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# Health effects classification and its role in the derivation of minimal risk levels: Renal effects

C.-H. Selene J. Chou *, Hana R. Pohl

*Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services, Atlanta, GA, USA*

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**Abstract**

The Agency for Toxic Substances and Disease Registry (ATSDR) derives minimal risk levels (MRLs) for priority hazardous substances. MRLs are health guidance values intended to serve as screening levels for health assessors to select contaminants of concern and to assess potential health effects at hazardous waste sites and areas affected by unplanned releases. Current MRLs are published in ATSDR toxicological profiles and are listed at the ATSDR website at www.atsdr.cdc.gov. To date, ATSDR has derived 125 inhalation MRLs, 207 oral MRLs, and eight external radiation MRLs; 19 MRLs are based on renal effects. This article reports on endpoints used to derive the MRLs. It also presents the ranking of effects into less serious and serious categories as described in ATSDR's *Guidance for Developing Toxicological Profiles*.
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*Keywords:* Minimal risk levels; MRLs; Non-cancer risk assessment; Rental toxicity; Screening levels; Hazardous substances; Health guidance values

## 1. Introduction

After having compiled and evaluated the current database of toxicological and epidemiological studies in toxicological profiles, the Agency for Toxic Substances and Disease Registry (ATSDR) derives minimal risk levels (MRLs) for the profiled substances. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. MRLs are substance-specific health guidance values intended to serve as screening levels to be used by ATSDR health assessors or other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. MRLs are not intended to define clean-up or action levels. MRLs are based on the most sensitive non-cancer health-effect end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Proper categorization of health effects is, therefore, critical for deriving MRLs. This paper presents ATSDR's guidance for classifying renal effects as described in *Guidance for Developing Toxicological Profiles* (ATSDR, 1996, 2003) and the MRLs that are based on renal effects. So far, the guidance has served as an internal document. However, parts of the guidance related to hematologic, neurologic, developmental, and respiratory end points and related MRLs were previously published (Abadin et al., 1998; Chou and Williams-Johnson, 1998; Pohl et al., 1998; Wilbur, 1998).

## 2. Methods

### 2.1. Deriving minimal risk levels

MRLs are derived using the no-observed-adverse-effect level/uncertainty factor (NOAEL/UF) approach.

* Corresponding author.
*E-mail address:* cjc3@cdc.gov (C.-H.S.J. Chou).

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They are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) exposure durations, and for the oral and inhalation routes of exposure. MRLs are based on non-cancer health end points (ATSDR, 1996; Chou et al., 1998; Pohl and Abadin, 1995) and are derived based on the highest NOAEL, or in the absence of a NOAEL, the lowest less-serious lowest-observed-adverse-effect level (LOAEL) for the most sensitive health effect end point for a given route and exposure duration in the database. Uncertainty factors (UFs) are applied to account for human variability, for use of a LOAEL, for interspecies extrapolation when animal studies are used in the absence of adequate human data, and for extrapolation across exposure duration. Also a modifying factor (MF) may be used to account for additional uncertainty on a case-by-case basis. MRLs for each substance are derived on the basis of current data, and reviewed by the ATSDR MRL Workgroup, submitted for public comment, and published in the ATSDR toxicological profiles. A list of all current MRLs (updated in December 2004) is available on ATSDR's Website (www.atsdr.cdc.gov). The MRLs are subject to change as new information becomes available concomitant with updating the toxicological profiles.

### 2.2. ATSDR's guidance document

ATSDR's guidance document (ATSDR, 1996, 2003) provides instructions on classifying target-organ-specific end points. The urinary system is evaluated along with other systems in the toxicological profiles; renal effects include any effects related to the kidneys and their functioning. Risk assessment approaches generally assume that chemicals producing toxicity in laboratory animals pose similar hazards to humans. For most chemicals, this extrapolation remains appropriate. However, a growing body of evidence indicates that certain chemicals cause nephropathy through a mechanism that occurs in male rats but not in humans (or in female rats, mice, or other species). The following text presents specific instructions described in ATSDR's guidance document that are related to $\alpha_{2u}$-globulin-induced renal pathology in male rats and to chronic progressive nephropathy in male and female rats.

### 2.3. $\alpha_{2u}$-Globulin-induced renal pathology in male rats

Numerous investigations have demonstrated a consistent association between the accumulation of hyaline droplets containing $\alpha_{2u}$-globulin ($\alpha_{2u}$-g), a low-molecular-weight protein, and certain lesions in the male rat kidney (Borghoff et al., 1991; Hard et al., 1993; Swenberg et al., 1989). These renal lesions have not been identified in female rats, in mice, or in other laboratory species tested. Thus, nephropathy associated with chemicals that induce accumulation of $\alpha_{2u}$-g appears to be a unique response of the male rat. EPA (1991) has established three criteria for determining that renal lesions in male rats are caused by $\alpha_{2u}$-g accumulation; a positive response is required for each criterion:

1. The number and size of hyaline droplets in renal proximal tubule cells of treated male rats have increased.
2. The accumulated protein in the hyaline droplets is $\alpha_{2u}$-g (usually demonstrated immunohistochemically).
3. Additional aspects of the pathological sequence of lesions associated with $\alpha_{2u}$-g nephropathy are demonstrated.

Typical lesions include single-cell necrosis, sloughing of epithelial cells into the proximal tubular lumen, formation of granular casts, linear mineralization of the papilla, and tubule hyperplasia and regeneration. If the response is mild, not all of these lesions may be observed; however, some elements consistent with the pathological sequence must be present. Because nephropathy in the male rat that is associated with $\alpha_{2u}$-g accumulation is unique and cannot be extrapolated to humans, it should not be used as an end point to derive MRLs.

### 2.4. Chronic progressive nephropathy in rats

Another factor to consider is the species-related condition chronic progressive nephropathy (CPN). CPN is an age-related spontaneous disorder of rats that is more severe in males than in females. CPN is more common in the Sprague–Dawley and F344 strains of rats than in the Wistar strain (Gray, 1986), and it is also common in the Osborne–Mendel strain (Goodman et al., 1980). Histopathologic characteristics of CPN (EPA, 1991; UAREP, 1983) include some lesions that are also found in $\alpha_{2u}$-g nephropathy, as well as lesions that are distinctive. Single-cell necrosis, regenerating tubules, and focal hyperplasia of the proximal tubule epithelium are common to CPN and to $\alpha_{2u}$-g nephropathy. CPN lesions that are not components of $\alpha_{2u}$-g nephropathy include prominent thickening of tubules and glomerular basement membranes; hyaline casts consisting of homogenous, proteinaceous material (distinct from granular casts containing cellular debris); interstitial mononuclear cell infiltration; fibrosis; tubule atrophy; and sclerotic glomeruli.

CPN in the aging male rat can therefore complicate the interpretation of other renal lesions. However, nephropathy in the male rat that is not attributable to either CPN or $\alpha_{2u}$-g accumulation may provide end points that are suitable for consideration in deriving MRLs, particularly if similar effects are seen in female rats, mice, or other species. Lesions related to CPN in exposed rats should not be used as end points in deriving



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Table 1
Renal-effect end points for deriving minimal risk levels

| Effect | Less serious | Serious |
|---|---|---|
| Fatty degeneration of tubules | + | |
| Increased blood urea nitrogen (BUN) | + | |
| Urinary bladder effects | + | + |
| Altered urinary creatinine excretion | + | |
| Proteinuria (excess of serum proteins in urine) | + | |
| Renal tubular degeneration | + | + |
| Decreased urine volume | + | |
| Hematuria | | + |
| Hemoglobinuria | | + |
| Renal tubular casts | + | |
| Tubular necrosis | + | + |

MRLs, with some exceptions. Lesions of CPN in exposed rats may be considered as potential end points for deriving MRLs if exposed male and female or only female rats have CPN lesions that exhibit a clearly defined dose response. More specifically, with increasing exposure doses, a progressive significance of CPN lesions should exist, as characterized by (1) an earlier age of onset, (2) increasing severity, and (3) an increased frequency of animals affected. Observation of renal effects in other similarly exposed species contributes to the weight of evidence. In cases where the above criteria are met, NOAEL values for lesions of CPN can be considered for deriving MRLs.

Examples of specific renal-effect end points are listed and classified as less serious or serious in Table 1. Health effects are categorized according to severity. A dose that evokes failure in a biologic system and that can lead to morbidity or mortality is referred to as a serious LOAEL. Some effects can be considered either less serious or serious; more information is needed to make a determination on a case-by-case basis. For example, increased blood urea nitrogen (BUN) levels are commonly found in inadequate excretion due to kidney disease or urinary obstruction (e.g., prostate enlargement). Increased BUN levels can be associated not only with impaired renal function, but also with shock, dehydration, gastrointestinal hemorrhage, infection, diabetes, some malignancies, acute myocardial infarction, chronic gout, excessive protein intake or protein catabolism. It is therefore important to look at the whole clinical picture and not to make rush decisions about severity of the disease based on result of one biochemical indicator.

## 3. Results and discussion

### *3.1. ATSDR's assessment of renal effects*

Of the 332 oral and inhalation MRLs that ATSDR has derived to date, 19 MRLs are based on renal effects. These 19 MRLs are listed in Table 2. Any injury to the urinary system is of interest to ATSDR; however, most studies have concentrated on chemically induced effects in kidneys. According to the site of the renal injury, glomerular, tubular, or interstitial damage is recognized.

Only one MRL is based on renal effects in humans: the MRL for chronic oral exposure to cadmium. Heavy metals such as cadmium, chromium, lead, and mercury are known inducers of nephrotoxicity. Multiple studies have shown that chronic exposure to cadmium produces proximal tubule damage with subsequent proteinuria, glycosuria, amino aciduria, polyuria, decreased absorption of phosphate, and enzymuria. The clinical symptoms result from the degeneration and atrophy of the proximal tubules with possible further progression demonstrated as interstitial fibrosis of the kidney (Stowe et al., 1972). On the molecular level, the toxic effects of cadmium are generally attributed to free cadmium ions that induce adverse effects, including inactivating metal-dependent enzymes and initiating production of oxidation derivatives. Cadmium accumulates in the body; half-times for the human kidney have been estimated at between 6 and 38 years (Kjellstrom and Nordberg, 1986). Quantitative analysis of the prevalence of elevated urinary $\beta_2$-microglobulin as a function of cadmium ingestion indicates that renal damage will occur for a 53-kg person after a total intake of approximately 2000 mg cadmium (Nogawa et al., 1989). This intake corresponds to a 50-year dose of approximately 0.0021 mg/kg/day, which serves as the basis of the chronic oral MRL for cadmium. Although toxicological profiles for other metals have included data on renal toxicity (e.g., mercury and lead-induced tubular necrosis), other target systems have proven to be more sensitive end points for deriving MRL (e.g., developmental neurotoxicity for methylmercury exposure).

Injury to the renal tubule is a frequently occurring critical effect of reported nephrotoxicity following chemical exposure in animal studies. The renal tubule is sensitive to chemical damage because of its ability to concentrate the toxicants that enter it from the blood stream either by filtration through the glomerulus or by active transport through the tubular cells. Chemicals may cause the damage by interfering with essential metabolic and functional processes either directly or as active metabolites. Again, the major cause of damage is binding to proteins, alteration of enzymes, and inducing lipid peroxidation derivatives. Histologically, the changes range from focal necrosis to extensive tubular degeneration. MRLs based on effects in the renal tubule include MRLs for bromodichloromethane, ethylene oxide, hexachlorobutadiene, hexachlorocyclopentadiene, highly soluble salts of uranium, and insoluble salts of uranium. Increased absolute and relative kidney weights have been reported in animals following exposure to ethylene glycol, mercuric chloride, and 1,2-dichloroethane. Histopathological changes in the tubules accompanied the weight changes at higher-dose exposures to mercuric chloride and 1,2-dichloroethane.

Table 2
Minimal risk levels (MRLs) based on renal effects

| Substance | Route | Duration | MRL value | UF[a] | End point | Reference |
|---|---|---|---|---|---|---|
| Bromodichloromethane | Oral | Chronic | 0.02 mg/kg/day | 1000 | LOAEL[b] in mice; cytomegaly; focal necrosis in the proximal tubular epithelium at higher doses | NTP (1987a) |
| Cadmium | Oral | Chronic | 0.0002 mg/kg/day | 10 | NOAEL[c] in humans; renal damage (increased prevalence of elevated urinary $\beta_2$-microglobulin) after a total intake of 2000 mg (for a 53-kg person) cadmium over 50-year lifetime | Nogawa et al. (1989) |
| Chlordecone | Oral | Intermediate | 0.0005 mg/kg/day | 100 | NOAEL in rats; proteinuria and increased severity of glomerulosclerosis at higher doses | Larson et al. (1979) |
| Chlordecone | Oral | Chronic | 0.0005 mg/kg/day | 100 | NOAEL in rats; proteinuria and increased severity of glomerulosclerosis at higher doses | Larson et al. (1979) |
| Ethylene glycol | Inhalation | Acute | 0.5 ppm | 100 | NOAEL in mice; increased absolute kidney weight | Tyl (1988) |
| Ethylene glycol | Oral | Chronic | 2.0 mg/kg/day | 100 | NOAEL in rats; oxalate nephrosis in male rats, chronic nephritis at higher doses | Depass et al. (1986), Woodside (1982) |
| Ethylene oxide | Inhalation | Intermediate | 0.09 ppm | 100 | NOAEL in mice; tubular degeneration and tubular necrosis at higher doses | NTP (1987b) |
| Hexachlorobutadiene | Oral | Intermediate | 0.0002 mg/kg/day | 1000 | LOAEL in mice; tubular degeneration | NTP (1991a), Yang et al. (1989) |
| Hexachlorocyclopentadiene | Oral | Intermediate | 0.1 mg/kg/day | 100 | NOAEL in rats; nephrosis in the terminal portion of the proximal convoluted tubules in the inner cortex at higher doses | Abdo et al. (1984) |
| Mercuric chloride | Oral | Acute | 0.007 mg/kg/day | 100 | NOAEL in rats; increased absolute and relative kidney weights, increased incidence of renal tubular necrosis at higher doses | NTP (1993) |
| Mercuric chloride | Oral | Intermediate | 0.002 mg/kg/day | 100 | NOAEL in rats; Increased absolute and relative kidney weights, increased incidence of nephropathy (foci of tubular regeneration, thickened tubular basement membrane, and scattered dilated tubules containing hyaline casts) at higher doses | Dieter et al. (1992), NTP (1993) |
| Methyl *t*-butyl ether | Inhalation | Chronic | 0.7 ppm | 100 | NOAEL in female rats; increased incidence and severity of chronic progressive nephropathy at higher doses | Chun et al. (1992) |
| Uranium, highly soluble salts | Inhalation | Intermediate | 0.0004 mg/m$^3$ | 90 | LOAEL in dogs; microscopic lesions in the renal tubules. Proteinuria and severe renal damage at higher doses | Rothstein (1949a) |
| Uranium, highly soluble salts | Inhalation | Chronic | 0.0003 mg/m$^3$ | 30 | NOAEL in dogs; microscopic lesions in the renal tubules | Stokinger et al. (1953) |
| Uranium, highly soluble salts | Oral | Intermediate | 0.002 mg/kg/day | 30 | LOAEL in rabbits; renal cytoplasmic vacuolation, anisokaryosis, nuclear vesiculation and interstitial collagen and/or reticulin sclerosis at higher doses | Gilman et al. (1998) |
| Uranium, insoluble compounds | Inhalation | Intermediate | 0.008 mg/m$^3$ | 30 | NOAEL in dogs; microscopic lesions in the renal tubules at higher doses | Rothstein (1949b) |
| Vanadium | Oral | Intermediate | 0.003 mg/kg/day | 100 | NOAEL in rats; altered renal function (increased plasma urea, and mild histological changes such as hemorrhagic foci) at higher doses | Domingo et al. (1985) |
| 1,2-Dichloroethane | Oral | Intermediate | 0.2 mg/kg/day | 300 | LOAEL in rats; increased absolute and relative kidney weights with renal tubular regeneration at higher doses | NTP (1991b) |
| 1,2-Dichlorobenzene | Oral | Chronic | 0.4 mg/kg/day | 100 | NOAEL in mice; increased incidence of renal tubular regeneration | NTP (1985) |

[a] UF, uncertainty factor.
[b] LOAEL, lowest-observed-adverse-effect level.
[c] NOAEL, no-observed-adverse-effect level.



Oxalate nephrosis and nephritis in male rats served as the basis for ATSDR's chronic oral MRL for ethylene glycol. Exposure to ethylene oxide causes the same effects in male mice at a higher dose (NTP, 1992). The inhalation MRL for methyl *t*-butyl ether is based on a NOAEL for increased incidence and severity of CPN in female rats, even though CPN is observed in male rats at the same dose. Derivation of this MRL was consistent with the guidance on derivation of MRLs based on CPN in rats, as described previously.

CPN changes can be observed in tubuli and in glomeruli. Otherwise, the glomerulus is a relatively uncommon site of toxic injury from chemicals (Greaves, 1998). An example of such injury is a mercury-induced glomerulonephritis based on the immunological mechanism in humans. Damage to the glomerular filtration mechanism allows protein to get into the urine. Proteinuria is therefore a biomarker of glomerular damage; a massive loss of circulating albumin may result in edema (i.e., nephrotic syndrome). In case the capillary walls are damaged and red blood cells get into the urine, hematuria is detected (i.e., nephritic syndrome). Proteinuria resulting from glomerulosclerosis is the basis for the oral MRLs for chlordecone and for the inhalation MRL for highly soluble salts of uranium. Altered renal function as indicated by increased plasma urea is the basis for the oral MRL for vanadium.

### *3.2. Comparison of ATSDR's MRLs and EPA's RfCs/RfDs for renal effects*

The U.S. Environmental Protection Agency (EPA) also derives health-based guidance values for hazardous chemicals; EPA's values are called reference concentrations (RfCs) and reference doses (RfDs) for inhalation and oral exposures, respectively. The RfC and RfD values are posted on the EPA's Integrated Risk Information System (IRIS) Website at www.epa.gov/iris. As of July 2004, 69 RfCs and 358 RfDs were listed on the IRIS Website. EPA has developed 55 RfDs that list kidney effects as part of the justification for derivation of these guidance values. EPA based a RfC of 3 mg/m$^3$ for methyl *t*-butyl ether (MTBE) on a NOAEL for increased kidney weights and "increased severity of spontaneous renal lesions." ATSDR's chronic inhalation MRL of 0.7 ppm (or 2.5 mg/m$^3$) for MTBE is practically equal to EPA's value and is based on the same end points. The RfCs for chlorodifluoromethane and cumene also were based on increased kidney weights. However, like many chemicals evaluated by EPA, these chemicals were not evaluated under ATSDR's program.

Both ATSDR and EPA derived oral MRLs/RfDs based on renal effects for the following chemicals: cadmium, ethylene glycol, and uranium (highly soluble salts). ATSDR derived chronic duration oral MRL of 0.0002 mg/kg/day for cadmium. EPA developed two RfDs for cadmium: 0.0005 mg/kg/day of cadmium through water intake and 0.001 mg/kg/day of cadmium through food intake. ATSDR's cadmium MRL is close to EPA's value for exposure through water intake and is a good screening tool for ATSDR's health assessments. The chronic oral MRL for ethylene glycol is 2.0 mg/kg/day; this MRL is the same value and is based on the same end point as EPA's RfD. ATSDR derived an intermediate-duration oral MRL of 0.002 mg/kg/day for highly soluble uranium salts. If extrapolated to chronic exposure, this MRL would be one order of magnitude lower than the RfD. The reason for the difference is that ATSDR used a LOAEL of 0.05 mg U/kg/day in rabbits from the Gilman et al. (1998) study and a UF of 30, whereas EPA derived the RfD for soluble uranium salts of 0.003 mg/kg/day using a LOAEL of 2.8 mg/kg/day and a UF of 1000 on the basis of a 30-day oral bioassay in rabbits by Maynard and Hodge (1949). The difference in health guidance values stems from the availability of new information in the literature.

The chronic oral MRL of 0.4 mg/kg/day for 1,2-dichlorobenzene was based on a NOAEL of 60 mg/kg/day for increased tubular regeneration in mice observed in the NTP (1985) study. In comparison, the RfD of 0.09 mg/kg/day was based on a free-standing NOAEL of 120 mg/kg/day in mice from same study. EPA considers the treatment-related renal effects at 120 mg/kg/day a NOAEL, whereas ATSDR considers the increased tubular regeneration reflective of tubular injury, and therefore calls the lower dose of 60 mg/kg/day a NOAEL. Other oral MRLs based on renal effects were derived for periods of duration shorter than those of the RfDs making the comparison difficult, or the chemicals in question were not even evaluated under the EPA IRIS program.

## 4. Conclusion

The kidney is frequently affected by chemicals because of its function as a major excretory organ and because of its structure. The MRL workgroup review of toxicological health-effect data ensures proper interpretation of the data in the context of the guidance and also ensures consistency in derivation of health guidance values across toxicological profiles. ATSDR has derived 19 MRLs based on renal effects. The renal tubuli was the site of greatest damage for most chemicals. Comparison between MRLs with RfCs/RfDs based on renal effects shows that many of the chemicals have not been evaluated by both agencies. When both agencies use the same up-to-date literature from which to derive guidance, a good correlation exists between the health guidance values.