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

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Abstract

The Agency for Toxic Substances and Disease Registry (ATSDR) derives health based guidance values called minimal risk levels (MRLs) to assist with assessment of risks posed by exposures to hazardous chemicals. Current MRLs are posted on ATSDR's web site (www.atsdr.cdc.gov). From the total 326 MRLs currently posted, 79 MRLs are based on hepatic endpoints. The paper reports on endpoints used for the derivation of these MRLs and the use of uncertainty factors. It also describes 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: Hepatic effects; Health guidance values; MRL; RfC; RfD

1. Introduction

Over 600 drugs and numerous environmental chemicals have demonstrated toxicity to the liver in humans or in laboratory animals (Evans and Lake, 1998). The liver is a target organ for toxic chemicals because of its position in the organism, metabolic capabilities, and secretory and excretory functions. Chemicals that enter the organism by oral route first traverse the hepatic portal system before reaching the systemic circulation. Metabolism may change the toxicity (active or inactive metabolites) or the bioavailability (first-pass effect) of the parent chemicals (Bryson, 1997). In fact, most chemicals featured in ATSDR's toxicological profiles display some hepatotoxic effects. However, hepatotoxicity was the most sensitive target endpoint for only 53 chemicals. Identifying the most sensitive endpoint is important for ATSDR to derive the health-based guidance values minimal risk levels (MRLs). An MRL is defined as "an estimate of the daily human exposure to a substance that is likely to be without an appreciable risk of adverse, noncancer effects over a specified duration of exposure" (ATSDR, 1992, 1996a). ATSDR uses MRLs as a screening tool for evaluation of chemicals around hazardous waste sites and their possible impact on human populations living in the vicinity of the sites.

The purpose of this paper is to inform the public about MRLs based on hepatobiliary effects and about the guidance provided for the sections of toxicological profiles describing these health effects and their categorization in ATSDR's *Guidance for Developing Toxicological Profiles* (ATSDR, 1996b, 2003). So far, the guidance has served as an internal document. However, parts of the guidance related to neurological, developmental, hematological, and respiratory effects and the respective MRLs were previously published (Abadin et al., 1998; Chou and Williams-Johnson, 1998; Pohl et al., 1998; Wilbur, 1998).

2. Materials and methods

By Congressional mandate, ATSDR develops toxicological profiles for hazardous substances found at

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National Priority List (NPL) sites. ATSDR also prepares toxicological profiles for the Department of Defense (DOD) and the Department of Energy (DOE) on substances related to federal sites. So far, about 250 profiles were published as final documents. The profiles focus on health and toxicological information. Toxicological profiles (final and draft documents) can be found on ATSDR's web site (www.atsdr.cdc.gov). MRLs are an integral part of the toxicological profiles.

MRLs are derived according to current ATSDR methodology (Chou et al., 1998; Pohl and Abadin, 1995). ATSDR uses the highest no-observed-adverse-effect level (NOAEL) or lowest low-observed-adverse-effect level (LOAEL) in the available literature to derive the MRLs. Proper categorization of health effects is, therefore, critical for the MRL derivation. The 79 MRLs related to hepatotoxicity were based on vast databases compiled in the 53 toxicological profiles for the respective chemicals. A list of all current MRLs (updated on May 11, 2004) is available on ATSDR's web site (www.atsdr.cdc.gov).

3. Results and discussion

3.1. ATSDR's health effects classification

To determine the levels of significant human exposure to a given chemical and associated health effects, ATSDR's toxicological profiles examine and interpret available toxicological and epidemiological data. As described in the preceding papers (Chou et al., 1998; Pohl and Abadin, 1995), ATSDR categorizes health effects according to the seriousness as "serious," "less serious," or "minimal." A "less-serious" effect can be defined as changes that will prevent an organ or organ system from functioning in a normal manner but will not necessarily lead to the inability of the whole organism to function normally. "Serious" effects are defined as effects that prevent the organism from functioning normally or that can cause death. Subtle effects that they may be components in the sequence of events that leads to toxicity are usually categorized as "minimal" (Pohl and Abadin, 1995).

3.2. ATSDR's guidance document

The guidance document (ATSDR, 2003) provides instructions on classification of some endpoints that may be controversial as to the seriousness of the effects. As noted in the guidance document, "exposure to many substances may result in adaptive changes in the liver that are characterized by induction of the mixed function oxidase enzyme system and proliferation of smooth endoplasmic reticulum. Modifications occurring in the mixed function oxidase system as a consequence of the adaptive response may potentiate or inhibit toxic responses to other exogenous substances. Agents that induce chemical metabolizing enzyme systems (e.g., acetone) generally tend to potentiate hepatic injury produced by compounds such as chloroform, carbon tetrachloride, or halothane. For ATSDR, this is an especially important concept to consider because, in addition to the specific chemical causing adaptive changes, there is the potential for exposure to many other substances at NPL sites" (ATSDR, 1996b, 2003).

"The borderline between adaptive physiology and toxicity (functional impairment) is not always well delineated. The following guidance provides general direction for assessing hepatic adaptive responses; although this guidance is appropriate in most cases, there may be exceptions. However, for the purpose of assessing the biological significance of adaptive responses in the liver, the following criteria should be used: biochemical changes characterized by induction of enzymes of the mixed function oxidase system along with morphologic changes of hepatocellular hypertrophy and proliferation of smooth endoplasmic reticulum should be considered potentially adverse and should be classified as a less serious LOAEL. Other supportive changes that may be observed include increased organ weight, hepatic enlargement, and accentuated cytoplasmic eosinophilia. To maximize the accuracy of assessing hepatic (or other) adaptive responses, in addition to the guidance given here, this interpretative process is accompanied by insightful case-by-case analysis" (ATSDR, 1996b, 2003).

Similarly, the whole clinical picture has to be evaluated for effects classified as less serious LOAELs versus serious LOAELs. In animal studies, normal ranges are often not well established and statistical increase in liver enzymes is frequently classified as a less serious effect; however, when the increases are combined with other effects showing a threat to the organism from a serious damage to the liver, they would be classified as a serious LOAEL. In contrast, normal ranges and clinically defined pathological levels are used to identify LOAELs in human studies.

Other instructions in the guidance document pertain to a table with examples of hepatic health effects classification (Table 1). Some effects need further evaluation as

Table 1
Hepatic effect end points

Effect	Less serious	Serious
Altered liver enzymes	+	
Hepatomegaly (enlargement of the liver)	+	
Porphyria (disturbance of porphyrin metabolism)	+	
Hepatocyte vacuolization	+	
Congestion of liver	+	+
Hepatic necrosis		+
Cirrhosis		+
Jaundice	+	
Gall bladder effects	+	+
Fatty changes in liver	+	+
Hepatocellular degeneration	+	+

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to the seriousness based on information provided in the study the effects were described in (i.e., they can be serious or less serious).

3.3. Hepatobiliary effects and related MRLs

MRLs based on specific hepatic and biliary endpoints are listed in Table 2. Changes in liver weight and hepatomegaly are the most commonly used endpoints as crude indicators of hepatotoxicity in animal studies. MRLs based on the LOAELs for these endpoints include MRLs for acenaphthene, chloroform, di-*N*-octyl phthalate, diethyl phthalate, fluoranthene, fluorene, vinyl chloride, 1,1,2,2-tetrachloroethane, and 1,4-dichlorobenzene. MRLs based on the NOAELs for these endpoints include MRLs for hexachlorocyclohexane, hexachloroethane, dieldrin, 1,2-dichloroethane, 1,2,3-trichloropropane, and 1,4-dichlorobenzene. Histologically, these effects are confirmed as hypertrophy (an increase in size of individual cells without an increase in cell numbers) or hyperplasia (an increase in liver size as a result of an increase in cell numbers) (Evans and Lake, 1998). MRLs based on the LOAELs for these endpoints include MRLs for aldrin and 2,4,6-trinitro-toluene. MRLs based on the NOAELs for these endpoints include MRLs for chlordane, HMX, and DDT.

Clinical chemistry is an important tool for detecting hepatobiliary effects; and serum enzymes are the markers most often used to detect the injury. Increased levels of enzymes such as sorbitol dehydrogenase (SDH), ornithine carbamoyltransferase (OCT), and alanine transaminase (ALT) [previously known as serum glutamic pyruvic transaminase (SGPT)] are typical markers for injury to hepatocytes. Other enzymes such as aspartate transaminase (AST) [previously known as serum glutamic oxaloacetic transaminase (SGOT)] and lactate dehydrogenase (LDH) are also used, but they are not specific to hepatic injury and may be increased following injury to other organs (e.g., kidneys) and muscles. MRLs based on the LOAELs for these endpoints include MRLs for chloroform, chloromethane, xylene, 4,4′-methylene bis(2-chloroaniline), 4,4′-methylene-dianiline. MRLs based on the NOAELs for these endpoints include MRLs for bromoform, carbon tetrachloride, chloroform, and 1,1-dichloroethene. Biliary injury is most often detected by elevated levels of enzymes such as alkaline phosphatase (ALP), 5′-nucleotidase (5′-NT), and γ-glutamyl transpeptidase (γ-GT). Again, ALP is not specific just for the biliary injury and can be increased in other conditions (e.g., bone disease). MRLs based on the NOAELs for these endpoints include MRLs for carbon tetrachloride, endosulfan, and 1,2-dichloroethene. Other biochemical changes are indicative of changes in the liver function. Therefore, LOAELs for decreased blood glucose levels (indicative of hepatic necrosis), decreased blood urea nitrogen (BUN) levels (indicative of liver failure), and increased serum bilirubin (indicative of hepatitis, cirrhosis, etc.) were the bases for MRLs for kerosene, methyl-*t*-butyl ether, and 2,3,4,7,8-pentachlorodibenzofuran, respectively. A LOAEL in rats that showed a decreased hepatic uptake, metabolism, and biliary excretion of imipramine (i.e., hepatic function test) was the basis for an acute oral MRL for toxaphene.

Histological examination of hepatic tissue gives the most accurate picture of liver injury. Findings are usually described with respect to site (i.e., centrilobular, midzonal, and periportal), extent, and cytological changes. Many hepatotoxic chemicals induce a whole range of effects, depending on the dose. On one end of the range are mild effects such as hepatic vacuolization. MRLs based on the LOAELs for this endpoint include MRLs for bromoform, carbon tetrachloride, JP-4, JP-5, JP-8, methylene chloride, and 1,1,2,2-tetrachloroethane; MRLs based on the NOAELs for this endpoint include MRLs for bromoform, chloroform, and mirex.

MRLs based on the LOAELs for fatty degeneration or steatosis include MRLs for chlorodibromomethane, hydrazine, JP-4, JP-5, JP-8, and 1,2-dichloroethene. An MRL based on a NOAEL for steatosis was derived for carbon tetrachloride. Inflammation of the liver was also reported with exposure to some chemicals. MRLs based on the LOAELs for hepatitis include MRLs for chloroform, JP-7, and 1,2-dimethyl hydrazine. An MRL based on the NOAEL for hepatitis was derived for bromoform. The most severe cell injury results in cell death. According to the extent, massive necrosis and focal necrosis are recognized. Focal necrosis can be repaired by the liver repair mechanism. MRLs based on the LOAELs for focal cell necrosis (i.e., less serious effect) include MRLs for isophorone and 1,2-dichloropropane. An MRLs for mirex was based on the NOAELs for necrosis. Another serious effect is liver cirrhosis, defined as hepatic fibrosis and nodular regeneration and associated with chronic exposure to chemicals such as carbon tetrachloride and ethanol.

By definition, MRLs are based only on non-cancer effects (Chou et al., 1998). However, pre-cancer endpoints need further evaluation. It is recognized that hepatocellular tumors develop from foci of altered hepatocytes (Evans and Lake, 1998). The alteration is expressed phenotypically as foci with increased eosinophilia or basophilia, or they may appear vacuolated (high glycogen levels). They may express fetal enzymes such as γ-GT or the placental form of GSH *S*-transferase, and changes in phase I enzymes (decreases) and phase II enzymes (increases) that are used for metabolism of xenobiotics. It is not clear if all the foci can develop into tumors; if some of them are already small in situ carcinomas or if they need further genetic damage to develop malignancy (Evans and Lake, 1998). A NOAEL for dose-related, statistical significant liver cellular

Table 2
MRLs based on hepatic effects

Substance	Route	Duration	MRL value	UF	End point	Reference
Acenaphthene	Oral	Intermediate	0.6 mg/kg/day	300	LOAEL in mice; increased liver weight	EPA (1989c)
Aldrin	Oral	Chronic	0.00003 mg/kg/day	1000	LOAEL in rats; enlarged hepatocytes, eosinophilia, possible vacuolization	Fitzhugh et al. (1964)
Anthracene	Oral	Intermediate	10 mg/kg/day	100	NOAEL in mice; no effects in the study	EPA (1989d)
Bromodichloro-methane	Oral	Acute	0.04 mg/kg/day	1000	LOAEL in mice; minimal histological changes	Condie et al. (1983)
Bromoform	Oral	Acute	0.7 mg/kg/day	100	NOAEL in mice; increased SGPT and focal inflammation at higher doses	Condie et al. (1983)
Bromoform	Oral	Intermediate	0.2 mg/kg/day	100	NOAEL in rats; hepatic vacuolization at higher doses	NTP (1989)
Bromoform	Oral	Chronic	0.2 mg/kg/day	300	LOAEL in rats; hepatic vacuolization	NTP (1989)
Carbon disulfide	Oral	Acute	0.01 mg/kg/day	300	LOAEL in rats; dose-dependent decreases in hepatic microsomal drug-metabolizing enzymes	Masuda et al. (1986)
Carbon tetrachloride	Inhalation	Intermediate	0.03 ppm	30	NOAEL in rats; fatty degeneration, cirrhosis at higher doses	Adams et al. (1952)
Carbon tetrachloride	Inhalation	Chronic	0.03 ppm	30	NOAEL in rats; increased total bilirubin, SGOT, SGPT; increased fatty changes, granulation, foci in the liver, deposition of ceroid, and serious effects such as fibrosis and cirrhosis at higher doses.	Japan Bioassay Research Center (1998)
Carbon tetrachloride	Oral	Acute	0.05 mg/kg/day	90	LOAEL in rats; minimal vacuolar degeneration at the dose, minimal hepatocellular necrosis at the higher dose	Smialowicz et al. (1991)
Carbon tetrachloride	Oral	Intermediate	0.02 mg/kg/day	30	NOAEL in rats; mild centrilobular vacuolization and increased serum sorbitol dehydrogenase activity at higher dose; cirrhosis and increased serum enzyme (OCT, ALT, sorbitol dehydrogenase) activities at the highest dose	Bruckner et al. (1986)
Chlordane	Inhalation	Intermediate	0.0002 mg/m^3	100	NOAEL in rats; hepatocellular hypertrophy at higher dose	Khasawinah et al. (1989a); Velsicol Chemical Co (1984)
Chlordane	Inhalation	Chronic	0.00002 mg/m^3	1000	extrapolated from the intermediate duration MRL by applying a UF of 10	Khasawinah et al. (1989a); Velsicol Chemical Co (1984)
Chlordane	Oral	Intermediate	0.0006 mg/kg/day	100	NOAEL in rats; hepatocellular hypertrophy at higher dose	Khasawinah and Grutsch (1989b); Velsicol Chemical Co (1983)
Chlordane	Oral	Chronic	0.0006 mg/kg/day	100	NOAEL in rats; hepatocellular hypertrophy at higher dose	Khasawinah and Grutsch (1989b); Velsicol Chemical Co (1983)
Chlorobenzene	Oral	Intermediate	0.4 mg/kg/day	100	NOAEL in rats; increased enzymes and necrosis at higher dose	NTP (1985a)
Chlorodibromo-methane	Oral	Chronic	0.09 mg/kg/day	300	LOAEL in rats; fatty and "ground glass" cytoplasmic changes	NTP (1985b)
Chloroform	Inhalation	Acute	0.1 ppm	30	NOAEL in mice; centrilobular vacuolization at higher dose	Larson et al. (1994a)
Chloroform	Inhalation	Intermediate	0.05 ppm	100	LOAEL in humans; toxic hepatitis	Phoon et al. (1983)
Chloroform	Inhalation	Chronic	0.02 ppm	100	LOAEL in humans; hepatomegaly, toxic hepatitis, hepatosteatosis	Bornski et al. (1967)
Chloroform	Oral	Acute	0.3 mg/kg/day	100	NOAEL in mice; cytoplasmic eosiniphilia in centrilobular hepatocytes	Larson et al. (1994b)

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for acenaphthene, fluoranthene, and 1,1,2-trichloroethane. These MRLs correspond with the respective RfDs when adjusted for duration of exposure (i.e., divided by 10). MRLs for carbon tetrachloride, chlorobenzene, styrene, 1,4-dichlrobenzene, and PBDEs differ very slightly. The differences are due to the studies and/or endpoints, and uncertainty factors used for the derivation. The only noteworthy difference was between the chronic oral MRL of 2×10^{-5} mg/kg/day for vinyl chloride and a corresponding RfD of 3×10^{-3} mg/kg/day. The RfD for vinyl chloride is based on liver cell polymorphism in rats reported in the Til et al. (1983, 1991) studies. EPA used a PBPK model to calculate a human equivalent NOAEL of 0.09 mg/kg/day. An UF of 30 was applied; 3 for animal to human extrapolation and 10 for human variability. A LOAEL of 0.018 mg/kg/day for basophilic foci in rats in the Til et al. (1983, 1991) studies was used to derive a chronic oral MRL for vinyl chloride. A UF of 1000 was applied; 10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability. As mentioned previously, a recent re-evaluation of the chronic oral MRL for vinyl chloride concluded that liver basophilic foci are generally considered preneoplastic, and that it would be more appropriate to base the vinyl chloride chronic oral MRL on the NOAEL for liver cell polymorphism, which is considered non-preneoplastic. The proposed revised chronic oral MRL for vinyl chloride is 3×10^{-3} mg/kg/day (ATSDR, 2004). This MRL is currently released for public comments in the draft toxicological profile.

4. Conclusion

As demonstrated here, the hepatobiliary endpoints are important in the derivation of MRLs. Hepatoxicity is seen with many chemicals, and for some the liver is a primary target of their toxicity. Proper classification of effects is crucial for the process of MRL derivation. This requires clear understanding of pathology and pathophysiology. Consistency in classification of similar endpoints across the different studies and chemicals has great significance in MRL derivation. That is why ATSDR has a guidance document to help with the classification and a workgroup of scientists discussing the proper classification of health effects on a case-by-case basis. In reviewing the past decisions regarding classification of hepatic effects, this article strives to bring this issue in focus. ATSDR uses up-to-date methodology for the MRL derivation where biomedical judgment plays an important role (e.g., application of UFs). It is helpful to realize that ATSDR's results are comparable with other agencies that derive health based guidance values for hazardous chemicals.

ATSDR has joined the search for alternative methodologies to refine the chemical health risk assessment. New approaches to risk assessment, e.g., benchmark dose calculations, physiologically based pharmacokinetic (PBPK) modeling, and quantitative structure-activity relationships (QSARs) are being explored. Better understanding of toxicokinetics and toxicodynamics of environmental chemicals and their interactions with the living organisms on molecular levels will enable the health assessors a better evaluation of the health risks. This understanding will also improve the risk assessment of joint toxic action of environmental chemicals in mixtures, and in combinations with pharmaceuticals, viral agents, and other hepatotoxicants.

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Chloroform	Oral	Intermediate	0.1 mg/kg/day	100	NOAEL in dogs; increased SGPT at higher dose	Heywood et al. (1979)
Chloroform	Oral	Chronic	0.01 mg/kg/day	1000	LOAEL in dogs; increased SGPT	Heywood et al. (1979)
Chloromethane	Inhalation	Intermediate	0.2 ppm	300	LOAEL in mice; increased ALT, histopathological changes at higher doses	CIIT (1981).
Cyclotetra-methylene tetra-nitramine (HMX)	Oral	Intermediate	0.05 mg/kg/day	1000	NOAEL in rats; enlarged centrilobular cells with pale nuclei and dark cytoplasm at higher dose	Army (1985)
DDT, *p,p'*-	Oral	Intermediate	0.0005 mg/kg/day	100	NOAEL in rats; hepatocytomegaly in central lobules, increased cytoplasmic oxyphilia, peripherally basophilic cytoplasmic granules.	Fitzhugh and Nelson (1947); Laug et al. (1950)
Di-*N*-octyl phthalate	Oral	Acute	3 mg/kg/day	300	LOAEL in rats; increased relative liver weight, reduced 7-ethoxycoumarin-*O*-deethylase activity	Lake et al. (1986)
Di-*N*-octyl phthalate	Oral	Intermediate	0.4 mg/kg/day	100	NOAEL in rats; increased ethoxy-resorufin-*O*-deethylase activity, mild-to-moderate increases in perivenous cytoplasmic vacuolation at higher dose	Peon et al. (1995)
Dieldrin	Oral	Chronic	0.00005 mg/kg/day	100	NOAEL in rats; liver weight and histopathological changes (not specified) at higher dose	Walker et al. (1969)
Diethyl phthalate	Oral	Intermediate	6 mg/kg/day	300	LOAEL in rats; peroxisomal proliferation, slightly elevated liver weight, enzyme activities	Moody and Reddy (1978)
Endosulfan	Oral	Chronic	0.002 mg/kg/day	100	NOAEL in dogs; increased alkaline phosphatase at higher dose	Hoechst (1989)
Fluoranthene	Oral	Intermediate	0.4 mg/kg/day	300	LOAEL in mice; increased liver weight	EPA (1988)
Fluorene	Oral	Intermediate	0.4 mg/kg/day	300	LOAEL in mice; increased liver weight	EPA (1989e)
Hexachloro-cyclohexane, α	Oral	Chronic	0.008 mg/kg/day	100	NOAEL in rats; dose-related increase in liver weight and histological changes at higher doses	Fitzhugh et al. (1950)
Hexachloro-cyclohexane, β	Oral	Intermediate	0.0006 mg/kg/day	300	LOAEL in rats; hyalinization of centrilobular cells	Van Velsen et al. (1986)
Hexachloro-ethane	Oral	Acute	1 mg/kg/day	100	NOAEL in rabbits; liver degeneration and necrosis at higher doses	Weeks et al. (1979)
Hexachloro-ethane	Oral	Intermediate	0.01 mg/kg/day	100	NOAEL in rats; increased relative liver weights, welling in hepatocytes at higher doses	Gorzinski et al. (1985)
Hydrazine	Inhalation	Intermediate	0.004 ppm	300	LOAEL in mice; moderate to severe fatty changes	Haun and Kinkead (1973)
Isophorone	Oral	Chronic	0.2 mg/kg/day	1000	LOAEL in mice; necrosis	NTP (1986a)
JP-4	Inhalation	Intermediate	9 mg/m^3	300	LOAEL in mice; vacuoles, fatty changes	Air Force (1984)
JP-5/JP-8	Inhalation	Intermediate	3 mg/m^3	300	LOAEL in mice; vacuoles, fatty changes	Gaworski et al. (1984)
JP-7	Inhalation	chronic	0.3 mg/m^3	300	LOAEL in rats; hepatic inflammation	Air Force (1991)
Kerosene	Inhalation	Intermediate	0.01 mg/m^3	1000	LOAEL in rats; decreased blood glucose levels	Starek and Vojtisek (1986)
Methyl-*t*-butyl ether	Oral	Intermediate	0.3 mg/kg/day	300	LOAEL in rats; decreased BUN levels	Robinson et al. (1990)
Methylene chloride	Inhalation	Intermediate	0.3 ppm	90	LOAEL in rats; vacuolization	Haun et al. (1972)
Methylene chloride	Inhalation	Chronic	0.3 ppm	30	NOAEL in rats; fatty changes at higher doses	Nitschke et al. (1998)
Methylene chloride	Oral	Chronic	0.06 mg/kg/day	100	NOAEL in rats; hepatic foci at higher doses	Serota et al. (1986)
Mirex	Oral	Chronic	0.0008 mg/kg/day	100	NOAEL in rats; cytoplasmic vacuoles, necrosis at higher doses	NTP (1990)
N-nitrosodi-*N*-propylamine	Oral	Acute	0.095 mg/kg/day	100	NOAEL in mice;	Tyndall et al. (1978)
Styrene	Oral	Intermediate	0.2 mg/kg/day	1000	LOAEL in rats;	Srivastava et al. (1982)
Toxaphene	Oral	Acute	0.005 mg/kg/day	1000	LOAEL in rats; decreased hepatic uptake, metabolism, and biliary excretion of imipramine	Mehendale (1978)
Toxaphene	Oral	Intermediate	0.001 mg/kg/day	300	NOAEL in rats; peripheralized basophilia and anisokaryosis at higher doses	Chu et al. (1986)

(*continued on next page*)

Table 2 (*continued*)

Substance	Route	Duration	MRL value	UF	End point	Reference
Vinyl chloride	Inhalation	Intermediate	0.03 ppm	300	LOAEL in rats; increased liver weight	Bi et al. (1985)
Vinyl chloride	Oral	Chronic	0.00002 mg/kg/day	1000	LOAEL in rats; increase in basophilic foci	Til et al. (1983, 1991)
Xylene, *m*-	Oral	Intermediate	0.6 mg/kg/day	1000	LOAEL in rats; increased plasma ALT, membrane damage	Elovaara et al. (1989)
1,1-Dichloroethene	Inhalation	Intermediate	0.02 ppm	100	NOAEL in guinea pigs; increased SGPT and alkaline phosphatase activity and decreased lipid content at higher dose	Prendergast et al. (1967)
1,1-Dichloroethene	Oral	Chronic	0.009 mg/kg/day	1000	LOAEL in rats; hepacellular changes	Quast et al. (1983)
1,1-Dimethyl-hydrazine	Inhalation	Intermediate	0.0002 ppm	300	LOAEL in mice; hyaline degeneration of the gallbladder	Haun et al. (1984)
1,1,2-Trichloroethane	Oral	Intermediate	0.04 mg/kg/day	100	NOAEL in mice; decreased glutathione at higher dose	White et al. (1985)
1,1,2,2-Tetra-chloroethane	Inhalation	Intermediate	0.4 ppm	300	LOAEL in rats; increased liver weights, granulation and vacuolization	Truffert et al. (1977)
1,2-Dichloroethane	Inhalation	Chronic	0.6 ppm	90	NOAEL in rats; intrahepatic bile duct cholangiomas	Cheever et al. (1990)
1,2-Dichloro-propane	Oral	Chronic	0.09 mg/kg/day	1000	LOAEL in mice; necrosis	NTP (1986b)
1,2-Dichloro-ethene, *trans*	Inhalation	Acute	0.2 ppm	1000	LOAEL in rats; slight to severe fatty degeneration of the hepatic lobules and Kupffer cells	Freundt et al. (1977)
1,2-Dichloro-ethene, *trans*	Inhalation	Intermediate	0.2 ppm	1000	LOAEL in rats; slight to severe fatty degeneration of the hepatic lobules and Kupffer cells	Freundt et al. (1977)
1,2-Dichloro-ethene, *trans*	Oral	Intermediate	0.2 mg/kg/day	100	NOAEL in mice; increased relative liver weights; increased serum alkaline phosphatase	Barnes et al. (1985)
1,2-Dimethyl-hydrazine	Oral	Intermediate	0.0008 mg/kg/day	1000	LOAEL in mice; mild hepatitis	Visek et al. (1991)
1,2,3-Trichloropropane	Oral	Intermediate	0.06 mg/kg/day	100	NOAEL in rats; increased liver weight, decreased serum cholinesterase at higher doses	NTP (1983)
1,4-Dichlorobenzene	Inhalation	Intermediate	0.2 ppm	100	NOAEL in rats; cloudy swelling or granular degeneration at higher doses	Hollingsworth et al. (1956)
1,4-Dichlorobenzene	Inhalation	Chronic	0.1 ppm	100	NOAEL in rats; increased liver weight at higher doses	Riley et al. (1980)
1,4-Dichlorobenzene	Oral	Intermediate	0.4 mg/kg/day	300	LOAEL in rats; increased liver weight	Hollingsworth et al. (1956)
2-Butoxyethanol	Oral	Intermediate	0.07 mg/kg/day	1000	LOAEL in rats; hepatocellular alteration,	NTP (1993)
2,3,4,7,8-Penta-chlorodibenzo-furan	Oral	Intermediate	0.00003 µg/kg/day	3000	LOAEL in rats; increased serum bilirubin, decreased serum triglycerides	Pluess et al. (1988); Poiger et al. (1989)
2,4,6-Trinitro-toluene	Oral	Intermediate	0.0005 mg/kg/day	1000	LOAEL in dogs; cloudy swelling, hepatocytomegaly	Levine et al. (1990)
4-Chlorophenol	Oral	Acute	0.01 mg/kg/day	100	NOAEL in rats; foamy cytoplasm, clustering of mitochondria and endoplasmic reticulum at higher dose	Phornchirasilp et al. (1989)
4,4′-Methylenebis (2-chloroaniline)	Oral	Chronic	0.003 mg/kg/day	3000	LOAEL in dogs; increased SGPT, nodular hyperplasia	Stula et al. (1977)
4,4′-Methylene-dianiline	Oral	Acute	0.2 mg/kg/day	300	LOAEL in rats; increased serum ALT and γ-glutamyl transferase	Bailie et al. (1993)
4,4′-Methylene-dianiline	Oral	Intermediate	0.08 mg/kg/day	100	NOAEL in rats; unspecified histological lesions at higher dose	Pludro et al. (1969)

ALT, alanine transaminase; BUN, blood urea nitrogen; LOAEL, lowest-observed-adverse-effect level; MRL, minimal risk level; NOAEL, no-observed-adverse-effect level; OCT, ornithine carbamoyltransferase, SGOT, serum glutamic oxaloacetic transaminase (i.e., aspartate transaminase); and SGPT, serum glutamic pyruvic transaminase (i.e., alanine transaminase, ALT).

changes (hepatic foci, areas of cellular alterations) in rats was used to derive a chronic oral MRL for methylene chloride. A LOAEL for basophilic foci in rats was used to derive a chronic oral MRL for vinyl chloride. A recent re-evaluation of the chronic oral MRL for vinyl chloride concluded that liver basophilic foci are generally considered preneoplastic, and that it would be more appropriate to base the vinyl chloride chronic oral MRL on the NOAEL for liver cell polymorphism, which is considered non-preneoplastic. In contrast, ATSDR did not derive an oral chronic MRL for decabromodiphenyl ether based on a LOAEL for thrombosis because the LOAEL for thrombosis was also associated with preneoplastic nodules in the liver.

3.4. Use of uncertainty factors

Uncertainty factors (UFs) are used in the process of MRL derivation to account for uncertainties associated with extrapolation from a LOAEL to a NOAEL and from animal to human data, and with adjustments for intraspecies variability. UFs with default values of 10 are usually used for all three categories of extrapolation. However, in some cases, the uncertainty is decreased, resulting in utilization of a lower UF (Pohl and Abadin, 1995). Following are examples of the application of UFs other than 10 in the derivation of MRLs based on hepatic effects.

Just a few MRLs were based on the endpoints considered the borderline between adaptive physiology and toxicity (see the section on ATSDR's guidance document). An oral acute MRL for carbon disulfide was based on a LOAEL in rats (ATSDR, 1996c). Dose-dependent decreases in hepatic microsomal drug-metabolizing enzymes were detected. Similarly, an intermediate-duration oral MRL for diethyl phthalate was based on a LOAEL in rats that showed peroxisomal proliferation, slightly elevated liver weight, and enzyme activities (ATSDR, 1995). The LOAELs were considered minimal, and an UF of 3 was used for LOAEL to NOAEL extrapolation in the derivation of both MRLs. In contrast, the acute oral MRL for 4-chlorophenol was based on a NOAEL for hepatic effects in rats (ATSDR, 1999). At the LOAEL level, foamy cytoplasm, clustering of mitochondria and endoplasmic reticulum were reported. These electron microscopic changes could be considered borderline; however, further evaluation that considered progression of changes with increasing dose in the database caused the endpoints to be classified as LOAEL rather than NOAEL. Other MRLs based on "minimal" LOAELs that warranted the use of UFs of 3 include MRLs for bromodichloromethane, carbon tetrachloride, chlorodibromomethane, chloromethane, di-*N*-octyl phthalate, β-hexachlorocyclohexane, methyl-*t*-butyl ether, methylene chloride, vinyl chloride, 1,1,2,2-tetra-chloroethane, 1,4-dichlorobenzene, and 4,4′-methylene-dianiline. For respective endpoints that were considered as "minimal" see descriptions in Table 2. A default UF of 10 was used for most of the animal to human extrapolation of study results. An UF of 3 was used for inhalation exposure route in cases of MRLs derived for carbon tetrachloride, chloroform, hydrazine, JP-4, JP-5, JP-7, JP-8, methylene chloride, 1,1-dimethylhydrazine, and 1,2-dichloroethane. The change was mostly justified by calculating the NOAEL human equivalency concentration (HEC) (EPA, 1994). Similarly, an UF of 3 for interspecies extrapolation was used for acute inhalation exposure scenarios in case of chloroform because dosimetry adjustment was made, and an UF of 3 was used to account for toxicodynamic differences.

In some instances, modifying factors (MFs) are used to account for additional uncertainty associated with the guidance value. For example, an MF of 3 was applied for insufficient diagnostic data to determine the seriousness of hepatotoxic effects in a study in exposed workers (Phoon et al., 1983) used for deriving the intermediate inhalation MRL for chloroform. Similarly, an insufficient database was the reason a MF of 3 was used for the derivation of a chronic inhalation MRL for 1,2-dichloroethane.

3.5. Comparison with other guidance values

Other agencies also derive health-based guidance values. For example, the U.S. Environmental Protection Agency (EPA) derives reference concentrations (RfCs) for chronic duration inhalation exposures and reference doses (RfDs) for chronic duration oral exposures. Current RfCs and RfDs are posted on the EPA's web site (www.epa.gov/iris/). In July 2004, 69 RfCs were posted, including 8 based on hepatic endpoints. From the 358 RfDs posted, 94 were based on hepatic endpoints. Many of the chemicals with RfCs/RfDs derived from hepatic effects were not evaluated by ATSDR as ATSDR evaluates only chemicals on its priority list (Roney et al., 1998). In fact, only four chemicals had both the RfC and the inhalation MRL. These included chlordane with a chronic MRL of 2×10^{-5} mg/m^3 and an RfC of 7×10^{-4} mg/m^3, vinyl chloride with an intermediate-duration MRL of 3×10^{-2} ppm (8×10^{-2} mg/m^3) and an RfC of 1×10^{-1} mg/m^3, 1,1-dichloroethene with an intermediate-duration MRL of 2×10^{-2} ppm (8×10^{-2} mg/m^3) and an RfC of 2×10^{-1} mg/m^3, and 1,4-dichlorobenzene with a chronic MRL of 1×10^{-1} ppm (6×10^{-1} mg/m^3) and an RfC of 8×10^{-1} mg/m^3.

For oral exposure, only 14 chemicals had both the RfD and the MRL derived. Chronic duration MRLs were equal in value to RfDs in the case of aldrin, chloroform, DDT, and dieldrin. ATSDR did not derive chronic MRLs but has intermediate duration MRLs