity (except for the high mortality observed at the highest doses).

I.A.5. Confidence in the Oral RfD

Study -- Medium
Database -- Low
RfD -- Low

Confidence in the principal study is rated medium because although the study was well-designed, interpretation of some data was difficult and some endpoints were not evaluated at the lower doses. Confidence in the data base is low because of a lack of chronic, reproductive, and other specialized data. Low confidence in the RfD is due to the weakness of the data base.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1988

Agency Work Group Review -- 05/25/1988

Verification Date -- 05/25/1988

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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__I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name -- Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX)
CASRN -- 2691-41-0

Not available at this time.

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__II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX)
CASRN -- 2691-41-0
Last Revised -- 02/01/1993

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification -- D; not classifiable as to human carcinogenicity

Basis -- No cancer bioassays or epidemiological studies are available.

__II.A.2. Human Carcinogenicity Data

None.

Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine is an explosive polynitramine commonly known as HMX (derived from High Melting Explosive). There are no human studies evaluating carcinogenicity.

II.A.3. Animal Carcinogenicity Data

There are no lifetime (chronic) bioassays that evaluate carcinogenicity.

II.A.4. Supporting Data for Carcinogenicity

Genetic toxicology assays in the literature have been limited to microbial systems. Saturated solutions of HMX, before and after chlorination or ozonation, were not mutagenic for *Salmonella typhimurium* either with or without hepatic homogenates (S9) (U.S. Army, 1977). However, the concentrations assayed were low due to limited solubility of HMX in water, and the authors conceded that the findings may represent false negatives. The *Saccharomyces cerevisiae* mitotic gene conversion assay with untreated and with postchlorinated or ozonated samples of saturated HMX was also negative, but the limited solubility of HMX lowers confidence in the studies. Whong et al. (1980) reported that HMX (1.25 and 0.625 mg/spot in the *Salmonella* spot test) was negative in five strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, and TA100). In a plate incorporation assay with S9 activation, a negative response with all five *Salmonella* strains was obtained up to 2.5 mg/plate. However, the actual data on HMX were not reported in the Whong et al. (1980) paper.

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II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

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II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

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II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document -- U.S. EPA, 1988

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review -- 09/22/1988

Verification Date -- 09/22/1988

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline IRIS@epamail.epa.gov (internet address).

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- _III. [reserved]
 - _IV. [reserved]
 - _V. [reserved]
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_VI. Bibliography

Substance Name -- Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX)
CASRN -- 2691-41-0
Last Revised -- 12/01/1990

_VI.A. Oral RfD References

U.S. Department of Defense. 1985a. AD-A171 601. Available from Defense Technical Information Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1985b. AD-A171 602. Available from Defense Technical Information Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. EPA. 1988. Drinking Water Health Advisory for Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX). Office of Drinking Water, Washington, DC.

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_VI.B. Inhalation RfC References

None

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_VI.C. Carcinogenicity Assessment References

U.S. EPA. 1988. Health Advisory on Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX). Office of Drinking Water, Washington, DC.

U.S. Army Medical Research and Development Command. 1977. DAMD 17-76-C-6013. Ft. Detrick, Frederick, MD 21701.

Whong, W.Z., N.D. Speciner and G.S. Edwards. 1980. Mutagenic activity of tetryl, a nitroaromatic explosive, in three microbial test systems. Toxicol. Lett. 5: 11-17.

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_VII. Revision History

Substance Name -- Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX)
CASRN -- 2691-41-0

| Date | Section | Description |
|------------|---------------|--|
| 09/26/1988 | I.A. | Oral RfD summary on-line |
| 03/01/1989 | II. | Carcinogen summary on-line |
| 04/01/1989 | II.A.4. | Correct citation |
| 04/01/1989 | II.D.1. | Correct citation |
| 08/01/1990 | I.A. | Text edited |
| 08/01/1990 | I.A.7. | Primary contact changed |
| 08/01/1990 | II. | Text edited |
| 08/01/1990 | II.D.3. | Primary contact changed |
| 12/01/1990 | I.A.6. | Source document statement added |
| 12/01/1990 | III.A. | Health Advisory on-line |
| 12/01/1990 | VI. | Bibliography on-line |
| 02/01/1993 | I.A.7. | Primary contact changed |
| 02/01/1993 | II.D.3. | Primary contact changed |
| 02/01/1993 | III.A.10 | Primary contact changed |
| 04/01/1997 | III., IV., V. | Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information. |

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VIII. Synonyms

Substance Name -- Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX)
 CASRN -- 2691-41-0
 Last Revised -- 09/26/1988

2691-41-0
 beta HMY
 cyclotetramethylenetetranitramine
 HMX
 HW 4
 LX 14-0
 Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine
 octogen
 oktogen
 tetramethylenetetranitramine
 1,3,5,7-tetrazocine, octahydro-1,3,5,7-tetranitro-
 UN 0226

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