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

Received 25 February 2005
Available online 24 May 2005

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. Published by Elsevier Inc.

Keywords: Minimal risk levels; MRLs; Non-cancer risk assessment; Renal 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.
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., 1996; Pohl and Abadin, 1995) and are derived based on the highest NOAEL, or in the absence of a NOAEL, the lowest least-serious lowest-observed-adverse-effect level (LOAEL) for the most sensitive health effect endpoint 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 α2u-globulin-induced renal pathology in male rats.

2.3. α2u-Globulin-induced renal pathology in male rats

Numerous investigations have demonstrated a consistent association between the accumulation of hyaline droplets containing α2u-globulin (α2u-g) 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 α2u-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 α2u-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 α2u-g (usually demonstrated immunohistochemically).
3. Additional aspects of the pathological sequence of lesions associated with α2u-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 α2u-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 α2u-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 α2u-g nephropathy. CPN lesions that are not components of α2u-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; fibrous 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 α2u-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...
Acknowledgments

We express appreciation to all MRL workgroup members, past and present, especially Dr. Malcolm Williams, for their valuable contribution to the development of MRLs based on renal effects.

References

clorocyclopentadiene: subchronic (3-week) administration by gavage of F344 rats and B6C3F1 mice. I. Appl. Toxicol. 4, 75-81.
ATSDR, 1996. Minimal risk levels for priority substances and guid­
lines for derivation. Agency for Toxic Substances and Disease Reg­
dates, Atlanta, GA.
y and kidney cancer in male rat qualitative and quantitative issues and relevant human cases. CIT Activities 11, 1-8.
Chou, C.-H.S., Williams-Johnson, M., 1998. Health effects classification and its role in the derivation of minimal risk levels: neurologi­
ary butyl ether: vapor inhalation oncogenicity study in Fischer 344 rats. Bethesda: National Cancer Institute, Toxicology, Project No. NIH-10189.
ity studies of venlafaxine in rats. J. Appl. Toxicol. 5, 418-421.
EPA, 1993. Toxicology and carcinogenesis studies of bromodichlo­
Hare, D.C., Rodgers, I.S., Basteke, K.P., et al., 1993. Hazard evaluation of acute and subchronic oral administration of cadmium, hydrox­
chronic and chronic toxicity of chlorodifluoromethane. Toxicol. Appl. Phar­
macol. 48, 29-34 (BUN) +
Uric acid +
Urinary bladder effects •
Altered creatinine excretion •
Proteinuria (excess of serum proteins in urine) •
Tubular renal degeneration •
Decreased creatinine +
Nematuria •
Hematuria •
Renal tubular cells +
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 reference dose. 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 fre­
quency 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 consid­
dered for deriving MRLs.
Examples of specific renal-effect end points are listed and assessed as less serious or serious in Table 1. Health status 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 intraocular pressure in exposed cynomolgus monkey (BUN) levels and 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 then critical to look at the whole clinical picture and not make such decisions about severity of the dis­
ease base 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. In the case of the site of renal injury, gly­
mercurial, 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 met­
als such as cadmium, chromium, lead, and mercury are known inducers of nephrotoxicity. Multiple studies have shown that cadmium exposure causes progressive renal tubule damage with subsequent proteinuria, glycos­
uria, 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 (Stone et al., 1972). On the molecular level, the toxic effects of cadmium are gener­
ally attributed to free cadmium ions that induce adverse effects, including inactivating metal-dependent enzymes and initiating production of oxidative derivatives. Cad­
mium causes renal lesions through mechanisms that are similar to those that have been shown in the proximal renal tubules of human kidney that have been estimated at between 6 and 38 years (Kjellstrom and Nordberg, 1986). Quantitative analysis of the prevalence of elevated urinary β2-microglobulin as a function of cadmium ingestion indicates that renal dam­
age will occur for a 53-kg person after a total intake of approximately 2000 mg cadmium (Nogawa et al., 1989). This intake corresponds to an 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 tox­
icity (e.g., mercury and lead-induced tubular necrosis), other target systems have proven to be more sensitive end points for deriving MRLs (e.g., developmental neurotoxic­
ity for methylmercury exposure).

Injury to the renal tubule is a frequently occurring critical effect of reported nephrotoxicity following chem­
al exposure in animals. In the absence of a speci­
}
Table 2 Oxalate nephrosis and nephritis in male rats served as salts). ATSDR derived chronic duration oral MRL of 0.002 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/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 0.063 mg/kg/day using a LOAEL of 2.8 mg/kg/day and a UF of 1000 on the basis of a massive damage of circulating albumin in male 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 contrast, the RfD is based on increased kidney weights. Thus, the RfD is not 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 endogenous renal effects are common. Therefore, 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.

**Table 2**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Route</th>
<th>Duration</th>
<th>MRL value (mg/kg/day)</th>
<th>UF*</th>
<th>End point</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brominated thionitrate</td>
<td>Oral</td>
<td>Chronic</td>
<td>0.002</td>
<td>100</td>
<td>NOAEL</td>
<td>NTP (1981a)</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Oral</td>
<td>Chronic</td>
<td>0.0002</td>
<td>10</td>
<td>NOAEL</td>
<td>Nogawa et al. (1989)</td>
</tr>
<tr>
<td>Ethylene chloride</td>
<td>Oral</td>
<td>Intermediate</td>
<td>0.0005</td>
<td>100</td>
<td>NOAEL</td>
<td>Larson et al. (1979)</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Inhalation</td>
<td>Acute</td>
<td>0.5 ppm</td>
<td>100</td>
<td>NOAEL</td>
<td>Tytl (1988)</td>
</tr>
<tr>
<td>Hexachlorobutadiene</td>
<td>Oral</td>
<td>Intermediate</td>
<td>0.0002</td>
<td>100</td>
<td>LOAEL</td>
<td>NTP (1991a)</td>
</tr>
<tr>
<td>Mercuric chloride</td>
<td>Oral</td>
<td>Intermediate</td>
<td>0.002</td>
<td>100</td>
<td>NOAEL</td>
<td>NTP (1993)</td>
</tr>
<tr>
<td>Ethyl-t-butyl ether</td>
<td>Inhalation</td>
<td>Acute</td>
<td>0.7 ppm</td>
<td>100</td>
<td>NOAEL</td>
<td>Chun et al. (1992)</td>
</tr>
<tr>
<td>Uranium, highly soluble salts</td>
<td></td>
<td>Intermediate</td>
<td>0.0004</td>
<td>90</td>
<td>LOAEL</td>
<td>Rothstein (1949a)</td>
</tr>
<tr>
<td>Uranium, highly soluble salts</td>
<td></td>
<td>Intermediate</td>
<td>0.0003</td>
<td>30</td>
<td>LOAEL</td>
<td>Stockinger et al. (1953)</td>
</tr>
<tr>
<td>Uranium, highly soluble salts</td>
<td></td>
<td>Intermediate</td>
<td>0.0002</td>
<td>30</td>
<td>LOAEL</td>
<td>Gliozzi et al. (1998)</td>
</tr>
<tr>
<td>Uranium, insoluble compounds</td>
<td></td>
<td>Intermediate</td>
<td>0.008</td>
<td>30</td>
<td>NOAEL</td>
<td>Rothstein (1949b)</td>
</tr>
<tr>
<td>Vanadium</td>
<td>Oral</td>
<td>Intermediate</td>
<td>0.003</td>
<td>100</td>
<td>NOAEL</td>
<td>Domingo et al. (1981)</td>
</tr>
<tr>
<td>L,2-Dichloroethane</td>
<td>Oral</td>
<td>Intermediate</td>
<td>0.2</td>
<td>300</td>
<td>LOAEL</td>
<td>NTP (1991b)</td>
</tr>
<tr>
<td>L,2-Dichlorobenzene</td>
<td>Oral</td>
<td>Chronic</td>
<td>0.4</td>
<td>100</td>
<td>LOAEL</td>
<td>NTP (1993)</td>
</tr>
</tbody>
</table>

* UF, uncertainty factor.  
LOAEL, lowest-observed-adverse-effect level.  
NOAEL, no-observed-adverse-effect level.