HEALTH EFFECTS CLASSIFICATION AND ITS ROLE IN THE DERIVATION OF MINIMAL RISK LEVELS: NEUROLOGICAL EFFECTS

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The Agency for Toxic Substances and Disease Registry (ATSDR) uses substance-specific minimal risk levels (MRLs) to assist in evaluating public health risks associated with exposure to hazardous substances. By definition, "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 population living near hazardous waste sites and chemical releases. 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. The MRLs are derived from data compiled from a current comprehensive literature search and are presented in ATSDR's toxicological profile for that substance. In this paper we outline ATSDR's guidance for evaluating the neurological end point as discussed in the agency's toxicological profiles. Ranking neurological effects into less serious and serious categories and applying this procedure to the derivation of health guidance values or MRLs are also described. Specific examples of ATSDR MRLs based on neurological effects are presented.

INTRODUCTION

To determine the levels of significant human exposure to a given chemical associated with health effects, the Agency for Toxic Substances and Disease Registry (ATSDR) examines and interprets available toxicological and epidemiological data. The reported health effects are categorized according to severity: the no-observed-adverse-effect level (NOAEL), the less serious lowest-observed-adverse-effect level (LOAEL), and the serious LOAEL. In its Guidance for Developing Toxicological Profiles, ATSDR defines an adverse effect as "any effect that enhances the

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2. Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; LOAEL, lowest-observed-adverse-effect level; MF, modifying factor; MRLs, minimal risk levels; NOAEL, no-observed-adverse-effect-level; UF, uncertainty factor.

3. Key words: health guidance values, neurological effects, non-cancer risk assessment.

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susceptibility of an organism to the deleterious effects of other chemical, physical, microbiological, or environmental influences" (ATSDR, 1994). A dose that evokes failure in a biological system and can lead to morbidity or mortality is referred to as a serious LOAEL. After having compiled and evaluated the current database of toxicological and epidemiological studies, ATSDR derives minimal risk levels (MRLs) for the profiled substances. An MRL is an estimate of the daily human exposure to a chemical that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are derived using the NOAEL/ uncertainty factor approach. Though there are inherent uncertainties with this method, these chemical-specific estimates are intended to 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. They are not intended to define clean-up or action levels.

METHODS

Derivation of Minimal Risk Levels

MRLs are derived using the NOAEL/uncertainty factor approach and are based on the highest NOAEL or lowest LOAEL reported in the substance-specific database. 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. Neither cancer nor serious health effects are used as the basis for deriving MRLs. Thus, MRLs are based on non-neoplastic health end points and cancer effects are not a consideration (ATSDR, 1996; Chou et al., 1998). MRLs are derived based on the highest NOAEL not exceeding a LOAEL, or in the absence of a NOAEL, the lowest less serious LOAEL for the most sensitive health effect endpoint for a given route and exposure period in the database. An uncertainty factor (UF) is used to account for extrapolation from a LOAEL to a NOAEL. Additional UFs may also be used for human variability, for interspecies extrapolation when animal studies are used in the absence of adequate human data, and for extrapolation across exposure durations. In addition, a modifying factor (MF) may be used, on a case-by-case basis, to reflect concerns about the database not covered by the UFs. Thus,

$$\text{MRL} = \text{NOAEL (or LOAEL)} / (\text{product of UFs} \times \text{MF})$$

MRLs for each substance are derived from data compiled from a current worldwide literature search and are presented in ATSDR's toxicological profiles for that substance. Proposed MRLs undergo review by a Health Effects/MRL Workgroup within the Division of Toxicology, external expert peer reviewers, and an agency-wide MRL Workgroup (with participation from other federal agencies), and are submitted for public comment through the toxicological profile public comment process. Each MRL is subject to change as new information becomes available concomitant with updating the toxicological profile for the substance.

TABLE 1. Neurological Effects[a]

EFFECT	Less serious	Serious
MOTOR		
Activity changes (sedation, anesthesia, somnolence, hyperactivity/hypoactivity, ↓ locomotor activity)	+[b]	+
Convulsions		+
Lack of coordination (unsteadiness, intoxication, ↓ swimming response ability, ↓ psychomotor performance, ataxia)	+[b]	+
Paralysis		+
Reflex abnormalities	+[b]	+
Tremor, twitching (muscular spasm)		+
Weakness	+	
MOOD AND PERSONALITY		
Excitability	+	
Delirium		+
Depression	+[b]	+
Hallucinations		+
Irritability	+	
Nervousness, tension	+	
Restlessness	+	
Sleep disturbances	+	
SENSORY		
Auditory disorders		+
Equilibrium changes	+[b]	+
Pain disorders	+[b]	+
Tactile disorders	+[b]	+
Vision disorders		+
COGNITIVE		
Confusion		+
Learning impairment (↓ operant behavior)	+[b]	+
Memory problems		+
Speech impairment		+
GENERAL		
Depression of neuronal activity	+[b]	+
Fatigue (lethargy)	+	
Loss of appetite	+	
Narcosis, stupor		+
Nerve damage		+
Prostration		+
Other integrative effects (hand/eye coordination)	+[b]	+
Unconsciousness		+

TABLE 1. Neurological Effects[a] (cont'd)

EFFECT	Less serious	Serious
NEUROCHEMISTRY		
cAMP or cGMP changes, catecholamine changes, dopamine changes, (decreased enzyme activity)	+[b]	+
Changes in glial fibrillary acidic protein		+
Decreased neuronal membrane lipids	+[b]	+
Decreased metabolism (glucose utilization)	+[b]	+
NEUROPHYSIOLOGY		
Altered EEG	+[c]	+
Salivation	+	
NEUROPATHOLOGY		
(Peripheral neuropathy, demyelination, focal gliosis, cerebellar lesions, cerebellar degeneration, malacia, hemorrhage)		+

[a]Adapted from Anger et al., 1986.
[b]Neurological effects that could be less serious or serious are described as "slight" or "severe," or by another adjective describing severity.
[c]No other clinical effects.
↓ = decreased

Assessment of Neurological Effects

In the ATSDR guidance for the preparation of a ninth set toxicological profile (ATSDR, 1995), neurotoxicity is defined as any adverse effect on the structure or function of the central or peripheral nervous system by a biological, chemical, or physical agent. Neurological effects may be permanent or reversible, produced by neuropharmacological or neurodegenerative properties of a neurotoxicant, or may be the result of direct or indirect actions on the nervous system. Neurological effects can be categorized as motor, mood and personality, sensory, cognitive, neurochemical, neurophysiologic, or neuropathologic. To provide guidance to agency scientists, specific end points within these effect categories have been listed and classified as less serious or serious (Table 1). This listing is not intended to be inclusive of all possible neurological changes that may have been reported.

Cholinesterase Activity Inhibition

Inhibition of acetylcholinesterase results in accumulation of acetylcholine at synapses and neuromuscular junctions. Exposure to pesticides such as organophosphorus compounds may produce a broad spectrum of clinical symptoms such as headaches, weakness, dizziness, blurred vision, psychosis, respiratory difficulty, paralysis, convulsions, and coma. Kaloyanova and El Batawi (1991) have reported correlation of inhibition of erythrocyte/brain cholinesterase activity with clinical symptoms (Table 2).

TABLE 2. Acetylcholinesterase Activity (AChEA) Inhibition versus Severity of Neurological Symptoms[a]

Level of AChEA Inhibition	Severity of Neurological Symptoms
< 60% reduction of AChEA	Mild
60-90% reduction of AChEA	Moderate
90-100% reduction of AChEA	Severe

[a]Adapted from Kaloyanova and El Batawi, 1991.

In classifying the neurological health effect end point for inhibition of erythrocyte and/or brain acetylcholinesterase activity, ATSDR considers an exposure level that causes a 20–59% inhibition of enzyme activity a less serious LOAEL, and an exposure level that causes 60% or greater inhibition of enzyme activity a serious LOAEL. In addition, considerations are given to associated clinical symptoms. If clinical effects observed at a particular exposure level are most consistent with a moderate or severe classification, this exposure level is classified as a serious LOAEL, even if the degree of inhibition of acetylcholinesterase activity is less than 60%. Inhibition of acetylcholinesterase activity of 60% or greater is always classified as a serious effect.

RESULTS AND DISCUSSION

As mentioned previously, MRLs are based on the most sensitive end point. End points that may be used for MRL derivation include systemic effects (respiratory effects, cardiovascular effects, gastrointestinal effects, hematological effects, musculoskeletal effects, hepatic effects, renal effects, endocrine effects, dermal effects, ocular effects, body weight effects, metabolic effects), immunological and lymphoreticular effects, neurological effects, reproductive effects, and developmental effects. As of October 1997, ATSDR has derived 273 MRLs for 134 profiled substances. The neurological effects are among the most frequently used end points for deriving MRLs. To date 70 MRLs are based on neurological effects. Pertinent information on these MRLs and the associated health effects are shown in Table 3. Forty-four of the MRLs were based on neurological effects reported in animal studies, most of which were studies in rats (28 total rat studies). Studies in mice, dogs, rabbits, and gerbils were also used as the basis for deriving MRLs. NOAELs for neurological effects were reported in 38 of these investigations; MRL guidance values were derived from NOAELs reported for neurological effects in 31 of 44 studies in animals.

Among the neurological categories, 30 MRLs were derived from effects on motor function: 11 in humans and 19 in animals. Inhibition of acetylcholinesterase accounted for 15 MRLs: 1 in humans and 14 in animals. It should be noted that 14 MRLs based on developmental neurotoxicity were considered to be based on "developmental effects" and are therefore not included in Table 3.

TABLE 3. MRLs Based on Neurological Effects. As of October 1997

Substance Name (Tox profile status & cover date)	Route	Duration	MRL value	UFs x MF	Health Effects	Principal Study
Acetone (Final 5/94)	Inhal	Acute	26 ppm	9	LOAEL in humans; increases in response and % false negatives in auditory discrimination; increased anger, hostility.	Dick et al., 1989
Acetone (Final 5/94)	Inhal	Interm & chronic	13 ppm	100	LOAEL in humans; increased visual evoked response.	Stewart et al., 1975
Acrylonitrile (Final 12/90)	Inhal	Acute	0.1 ppm	10	NOAEL in humans.	Jakubowski et al., 1987
Benzene (Final 9/97)	Inhal	Interm	0.004 ppm	90	LOAEL in mice; increased rapid response time.	Li et al., 1992
Bromoform (Final 12/90)	Oral	Acute	0.6 mg/kg/d	100	LOAEL in humans; sedation.	Dwelle, 1903
Bromomethane (Final 9/92)	Inhal	Acute	0.05 ppm	100	NOAEL in rats; decreased brain neurotransmitters at higher dose.	Honma, 1987
Bromomethane (Final 9/92)	Inhal	Interm	0.05 ppm	100	NOAEL in rats; decreased brain neurotransmitters at higher dose.	Honma et al., 1982
Bromomethane (Final 9/92)	Inhal	Chronic	0.005 ppm	100	LOAEL in humans; increased prevalence of muscle ache, fatigue, and ataxia.	Anger et al., 1986
Carbon disulfide (Final 8/96)	Inhal	Chronic	0.3 ppm	30	LOAEL in humans; decreased peroneal motor nerve conduction velocity (MCV) and sural nerve sensory conduction velocity (SCV)	Johnson et al., 1983
Chlorfenvinphos (Final 9/97)	Oral	Acute	0.002 mg/kg/day	1000	LOAEL in rats; inhibition of plasma and erythrocyte cholinesterase activity.	Barna and Simon, 1973
Chlorfenvinphos (Final 9/97)	Oral	Chronic	0.0007 mg/kg/day	1000	LOAEL in rats; inhibition of plasma and erythrocyte cholinesterase activity.	Ambrose et al., 1970
Chloroethane (Final 12/89)	Inhal	Acute	1300 ppm	10	NOAEL in humans; intoxication at higher dose.	Davidson. 1925
Chloromethane (Draft 9/97)	Inhal	Acute	0.5 ppm	100	NOAEL in mice; cerebellar granule cell degeneration at higher dose.	Landry et al., 1985

TABLE 3. MRLs Based on Neurological Effects. As of October 1997 (cont'd)

Substance Name (Tox profile status & cover date)	Route	Duration	MRL value	UFs x MF	Health Effects	Principal Study
Chloromethane (Draft 9/97)	Inhal	Chronic	0.05 ppm	1000	LOAEL in mice; axonal swelling and slight degeneration of axons in spinal cord.	CIIT, 1981
Chlorpyrifos (Final 9/97)	Oral	Acute	0.003 mg/kg/day	10	NOAEL in humans; runny nose, blurred vision at higher dose.	Coulston et al., 1972
Chlorpyrifos (Final 9/97)	Oral	Interm	0.003 mg/kg/day	10	NOAEL in humans; runny nose, blurred vision at higher dose.	Coulston et al., 1972
Chlorpyrifos (Final 9/97)	Oral	Chronic	0.001 mg/kg/day	100	NOAEL in rats; decreased red blood cell ChE activity at higher dose.	McCollister et al., 1974
Cresol, ortho- (Final 7/92)	Oral	Acute	0.05 mg/kg/day	100	NOAEL in rabbits; hypoactivity at higher dose.	BRRC, 1988
Cresol, para- (Final 7/92)	Oral	Acute	0.05 mg/kg/day	100	NOAEL in rabbits; hypoactivity at higher dose.	BRRC, 1988
HMX (Final 9/97)	Oral	Acute	0.1 mg/kg/day	1000	LOAEL in mice; hyperkinesia when aroused at higher dose.	Army, 1985
RDX (Final 6/95)	Oral	Acute	0.06 mg/kg/day	100	NOAEL in rats; Convulsion, prostration in dams at higher dose.	Army, 1986
Diazinon (Final 8/96)	Inhal	Interm	0.009 mg/m^3	30	NOAEL in rats; inhibition of brain cholineesterase at higher dose	Hartmann, 1990
Diazinon (Final 8/96)	Oral	Interm	0.0002 mg/kg/day	100	NOAEL in dogs; inhibition of erythrocyte and brain acetylcholine esterase, and emesis at higher dose.	Barnes, 1988
Dichlorvos (Final 9/97)	Inhal	Acute	0.002 ppm	100	NOAEL in rats; inhibition of erythrocyte- acetylcholine esterase at higher dose.	Schmidt et al., 1979
Dichlorvos (Final 9/97)	Inhal	Interm	0.0003 ppm	100	NOAEL in rats; inhibition of erythrocyte and brain acetylcholine- esterase at higher doses.	Thorpe et al., 1972

TABLE 3. MRLs Based on Neurological Effects. As of October 1997 (cont'd)

Substance Name (Tox profile status & cover date)	Route	Duration	MRL value	UFs x MF	Health Effects	Principal Study
CDichlorvos (Final 9/97)	Inhal	Chronic	0.00006 ppm	100	NOAEL in rats; inhibition of erythrocyte and brain acetylcholine- esterase at higher doses.	Blair et al., 1976
Dichlorvos (Final 9/97)	Oral	Acute	0.004 mg/kg/day	1000	LOAEL in rats; inhibition of brain acetylcholine- esterase.	Teichert et al., 1976
Dichlorvos (Final 9/97)	Oral	Interm	0.003 mg/kg/day	10	NOAEL *in humans for* erythrocyte acetylcholine-esterase inhibition.	Boyer et al., 1977
Dichlorvos (Final 9/97)	Oral	Chronic	0.0005 mg/kg/day	100	NOAEL in dogs; inhibition of erythrocyte and brain acetylcholine- esterase at higher doses.	AMVAC Chemical Corp., 1990
Disulfoton (Final 8/95)	Inhal	Acute	0.006 mg/m^3	30	NOAEL in rats; inhibition of erythrocyte choline-esterase and unspecified behavioral disorders at higher doses.	Thyssen, 1978
Disulfoton (Final 8/95)	Inhal	Interm	0.0002 mg/m^3	30	NOAEL in rats; muscle tremors, convulsions, increased salivation, difficulty breathing at higher dose.	Thyssen, 1980
Disulfoton (Final 8/95)	Oral	Acute	0.001 mg/kg/day	100	NOAEL in rats; inhibition of plasma and erythrocyte cholinesterase at higher doses.	Lamb and Hixon, 1983
Disulfoton (Final 8/95)	Oral	Chronic	0.00006 mg/kg/day	1000	LOAEL in rats; inhibition of erythrocyte and brain cholinesterase.	Hayes, 1985
Endrin (Final 8/96)	Oral	Interm	0.002 mg/kg/day	100	NOAEL in dogs; convulsions, tremors, diffuse degenerative brain lesions at higher dose.	Treon et al., 1955

TABLE 3. MRLs Based on Neurological Effects. As of October 1997 (cont'd)

Substance Name (Tox profile status & cover date)	Route	Duration	MRL value	UFs x MF	Health Effects	Principal Study
Endrin (Final 8/96)	Oral	Chronic	0.0003 mg/kg/day	100	NOAEL in dogs; convulsions at higher dose.	Kettering, 1969
Fuel oil #2 (Final 6/95)	Inhal	Acute	0.02 mg/m^3	1000	LOAEL in mice; ataxia, disturbed gait.	Kainz and White, 1984
Hexachlorocyclo-hexane, gamma- (Draft 9/97)	Oral	Acute	0.01 mg/kg/day	100	NOAEL in rats; increased kindling acquisition; seizures at higher dose.	Joy, 1982
Hexachlorocyclo-hexane, beta- (Draft 9/97)	Oral	Acute	0.2 mg/kg/day	100	NOAEL in mice; ataxia at higher dose.	Cornacoff et al., 1988
Hexachloro-ethane (Final 9/97)	Inhal	Acute	6 ppm	30	NOAEL in rats; tremors at higher dose.	Weeks et al., 1979
Hexachloro-ethane (Final 9/97)	Inhal	Interm	6 ppm	30	NOAEL in rats; tremors at higher dose.	Weeks et al., 1979
Chlordecone (Final 8/95)	Oral	Acute	0.01 mg/kg/day	100	NOAEL in rats; increased startle response at higher dose.	EPA, 1986
n-Hexane (Draft 9/97)	Inhal	Chronic	0.6 ppm	100	LOAEL in humans; decreased motor nerve conduction velocity.	Sanagi et al., 1980
Manganese (Draft 10/97)	Oral	Chronic	0.00004 mg/m^3	900	LOAEL in humans; decreased reaction time, finger tapping.	Iregren, 1990
Mercury (Draft 8/97)	Inhal	Chronic	0.0002 mg/m^3	30	LOAEL in humans; increased frequency of mild intention tremors with weight load.	Fawer et al., 1983
Methyl parathion (Final 9/92)	Oral	Chronic	0.0003 mg/kg/day	100	NOAEL in rats; abnormal gait, slight tremors, peripheral neuropathy and inhibition of cholinesterases at higher doses.	Suba, 1984

TABLE 3. MRLs Based on Neurological Effects. As of October 1997 (cont'd)

Substance Name (Tox profile status & cover date)	Route	Duration	MRL value	UFs x MF	Health Effects	Principal Study
Methyl t-butyl ether (Final 8/96)	Inhal	Acute	2 ppm	100	NOAEL in rats; increased incidence/severity of ataxia and duck walk gait.	Gill, 1989
Methyl t-butyl ether (Final 8/96)	Inhal	Interm	0.7 ppm	100	NOAEL in rats; hypoactivity, lack of startle response, and blepharospasm at higher dose.	Neeper-Bradley, 1991
Methyl t-butyl ether (Final 8/96)	Oral	Acute	0.4 mg/kg/day	100	NOAEL in rats; drowsiness at higher dose.	Bioresearch Labs, 1990
Methylene chloride (Final 4/93)	Inhal	Acute	0.4 ppm	100	LOAEL in humans; critical flicker frequency depression, vigilance decrease; impaired psychomotor tasks at higher dose.	Winneke, 1974
Naphthalene (Final 8/95)	Oral	Acute	0.05 mg/kg/day	1000	LOAEL in rats; lethargy, slow breathing, increased rooting.	NTP, 1991
Propylene Glycol Dinitrate (Final 6/95)	Inhal	Acute	0.003 ppm	10	NOAEL in humans; altered visual evoked response, headache, and ataxia at higher doses.	Stewart et al., 1974
Styrene (Final 9/92)	Inhal	Chronic	0.06 ppm	100	LOAEL in humans; decreased verbal learning skills.	Mutti et al., 1984
Tetrachloro-ethylene (Final 9/97)	Inhal	Acute	0.2 ppm	10	NOAEL in humans; increased latency of visual evoked potentials at higher dose.	Altmann et al., 1990
Tetrachloro-ethylene (Final 9/97)	Inhal	Chronic	0.04 ppm	100	LOAEL in humans; increased reaction time.	Ferroni et al., 1992
Toluene (Final 5/94)	Inhal	Acute	3 ppm	30	LOAEL in humans; decreased manual dexterity and visual perception.	Baelum et al., 1985

TABLE 3. MRLs Based on Neurological Effects. As of October 1997 (cont'd)

Substance Name (Tox profile status & cover date)	Route	Duration	MRL value	UFs x MF	Health Effects	Principal Study
Toluene (Final 5/94)	Inhal	Chronic	1 ppm	30	LOAEL in humans; weak correlation with lower test scores for special tests.	Orbaek and Nise, 1989
Toluene (Final 5/94)	Oral	Acute	0.8 mg/kg/day	300	LOAEL in rats; decreased amplitude of the flash evoked potential N3 peaks.	Dyer et al., 1988
Toluene (Final 5/94)	Oral	Interm	0.02 mg/kg/day	300	LOAEL in mice; increased levels of dopamine and norepinephrine in hypothalamus.	Hsieh et al., 1990
Trichloro-ethylene (Final 9/97)	Inhal	Acute	2 ppm	30	LOAEL in humans; headache, fatigue, drowsiness, neurological effects.	Stewart et al., 1970
Trichloro-ethylene (Final 9/97)	Inhal	Interm	0.1 ppm	300	LOAEL in rats; decreased wakefulness during exposure, decreased postexposure sleeping heart rate.	Arito et al., 1994
Xylene, para- (Final 8/95)	Oral	Acute	1 mg/kg/day	100	NOAEL in rats; altered visual evoked potentials at higher dose.	Dyer et al., 1988
Xylenes, mixed (Final, 8/95)	Inhal	Acute	1 ppm	100	LOAEL in humans; increased reaction time.	Dudek et al., 1990
Xylenes, mixed (Final, 8/95)	Inhal	Chronic	0.1 ppm	100	LOAEL in humans; increased prevalence of anxiety, forgetfulness, inability to concentrate, and other subjective symptoms.	Uchida et al., 1993
1,1,1-Trichloro-ethane (Final 8/95)	Inhal	Acute	2 ppm	100	LOAEL in humans; decreased psychomotor performance.	Mackay et al., 1987

TABLE 3. MRLs Based on Neurological Effects. As of October 1997 (cont'd)

Substance Name (Tox profile status & cover date)	Route	Duration	MRL value	UFs x MF	Health Effects	Principal Study
1,1,1-Trichloro- ethane (Final 8/95)	Inhal	Interm	0.7 ppm	100	NOAEL in gerbils; increased glial fibrillary acidic protein indicating astrogliosis at high dose.	Rosengren et al. 1985
1,1,2-Trichloro-ethane (Final 12/89)	Oral	Acute	0.3 mg/kg/day	100	NOAEL in mice; taste aversion at higher dose.	Kallman et al., 1983
1,2-Dichloro-propane (Final 12/89)	Oral	Acute	0.1 mg/kg/day	1000	LOAEL in rats; slight CNS depression.	Bruckner et al. 1989
2,4-Dinitro-toluene (Draft 9/97)	Oral	Acute	0.05 mg/kg/day	100	NOAEL in dogs; incoordination, stiffness, and abnormal gait at higher dose.	Ellis et al., 1985; Lee et al., 1978
4,6-Dinitro-o-cresol (Final 8/95)	Oral	Acute	0.004 mg/kg/day	100	LOAEL in humans; fatigue and dizziness.	Plotz, 1936
4,6-Dinitro-o-cresol (Final 8/95)	Oral	Interm	0.004 mg/kg/day	100	LOAEL in humans; fatigue and dizziness.	Plotz, 1936

Classification of neurological effects into NOAEL, less serious LOAEL, or serious LOAEL is based on degree of severity. When a less serious LOAEL is used as the basis to derive an MRL, a default UF of 10 is generally used for extrapolation from a less serious LOAEL to a NOAEL. However, an effect level is considered to be a minimal LOAEL when only minimally toxic effects are observed that are thought to represent an early indication of toxicity. A UF of 3 is generally used to extrapolate from a minimal LOAEL to a NOAEL. Representative examples where a UF of 3 was used for use of a minimal LOAEL for neurological effects in deriving an MRL are as follows:

An acute inhalation MRL of 26 ppm for acetone was derived based on mild decrements on behavioral performance tests in volunteers after a 4 hr exposure to 237 ppm acetone (Dick et al., 1989). There were small statistically significant changes in performance from controls in two measures of the auditory tone discrimination task, i.e., increased response time to correct hits and false alarm percent rate, and on the anger hostility scale (men only) of the profile of mood states test. In deriving the MRL, a UF of 9 was applied to the LOAEL of 237 ppm, 3 for use of a minimal LOAEL and 3 for human variability.

A chronic inhalation MRL of 0.3 ppm for carbon disulfide was derived based on decreased peroneal motor nerve conduction velocity and sural nerve sensory conduction velocity in workers exposed occupationally to 7.6 ppm for 12.1 years (S.D. 6.9 years) in comparison to controls. Although the small reductions in nerve conduction velocities were still within the range of clinically normal values, the authors concluded that this decrement should be considered a minimal neurotoxic effect (Johnson et al., 1983). In calculating the MRL, a UF of 30 (3 for use of a minimal LOAEL, and 10 for human variability) was applied to the LOAEL of 7.6 ppm.

An acute inhalation MRL of 3 ppm for toluene was derived based on decreased psychomotor performance in manual dexterity and visual perception speed in workers exposed to 100 ppm toluene for 6.5 hours in comparison to unexposed controls (Baelum et al., 1985). In deriving the MRL, a UF of 30 (3 for use of a minimal LOAEL, and 10 for human variability) was applied to the LOAEL of 100 ppm.

Because MRLs are derived through workgroup consensus, the scientific judgment of the collective body is employed. The underlying mechanism and significance of the observed neurological effects are not always clearcut. The expertise of the workgroup members, coupled with their ability to achieve consistency in making biomedical judgments across profiled substances is crucial in deriving health-based guidance values.

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