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Evaluating toxicologic end points to derive minimal risk levels for hazardous substances

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Abstract

The Agency for Toxic Substances and Disease Registry (ATSDR) uses chemical-specific minimal risk levels (MRLs) to assist in evaluating public health risks associated with exposure to hazardous substances. MRLs are estimates of daily human exposure to a chemical that are likely to be without an appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs serve as screening levels for health assessors to identify contaminants and potential health effects that may be of concern for populations living near hazardous waste sites and chemical releases. MRLs are derived from toxicologic data compiled from a comprehensive literature search and are presented in ATSDR's toxicological profile for that substance. They are based on the most sensitive substance-induced end point considered to be of relevance to humans. MRLs for each substance 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. In this paper, we present an overview of the approach used for evaluating the toxicologic end points in deriving the MRLs. Examples are given to illustrate the agency's efforts to achieve increased understanding, reduced uncertainty and improved public health guidance.

Key words: Minimal risk levels – hazardous substances – toxicologic end point – noncancer adverse health effects

Introduction

The mission of the Agency for Toxic Substances and Disease Registry (ATSDR) is to prevent exposure and adverse human health effects and diminished quality of life associated with exposure to hazardous substances from waste sites, unplanned releases, and other sources of pollution present in the environment. The agency's major activities include public health assessments, health consultations, emergency response, health studies, disease registries, and toxicological profiles. Toxicological profiles are prepared for substances included on the Priority List of Hazardous Substances compiled by ATSDR and the U.S. Environmental Protection Agency (EPA). They include a comprehensive examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations of the hazardous substances. The toxicological profiles also identify significant data gaps associated with

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knowledge of the health effects of these chemicals. During the development of toxicological profiles, minimal risk levels (MRLs) are derived when ATSDR determines that reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration and route of exposure to the substance. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. Importantly, MRLs are not intended to define clean-up or action levels for ATSDR or other agencies.

Methods

MRLs are derived using the no-observed-adverse-effect level/uncertainty factor (NOAEL/UF) approach. They are set below levels that, based on current information, might cause adverse health effects in the people most sensitive to such substance-induced effects. MRLs 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. Inhalation MRLs are exposure concentrations expressed in units of parts per million (ppm) for gases and volatiles, or milligrams per cubic meter (mg/m^3) for particles. Oral MRLs are expressed as daily human doses in units of milligrams per kilogram per day (mg/kg/day).

MRLs are generally based on the most sensitive substance-induced end point considered to be of relevance to humans. ATSDR does not use serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur. Proposed MRLs undergo a rigorous review process. They are reviewed by the Health Effects/MRL Workgroup (WG) within the Division of Toxicology; an expert panel of external peer reviewers; and the agency wide MRL WG, with participation from other federal agencies, including EPA; and they are submitted for public comment through the toxicological profile public comment period. Each MRL is subject to change as new information becomes available concomitant with updating the toxicological profile for the substance. As of April 2001, 286 inhalation and oral MRLs had been derived for 138 profiled substances. A list of current MRLs can be found at this web address: http://www.atsdr.cdc.gov/mrls.html.

MRLs are intended to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain some degree of uncertainty because of the lack of precise toxicologic information on the people who might be most sensitive (e.g., infants, elderly, and nutritionally or immunologically compromised) to effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address these uncertainties consistent with the public health principle of prevention. In the process of characterizing health effects, responses associated with varying levels of significant exposure are assessed for each route (inhalation, oral, dermal), and each duration (acute, intermediate, chronic). The biologic significance of these effects is communicated through classification into the three categories: NOAEL (no-observed-adverse-effect level) – no morphologic or functional alterations are observed, or the effects that are seen are considered to be innocuous and insignificant; "less serious" LOAEL (lowest-observed-adverse-effect level) – these are adverse effects that are not expected to cause significant dysfunction; and "serious" LOAEL – these are adverse effects that may evoke failure in a biological system and can lead to morbidity or mortality. Distinguishing between these categories often is not a straight-forward process, and thus, requires a considerable amount of scientific judgment and expertise. The accurate designation of these categories represents pivotal decision points in the development of MRLs. NOAELs and "less serious" LOAELs may be used to derive MRLs, but it is the practice of ATSDR not to derive MRLs from "serious" LOAELs (Chou et al., 1998). Human data are preferred; however, MRLs often are based on animal studies when relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive than animals to the effects of hazardous substances and that certain persons may be particularly sensitive.

Results and discussion

Accurate characterization of health effects associated with exposure to hazardous substances is a key element in the process of risk assessment. Health effects may broadly be divided into two categories: quantal and continuous effects. In characterizing these health effects, the following questions must be addressed: 1) Are these effects adverse? 2) What is the biologic significance of these effects? It must first be determined whether an effect is adverse before the issue of biologic significance can be addressed. ATSDR defines an adverse health effect as: "A harmful or potentially harmful change in the physiologic function, physiologic state, or organ structure that may be manifested in pathophysiologic

changes in target organs, psychiatric effects, or overt disease. Additionally, any effect that enhances the susceptibility of an organism to the deleterious effects of other chemical, physical, microbiological, or environmental influences should be considered adverse." To achieve standards in the risk assessment process that promote prevention we often consider health effects that are subtle or not straight forward. One recurring issue is the designation of a given effect as being adverse. This designation usually poses no problem for quantal effects; these effects are finite, yes/no, and they are either present or they are not. Examples are liver necrosis, convulsions, and death. The biologic implications of quantal effects typically are understood, and their presence is indicative of adversity. However, the task of designating adversity becomes increasingly difficult as increasingly subtle effects are identified by more sophisticated ultrastructural and biochemical techniques. But, it is important that we are able to detect and interpret subtle chemically induced effects that may be preclinical indicators of disease. Continuous effects are those whose parameters extend over a broad spectrum; examples are heart rate, blood pressure, and enzyme levels. Because of the ranging nature of these effects, interpretation and designation of adversity are often difficult.

Some effects associated with exposure to hazardous substances are not necessarily considered to be adverse and may fall into one of several possible categories, including adaptive or compensatory responses, as well as those that are of uncertain significance. Adaptive effects are those that enhance an organism's performance as a whole and/or its ability to withstand a challenge, e.g., induction of the hepatic mixed-function oxidase enzyme system. Compensatory effects are those that maintain overall function without physiologic enhancement or significant cost, e.g., compensatory hypertrophy of the kidney. Examples of effects that fall into the category of uncertain significance include subtle biochemical changes such as decrease in serum alanine aminotransferase (ALT, formally known as SGPT).

Some of the most challenging problems in the risk assessment process involve the interpretation of adaptive versus toxic changes in organs in response to chemical exposure. Adaptive responses within organisms may occur at subcellular (biochemical) and cellular (structural) levels. Examples of adaptive biochemical responses are induction of the cytochrome P-450 mixed-function oxidase system in the liver and other organs, as well as glutathione depletion/synthesis in the liver. Examples of structural adaptive responses within tissues include atrophy, hypertrophy, hyperplasia, and metaplasia. Adaptive changes are generally considered to be effects that enhance an organism's performance as a whole and/or its ability to withstand a challenge (i.e., homeostatic mechanisms). However, the boundary between adaptive responses and toxic responses is not always well delineated. Adaptive responses may result in changes that are beneficial or potentially detrimental to the host. Hypertrophy of skeletal muscle in response to an increased work load is an example of an adaptive change that would be expected to prove beneficial to the host. However, hypertrophy of the left heart ventricle due to arterial hypertension, even though it allows the heart to function against an increased work load, will eventually result in decreased cardiac ability to compensate against additional stress. Metaplasia may be considered an adaptive response, but the predictive value for lesion progression and secondary effects on other organs is not always clear. If metaplasia occurs in the pancreas, for example, squamous metaplasia of pancreatic ducts associated with exposure to a test substance, it does not interfere with pancreatic function. However, if squamous metaplasia occurs in the tracheal epithelium, it may interfere with normal respiratory defense function (mucociliary escalator).

A common biochemical adaptive response is induction of the cytochrome P-450 mixed-function oxidase system (Loomis, 1978; Kyle and Farber, 1991). Many chemicals (such as aldrin, chloroform, and DDT) can induce the cytochrome P-450 system in the liver and other organs. This induction leads to a stimulation of protein synthesis and a proliferation of smooth endoplasmic reticulum. Depending on the inducing agent, one or more isoenzymes of P-450 may be induced, each of which has different affinities for a variety of other substances. The P-450 system plays a critical role in the metabolism of both endogenous and exogenous compounds. In some cases, as with carbon tetrachloride, for example, this can be viewed as a toxification reaction (i.e., the parent compound is metabolized to a more toxic species). In other cases, as with ethanol for example, the cytochrome P-450 system detoxifies the parent compound resulting in less reactive metabolites. However, once induction of the mixed-function oxidase system has occurred (no matter what chemical initiated it), this adaptive response has significant implications for future chemical exposures. This adaptive modification may potentiate or inhibit toxic responses to subsequent chemical exposures. The enhancement or inhibition of a compound's metabolism can lead to toxicologic interactions that may be important in site-specific

assessments (Mumtaz et al., 1994). From ATSDR's stand point, this is an especially important concept to consider, since in addition to the specific chemical causing adaptive changes there is potential concurrent exposure to other substances at hazardous waste sites.

Within the framework of human health risk assessment, hepatic cytochrome P-450 induction should be classified as an adverse effect ("less serious" LOAEL) (ATSDR, 1995). This induction alters the normal functioning of the organ (i.e., the organ is able to metabolize compounds at a greater rate). Even though this effect is beneficial for some compounds, it will be detrimental for others. Additionally, the designation of hepatic P-450 induction as adverse reflects the judgment that involuntary environmental exposure to chemicals should not be at levels that alter the normal state of the organism. ATSDR used the above guidance for assessing hepatic adaptive responses, to derive a chronic oral MRL for aldrin. On the basis of a study in rats by Fitzhugh et al., 1964, an MRL of 0.03 μg/kg/day was derived for chronic-duration oral exposure (ATSDR, 2000a). This MRL was calculated by dividing the LOAEL of 0.025 mg/kg/day for hepatic effects by an uncertainty factor (UF) of 1000 (10 for extrapolating from a LOAEL to a NOAEL, 10 for extrapolating from animals to humans, and 10 for human variability). The hepatic effects that this MRL is based on included increased relative liver weight, and histopathologic alterations characterized by enlarged centrilobular hepatocytes with increased cytoplasmic eosinophilia and peripheral migration of basophilic granules.

Every effort is made to ensure that scientific knowledge is incorporated in evaluating data for MRL derivations. For example, chronic progressive nephropathy (CPN) in aging male rats is not considered a viable end point for MRL derivation because CPN is an age-related disorder of rats that is more severe in males than in females. Health effects not relevant to humans are not considered. For example, α-2μ-globulin nephropathy in male rats is not considered a relevant toxicological end point for humans because α-2μ-globulin is synthesized only in male rats, not in humans. In 1989, an intermediate oral MRL for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was derived based on a LOAEL of 0.001 μg/kg/day for reproductive effects (dilated pelvises and changes in gestational index) in rats (Nisbet and Paxton, 1982). A UF of 1000 was used to derive the MRL (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). The intermediate-duration exposure MRL was adopted for chronic exposure. No additional UF was used for extrapolation across durations. In 1998 when the toxicological profile for chlorinated dibenzo-p-dioxins was updated, a chronic oral MRL for TCDD was derived based on a LOAEL of 0.12 ng/kg/day for neurobehavioral effects in offspring of monkeys exposed to dietary TCDD (Schantz et al., 1992). In tests of cognitive function, object learning was significantly impaired, but no effect on spatial learning was observed. No significant alterations in reflex development, visual exploration, locomotor activity, or fine motor control were found. This LOAEL was classified as minimal; therefore, an UF of three instead of 10 was used. As the neurobehavioral effects in monkeys could also be expected in humans, a UF of 3 instead of 10 was used for extrapolation from monkeys to humans. A UF of 10 was used for human variability. Thus, the chronic oral MRL for TCDD of 0.001 ng/kg/day has not been changed since 1989. However, the UF associated with the TCDD chronic oral MRL has been reduced from 1,000 to 90 (ATSDR, 1989, 1998).

In addition, when adequate information is available, physiologically based pharmacokinetic (PBPK) modeling and benchmark dose (BMD) modeling have also been used as an adjunct to the NOAEL/UF approach in deriving MRLs. For example, the intermediate inhalation MRL for hexavalent chromium was derived using the BMD approach (ATSDR, 2000b), and the acute oral MRL for methylene chloride was derived using the PBPK modeling approach (ATSDR, 2000c). In conclusion, ATSDR is committed to continuing evaluation to achieve increased understanding, reduced uncertainty, and improved public health guidance.

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