Mercuric chloride (HgCl2); CASRN 7487-94-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Mercuric chloride (HgCl2)

File First On-Line 05/01/1995

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	05/01/1995
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	05/01/1995

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Mercuric chloride (HgCl2)
CASRN — 7487-94-7
Last Revised — 05/01/1995

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.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Autoimmune effects **Rat Subchronic Feeding and Subcutaneous Studies** **U.S. EPA, 1987**	NOAEL: None LOAEL: 0.226 mg/kg-day LOAEL: 0.317 mg/kg-day LOAEL: 0.633 mg/kg-day	1000	1	3E-4 mg/kg-day

* Conversion Factors and Assumptions -- Dose conversions in the three studies employed a 0.739 factor for HgCl2 to Hg2+, a 100% factor for subcutaneous (s.c.) to oral route of exposure, and a time-weighted average for days/week of dosing. This RfD is based on the back calculations from a Drinking Water Equivalent Level (DWEL), recommended to and subsequently adopted by the Agency, of 0.010 mg/L: (RfD = 0.010 mg/L x 2 L/day/70 kg bw = 0.0003 mg/kg bw/day). The LOAEL exposure levels, utilized in the three studies selected as the basis of the recommended DWEL, are from Druet et al. (1978), Bernaudin et al. (1981) and Andres (1984), respectively.

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

U.S. EPA. 1987. Peer Review Workshop on Mercury Issues. Summary Report. Environmental Criteria and Assessment Office, Cincinnati, OH. October 26-27.

On October 26-27, 1987, a panel of mercury experts met at a Peer Review Workshop on Mercury Issues in Cincinnati, Ohio, and reviewed outstanding issues concerning the health effects and risk assessment of inorganic mercury (U.S. EPA, 1987). The following five consensus conclusions and recommendations were agreed to as a result of this workshop:

1) The most sensitive adverse effect for mercury risk assessment is formation of mercuric-mercury-induced autoimmune glomerulonephritis. The production and deposition of IgG

antibodies to the glomerular basement membrane can be considered the first step in the formation of this mercuric-mercury-induced autoimmune glomerulonephritis.

2) The Brown Norway rat should be used for mercury risk assessment. The Brown Norway rat is a good test species for the study of Hg2+-induced autoimmune glomerulonephritis. The Brown Norway rat is not unique in this regard (this effect has also been observed in rabbits).

3) The Brown Norway rat is a good surrogate for the study of mercury-induced kidney damage in sensitive humans. For this reason, the uncertainty factor used to calculate criteria and health advisories (based on risk assessments using the Brown Norway rat) should be reduced by 10-fold.

4) Hg2+ absorption values of 7% from the oral route and 100% from the s.c. route should be used to calculate criteria and health advisories.

5) A DWEL of 0.010 mg/L was recommended based on the weight-of-evidence from the studies using Brown Norway rats and limited human tissue data.

Three studies using the Brown Norway rat as the test strain were chosen from a larger selection of studies as the basis for the panel's recommendation of 0.010 mg/L as the DWEL for inorganic mercury. The three studies are presented below for the sake of completeness. It must be kept in mind, however, that the recommended DWEL of 0.010 mg/L and back calculated oral RfD of 0.0003 mg/kg-day were arrived at from an intensive review and workshop discussions of the entire inorganic mercury database, not just from one study.

In the Druet et al. (1978) study, the duration of exposure was 8-12 weeks; s.c. injection was used instead of oral exposure. In this study the development of kidney disease was evaluated. In the first phase the rats developed anti-GBM antibodies. During the second phase, which is observed after 2-3 months, the patterns of fixation of antisera changed from linear to granular as the disease progressed. The immune response was accompanied by proteinuria and in some cases by a nephrotic syndrome.

Both male and female Brown Norway rats 7-9 weeks of age were divided into groups of 6-20 animals each. The numbers of each sex were not stated. The animals received s.c. injections of mercuric chloride (HgCl2) 3 times weekly for 8 weeks, with doses of 0, 100, 250, 500, 1000 and 2000 ug/kg. An additional group was injected with a 50 ug/kg dose for 12 weeks. Antibody formation was measured by the use of kidney cryostat sections stained with a fluoresceinated sheep anti-rat IgG antiserum. Urinary protein was assessed by the biuret method (Druet et al., 1978).

Tubular lesions were observed at the higher dose levels. Proteinuria was reported at doses of 100 ug/kg and above, but not at 50 ug/kg. Proteinuria was considered a highly deleterious effect, given that affected animals developed hypoalbuminemia and many died. Fixation of IgG antiserum was detected in all groups except controls (Druet et al., 1978).

Bernaudin et al. (1981) reported that mercurials administered by inhalation or ingestion to Brown Norway rats developed a systemic autoimmune disease. The HgCl2 ingestion portion of the study involved the forcible feeding of either 0 or 3000 ug/kg-week of HgCl2 to male and female Brown Norway rats for up to 60 days. No abnormalities were reported using standard histological techniques in either experimental or control rats. Immunofluorescence histology revealed that 80% (4/5) of the mercuric-exposed rats were observed with a linear IgG deposition in the glomeruli after 15 days of exposure. After 60 days of HgCl2 exposure, 100% (5/5) of the rats were seen with a mixed linear and granular pattern of IgG deposition in the glomeruli and granular IgG deposition in the arteries. Weak proteinuria was observed in 60% (3/5) of the rats fed HgCl2 for 60 days. The control rats were observed to have no deposition of IgG in the glomeruli or arteries as well as normal urine protein concentrations.

Andres (1984) administered HgCl2 (3 mg/kg in 1 mL of water) by gavage to five Brown Norway rats and two Lewis rats twice a week for 60 days. A sixth Brown Norway rat was given only 1 mL of water by gavage twice a week for 60 days. All rats had free access to tap water and pellet food. After 2-3 weeks of exposure, the Brown Norway HgCl2-treated rats started to lose weight and hair. Two of the HgCl2-treated Brown Norway rats died 30-40 days after beginning the study. No rats were observed to develop detectable proteinuria during the 60-day study. The kidneys appeared normal in all animals when evaluated using standard histological techniques, but examination by immunofluorescence showed deposits of IgG present in the renal glomeruli of only the mercuric-treated Brown Norway rats. The Brown Norway treated rats were also observed with mercury-induced morphological lesions of the ileum and colon with abnormal deposits of IgA in the basement membranes of the intestinal glands and of IgG in the basement membranes of the lomina propria. All observations in the Lewis rats and the control Brown Norway rat appeared normal.

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

UF — An uncertainty factor of 1000 was applied to the animal studies using Brown Norway rats as recommended in U.S. EPA (1987). An uncertainty factor was applied for LOAEL to NOAEL conversion: 10 for use of subchronic studies and a combined 10 for both animal to human and sensitive human populations.

MF — None

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

Kazantzis et al. (1962) performed renal biopsies in 2 (out of 4) workers with nephrotic syndrome who had been occupationally exposed to mercuric oxide, mercuric acetate and probably mercury vapors. Investigators reported that the nephrotic syndrome observed in 3 of the 4 workers may have been an idiosyncratic reaction since many other workers in a factory survey had similarly high levels of urine mercury without developing proteinuria. This conclusion was strengthened by work in Brown Norway rats indicating a genetic (strain) susceptibility and that similar mercury-induced immune system responses have been seen in affected humans and the susceptible Brown Norway rats (U.S. EPA, 1987).

The only chronic ingestion study designed to evaluate the toxicity of mercury salts was reported by Fitzhugh et al. (1950). In this study, rats of both sexes (20-24/group) were given 0.5, 2.5, 10, 40 or 160 ppm mercury as mercuric acetate in their food for up to 2 years. Assuming food consumption was equal to 5% bw/day, the daily intake would have been 0.025, 0.125, 0.50, 2.0 and 8.0 mg/kg for the five groups, respectively. At the highest dose level, a slight depression of body weight was detected in male rats only. The statistical significance of this body-weight depression was not stated. Kidney weights were significantly ($p<0.05$) increased at the 2.0 and 8.0 mg/kg dose levels. Pathological changes originating in the proximal convoluted tubules of the kidneys were also noted, with more severe effects in females than males. The primary weaknesses of this study were (1) the lack of reporting on which adverse effects were observed with which dosing groups and (2) that the most sensitive strain, the Brown Norway rat, was not used for evaluating the mercury-induced adverse health effects.

NTP (1993) conducted subchronic and chronic gavage toxicity studies on Fischer 344 rats and B6C3F1 mice to evaluate the effects of HgCl2, and the kidney appeared to be the major organ affected. In the 6-month study, Fischer 344 rats (10/sex /group) were administered 0, 0.312, 0.625, 1.25, 2.5 or 5 mg/kg-day of HgCl2 (0.23, 0.46, 0.92, 1.9 and 3.7 mg/kg-day) 5 days/week by gavage. Survival was not affected, although body-weight gains were decreased in males at high dose and in females at or above the 0.46 mg/kg-day dose. Absolute and relative kidney weights were significantly increased in both sexes with exposure to at least 0.46 mg/kg-day. In males, the incidence of nephropathy was 80% in the controls and 100% for all treated groups; however, severity was minimal in the controls and two low-dose groups and minimal to mild in the 0.92 mg/kg-day group and higher. In females, there was a significant increased incidence of nephropathy only in the high-dose group (4/10 with minimal severity). Nephropathy was characterized by foci of tubular regeneration, thickened tubular basement membrane and scattered dilated tubules containing hyaline casts. No treatment-related effects were observed in the other organs; however, histopathology on the other organs was performed only on control and high-dose rats.

B6C3F1 mice (10/sex/group) were administered 0, 1.25, 2.5, 5, 10 or 20 mg/kg-day HgCl2 (0, 0.92, 1.9,3.7, 7.4 or 14.8 mg/kg-day) 15 days/week by gavage for 6 months (NTP 1993). A decrease in body-weight gain was reported in only the males at the highest dose tested. Significant increases occurred in absolute kidney weights of male mice at 3.7 mg/kg-day or greater and relative kidney weights of male mice at 7.4 and 14.8 mg/kg-day doses. The kidney weight changes corresponded to an increased incidence of cytoplasmic vacuolation of renal tubule epithelium in males exposed to at least 3.7 mg/kg- day. The exposed female mice did not exhibit any histopathologic changes in the kidneys.

In the 2-year NTP study, Fischer 344 rats (60/sex/group) were administered 0, 2.5 and 5 mg/kg-day HgCl2 (1.9 and 3.7 mg/kg-day) 5 days week by gavage (NTP, 1993). After 2 years, survival was reduced in only the treated male rat groups compared with the control. Mean body weights were decreased in both male and female treated groups. After 2 years, an increased incidence of nephropathy of moderate-to-marked severity and increased incidence of tubule hyperplasia was observed in the kidneys of exposed males compared with the controls. The control males exhibited nephropathy, primarily of mild-to- moderate severity. Hyperparathyroidism, mineralization of various tissues and fibrous osteodystrophy were observed and considered secondary to the renal impairment. No significant differences were found in renal effects between exposed and control females. Other nonneoplastic effects included an increased incidence of forestomach hyperplasia in the exposed males and high- dose females.

NTP (1993) also administered to B6C3F1 mice (60/sex/group) daily oral gavage doses of 0, 5 or 10 mg/kg-day HgCl2 (0, 3.7 and 7.4 mg/kg-day) 5 days/week by gavage for 2 years. Survival and body weights of mice were slightly lower in HgCl2-treated mice compared with controls. Absolute kidney weights were significantly increased in the treated males, while relative kidney weights were significantly increased in high-dose males and both low- and high-dose females. Histopathology revealed an increase in the incidence and severity of nephropathy in exposed males and an increase in the incidence of nephropathy in exposed females. Nephropathy was defined as foci of proximal convoluted tubules with thickened basement membrane and basophilic cells with scant cytoplasm. Some affected convoluted tubules contained syaline casts. Also, an increase in nasal cavity inflammation (primarily infiltration of granulocytes in nasal mucosa) was observed in the exposed animals.

Gale and Ferm (1971) studied the teratogenic effects of mercuric acetate on Syrian golden hamsters. Single doses of 2, 3 or 4 mg/kg were injected by the i.v. route on day 8 of gestation. Growth retardation, increased resorption rates and edema of the fetuses were found at all three dose levels, while an increase in the number of abnormalities was detected at the two higher doses. In a more recent study, Gale (1981) compared the embryotoxic effects of a single s.c. dose of 15 mg/kg mercuric acetate on the eighth day of gestation in five inbred strains and one noninbred strain of Syrian hamsters. While strain differences were apparent, a variety of

abnormalities were reported in all the strains. Gale (1974) also compared the relative effectiveness of different exposure routes in Syrian hamsters. The following sequence of decreasing efficacy was noted for mercuric acetate; i.p. > i.v. > s.c. > oral. The lowest doses used, 2 mg/kg for i.p. and 4 mg/kg for the other three routes, were all effective in causing increased resorption and percent abnormalities.

In male mice administered a single i.p. dose of 1 mg/kg HgCl2, fertility decreased between days 28 and 49 post treatment with no obvious histological effects noted in the sperm (Lee and Dixon, 1975). The period of decreased fertility indicated that spermatogonia and premeiotic spermatocytes were affected. The effects were less severe than following a similar dose of methyl mercury. A single i.p. dose of 2 mg/kg HgCl2 in female mice resulted in a significant decrease in the total number of implants and number of living embryos and a significant increase in the percentage of dead implants (Suter, 1975). These effects suggest that mercury may be a weak inducer of dominant lethal mutations.

I.A.5. Confidence in the Oral RfD

Study — N/A
Database — High
RfD — High

No one study was found adequate for deriving an oral RfD; however, based on the weight-of-evidence from the studies using Brown Norway rats and the entirety of the mercuric mercury database, an oral RfD of high confidence results.

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

Source Document — U.S. EPA, 1988

This IRIS Summary is included in The Mercury Study Report to Congress, which was reviewed by OHEA and EPA's Mercury Work Group in November 1994. An Interagency Review by scientists from other federal agencies took place in January 1995. The report was also reviewed by a panel of non-federal external scientists in January 1995 who met in a public meeting on January 25-26. All reviewers comments have been carefully evaluated and considered in the revision and finalization of this IRIS summary. A record of these comments is summarized in the IRIS documentation files.

Other Docmentation -- U.S. EPA, 1987

Agency Work Group Review — 08/05/1985, 02/05/1986, 08/19/1986, 11/16/1988

Verification Date — 11/16/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Mercuric chloride (HgCl2) conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

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

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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

Sunstance Name -- Mercuric chloride (HgCl2)
CASRN — 7487-94-7

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Mercuric chloride (HgCl2)
CASRN — 7487-94-7
Last Revised — 05/01/1995

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 — C; possible human carcinogen

Basis — Based on the absence of data in humans and limited evidence of carcinogenicity in rats and mice. Focal papillary hyperplasia and squamous cell papillomas in the forestomach as well as thyroid follicular cell adenomas and carcinomas were observed in male rats gavaged with mercuric chloride for 2 years. The relevance of the forestomach papillomas to assessment of cancer in humans is questionable because no evidence indicated that the papillomas progressed to malignancy. The relevance of the increase in thyroid tumors has also been questioned because these tumors are generally considered to be secondary to hyperplasia; this effect was not observed in the high-dose males. It should also be noted that the authors considered the doses used in the study to exceed the MTD for male rats. In the same study, evidence for increases in squamous cell papillomas in the forestomach of female rats was equivocal. In a second study, equivocal evidence for renal adenomas and adenocarcinomas was observed in male mice; there was a significant positive trend. This tumor type is rare in mice, and the increase in incidence was statistically significant when compared with historic controls. Two other nonpositive lifetime rodent studies were considered inadequate. Mercuric chloride showed mixed results in a number of genotoxicity assays.

II.A.2. Human Carcinogenicity Data

None. No data are available on the carcinogenic effects of mercuric chloride in humans.

II.A.3. Animal Carcinogenicity Data

Limited. The results from a dietary study in rats and mice show equivocal evidence for carcinogenic activity in male mice and female rats and some evidence for carcinogenic activity in male rats. Two other dietary studies did not show any evidence for carcinogenicity, but these studies are limited by inadequacies in the data and experimental design, including the small number of animals/dose and/or a lack of complete histopathological examinations.

Mercuric chloride (purity >99%) was administered by gavage in water at doses of 0, 2.5 or 5 (mg/kg)/day (0, 1.9 and 3.7 (mg/kg)/day) to 60 F344 rats/sex/group, 5 days/week for 104 weeks (NTP, 1993). An interim sacrifice (10/sex/dose) was conducted after 15 months of exposure. Complete histopathological examinations were performed on all animals found dead, killed in extremis, or killed by design. Survival after 24 months was lower in low- and high-dose males at a statistically significant rate; survival was 43, 17 and 8% in control, low-, and high-dose males, respectively, and 58, 47 and 50% in control, low-, and high-dose females, respectively. During the second year of the study, body weight gains of low- and high-dose males were 91 and 85% of controls, respectively, and body weight gains of low- and high- dose females were 90 and 86% of controls, respectively. At study termination, nephropathy was evident in almost all male and female rats including controls, but the severity was much greater in treated males. The incidence of "marked" nephropathy was 6/50, 29/50 and 29/50 in control, low- and high-dose males, respectively. Squamous cell papillomas of the forestomach showed a statistically significant positive trend with dose by life table adjusted analysis; the incidences were 0/50, 3/50 and 12/50 in control, low- and high- dose males, respectively. For females, the incidence was 0/50, 0/49 and 2/50 in control, low- and high-dose groups, respectively. These neoplasms are rare in male rats and occurred in only 1/264 historical controls. The incidence of papillary hyperplasia of the stratified squamous epithelium lining of the forestomach was elevated at a statistically significant rate in all dosed males (3/49, 16/50 and 35/50 in control, low- and high-dose males, respectively) and in high-dose females (5/50, 5/49 and 20/50 in control, low- and high-dose females, respectively). The incidence of thyroid follicular cell carcinomas, adjusted for survival, showed a significant positive trend in males; the incidence was 1/50, 2/50 and 6/50 in control, low- and high-dose groups, respectively. The combined incidence of thyroid follicular cell neoplasms (adenoma and/or carcinoma) was not significantly increased (2/50, 6/50 and 6/50 in control, low- and high-dose males, respectively). In female rats a significant decrease in the incidence of mammary gland fibroadenomas was observed (15/50, 5/48 and 2/50 in control, low- and high-dose females, respectively). The high mortality in both groups of treated males indicates that the MTD was exceeded in these groups and limits the value of the study for assessment of carcinogenic risk. NTP (1993) considered the forestomach tumors to be of limited relevance to humans because the tumors did not appear to progress to malignancy. NTP (1993) also questioned the relevance of the thyroid carcinomas because these neoplasms are usually seen in conjunction with increased incidences of hyperplasia and adenomas. In this study, however, no increases in hyperplasia or adenomas were observed. Hyperplasia incidence was 2/50, 4/50 and 2/50 in control, low- and high-dose males, respectively; adenoma incidence was 1/50, 4/50 and 0/50 in control, low- and high-dose males, respectively.

In the same study, mercuric chloride was administered by gavage in water at doses of 0, 5 or 10 (mg/kg)/day (0, 3.7 and 7.4 (mg/kg)/day) to 60 B6C3F1 mice/sex/group 5 days/week for 104 weeks (NTP, 1993). An interim sacrifice (10/sex/dose) was conducted after 15 months of exposure. Terminal survival and body weight gain were not affected in either sex by the

administration of mercuric chloride. It should be noted that survival of high-dose females was lower than controls; female survival rates were 82, 70 and 62% in control, low- and high-dose females, respectively. Female mice exhibited a significant increase in the incidence of nephropathy (21/49, 43/50 and 42/50 in control, low- and high-dose females, respectively). Nephropathy was observed in 80-90% of the males in all groups. The severity of nephropathy increased with increasing dose. The incidence of renal tubular hyperplasia was 1/50, 0/50 and 2/49 in control, low- and high-dose males. The combined incidence of renal tubular adenomas and adenocarcinomas was 0/50, 0/50 and 3/49 in control, low- and high-dose males, respectively. Although no tumors were seen in the low-dose males, a statistically significant positive trend for increased incidence with increased dose was observed. These observations were considered important because renal tubular hyperplasia and tumors in mice are rare. The 2-year historical incidence of renal tubular adenomas or adenocarcinomas in males dosed by gavage with water was 0/205, and only 4 of the nearly 400 completed NTP studies have shown increased renal tubular neoplasms in mice. Data from this study were not statistically compared with historical control data by NTP. EPA's analysis of the reported data with Fisher's Exact test showed that the incidence of renal tubular adenomas or adenocarcinomas in the high-dose males was significantly elevated when compared with historical controls (Rice and Knauf, 1994).

A 2-year feeding study in rats (20 or 24/sex/group; strain not specified) was conducted in which mercuric acetate was administered in the diet at doses of 0, 0.5, 2.5, 10, 40 and 160 ppm (0, 0.02, 0.1, 0.4, 1.7 and 6.9 (mg Hg/kg)/day (Fitzhugh et al., 1950). Survival was not adversely affected in the study. Increases in kidney weight and renal tubular lesions were observed at the two highest doses. No statement was made in the study regarding carcinogenicity. This study was not intended to be a carcinogenicity assay, and the number of animals/dose was rather small. Histopathological analyses were conducted on only 50% of the animals (complete histopathology conducted on only 31% of the animals examined), and no quantitation of results or statistical analyses were performed.

No increase in tumor incidence was observed in a carcinogenicity study using white Swiss mice (Schroeder and Mitchener, 1975). Groups of mice (54/sex/group) were exposed until death to mercuric chloride in drinking water at 5 ppm Hg (0.95 (mg/kg)/day). No effects on survival or body weights were observed. After dying, mice were weighed and dissected. The animals were examined for gross tumors, and some sections were made of the heart, lung, liver, kidney and spleen for microscopic examination. No toxic effects of mercuric chloride were reported in the study. No statistically significant differences were observed in tumor incidences for treated animals and controls. This study is of limited use for evaluation of carcinogenicity because complete histological examinations were not performed, only a single dose was tested, and the MTD was not achieved.

II.A.4. Supporting Data for Carcinogenicity

The increasing trend for renal tubular cell tumors in mice observed in the NTP (1993) study receives some support from similar findings in mice after chronic dietary exposure to methylmercury (Hirano et al., 1986; Mitsumori et al., 1981, 1990). In these studies, dietary exposure to methylmercuric chloride resulted in increases in renal tubular tumors at doses wherein substantial nephrotoxicity was observed (see methylmercury file on IRIS).

As summarized in NTP (1993) and U.S. EPA (1985), mercuric chloride has produced some positive results for clastogenicity in a variety of in vitro and in vivo genotoxicity assays; mixed results regarding its mutagenic activity have been reported. Mercuric chloride was negative in gene mutation tests with Salmonella typhimurium (NTP, 1993; Wong, 1988) but produced DNA damage as measured in the Bacillus subtilis rec assay (Kanematsu et al., 1980). A weakly positive response for gene mutations was observed in mouse lymphoma (L5178Y) cells in the presence of microsomal activation (Oberly et al., 1982). DNA damage has also been observed in assays using rat and mouse embryo fibroblasts (Zasukhina et al., 1983), CHO cells and human KB cells (Cantoni and Costa, 1983; Cantoni et al., 1982, 1984a,b; Christie et al., 1984, 1986; NTP, 1993; Williams et al., 1987). Mercuric chloride also produced chromosome aberrations and SCEs in CHO cells (Howard et al., 1991) and chromosome aberrations in human lymphocytes (Morimoto et al., 1982). Sex-linked recessive lethal mutations were not observed in male Drosophila melanogaster (NTP, 1993).

Although mice given intraperitoneal doses of mercuric chloride have shown no increase in chromosomal aberrations in bone marrow cells (Poma et al., 1981) and no increase in aneuploidy in spermatogonia (Jagiello and Lin, 1973), mercuric chloride administered to mice by gavage induced a dose-related increase in chromosome aberrations and aberrant cells in the bone marrow (Ghosh et al., 1991). Similarly, an increased incidence of chromosomal aberrations (primarily deletion and numeric aberrations) was observed in livers of fetal mice exposed to mercury in utero as the result of maternal inhalation of aerosols of mercuric chloride (Selypes et al., 1984). Positive dominant lethal results (increased resorptions and post-implantation deaths in untreated females) have been obtained in studies in which male rats were administered mercuric chloride orally (Zasukhina et al., 1983). A slight increase in post-implantation deaths and a decrease in living embryos were also reported in treated female mice mated to untreated males (Suter, 1975); however, it was not clear whether these effects were the result of germ cell mutations or were secondary to maternal toxicity.

The effects of mercuric chloride on genetic material has been suggested to be due to the ability of mercury to inhibit the formation of the mitotic spindle, an event known as c-mitosis (U.S. EPA, 1985).

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

None. The incidences of squamous cell papillomas of the forestomach and thyroid follicular cell carcinomas were evaluated. No slope factor was derived using the forestomach tumors because these tumors are probably the result of doses of mercuric chloride above-MTD resulting in irritation of the forestomach and subsequent cell death and epithelial proliferation. The carcinogenic mechanism for mercuric chloride at the high doses observed may be specific to effects of irritation of the forestomach.

Regarding the thyroid carcinomas, a variety of drugs, chemicals and physiological perturbations result in the development of thyroid follicular tumors in rodents. For a number of chemicals, the mechanism of tumor development appears to be a secondary effect of long-standing hypersecretion of thyroid-stimulating hormone by the pituitary (Capen and Martin, 1989; McClain, 1989). In the absence of such long-term stimulatory effects, induction of thyroid follicular cell cancer by such chemicals usually does not occur (Hill, 1989). The mechanism whereby thyroid tumors developed in the NTP (1993) assay is very unclear given that hyperplasia was not observed. The study reviewers concluded that it was difficult to associate the increase in thyroid tumors with mercuric chloride administration. Thus, it would be of questionable value to use the thyroid tumors in rats as the basis for a quantitative cancer risk estimate for humans.

All tumors in rats were observed at doses equalling or exceeding the MTD. Kidney tumors in mice were observed in only the high-dose males. The increased incidence was not statistically significant in comparison to the concurrent controls, but was significant when compared with historical controls. A linear low-dose extrapolation based on the male mouse kidney tumor data (three tumors in the high-dose group only) is not appropriate.

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

None

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1995

This IRIS Summary is included in The Mercury Study Report to Congress which was reviewed by OHEA and EPA's Mercury Work Group in November 1994. An Interagency Review by scientists from other federal agencies took place in January 1995. The report was also reviewed by a panel of non-federal external scientists in January 1995 who met in a public meeting on January 25-26. All reviewers comments have been carefully evaluated and considered in the revision and finalization of this IRIS summary. A record of these comments is summarized in the IRIS documentation files.

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

Agency Work Group Review — 03/03/1994

Verification Date — 03/03/1994

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Mercuric chloride (HgCl2) conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

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

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Mercuric chloride (HgCl2)
CASRN — 7487-94-7

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

None

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VII. Revision History

Substance Name — Mercuric chloride (HgCl2)
CASRN — 7487-94-7

Date	Section	Description
05/01/1995	I.A.	Oral RfD summary on-line
05/01/1995	II.	Carcinogenicity assessment summary on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Mercuric chloride (HgCl2)
CASRN — 7487-94-7
Last Revised — 05/01/1995

- 7487-94-7
- HgCl2
- Mercuric chloride
- Mercury chloride (HgCl2)
- Mercury dichloride
- MERCURY(II) CHLORIDE
- Bichloride of mercury
- Bichlorure de mercure [French]
- Caswell No. 544
- Chlorid rtutnaty [Czech]
- Chlorure de mercure II [French]
- Chlorure mercurique [French]
- CLORURO di MERCURIO [Italian]
- Cloruro mercurico [Spanish]
- Corrosive mercury chloride
- Corrosive sublimate

- Dichloromercury
- EPA Pesticide Chemical Code 052001
- Mercuric bichloride
- Mercury bichloride
- Mercury perchloride
- NCI-C60173
- NSC 353255
- Quecksilber chlorid [German]
- Sublimat [Czech]
- Sulema [Russian]