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Health effects classification and its role in the derivation of minimal risk levels: Reproductive and endocrine 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. From the total of 326 MRLs currently posted on ATSDR's web site (www.atsdr.cdc.gov), 14 and 5 MRLs are based on reproductive and endocrine endpoints, respectively. The paper also describes the ranking of effects into less serious and serious categories according to ATSDR's *Guidance for Developing Toxicological Profiles*, endpoints used for the MRLs derivation, and the use of uncertainty factors.
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1. Introduction

In recent years, numerous studies have suggested that many environmentally persistent chemicals have a potential to disrupt normal functions of the endocrine system. Many chemicals have also serious impact on reproductive and developmental endpoints in humans and animals. Assessment of risks posed by chemicals causing reproductive effects and protection of future generations are important public health tasks.

To determine the levels of significant human exposure to a given chemical and associated health effects, Agency for Toxic Substances and Disease Registry's (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 the health effects according to their seriousness as "serious," "less serious," or "minimal." A "less-serious" effect is 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 (Pohl and Abadin, 1995). "Serious" effects are effects that prevent the organism from functioning normally or can cause death. "Minimal" effects are those that reduce the capacity of an organ or organ system to absorb additional toxic stress but will not necessarily lead to the inability of the organ or organ system to function normally.

ATSDR uses the highest no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level (LOAEL) in the available literature to derive a health-based guidance value called a minimal risk level (MRL). 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, 1992a,b). MRLs are derived for inhalation and oral exposures. For each route of exposure, MRLs can be derived for acute (up to 14 days), intermediate (15–364 days), and chronic (365 days or more) durations.

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Human data are preferred; however, human equivalent levels can be derived based on animal exposure. The formula for derivation of an oral MRL is

$$\mathrm{MRL} = \frac{\mathrm{NOAEL(LOAEL)}}{(\mathrm{UF} \times \mathrm{MF})},$$

where MRL is the minimal risk level (mg/kg/day), NOAEL is the no-observed-adverse-effect level (mg/kg/day), LOAEL is the lowest-observed-adverse-effect level (mg/kg/day), UF is the uncertainty factor (unitless), and MF is the modifying factor (unitless).

UFs are used 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. MFs may be applied to reflect additional scientific judgement on the database. The above concept is also used for the reference dose (RfD) derivation by U.S. Environmental Protection Agency (EPA) (Barnes and Dourson, 1988). MRLs provide health professionals with a concept of exposure levels at which adverse health effects are not expected in human populations living in the vicinity of hazardous waste sites or chemical emissions.

The purpose of this review was to inform the public about MRLs based on reproductive and endocrine effects and about the guidance provided for the sections of toxicological profiles describing these health effects and their categorization in the ATSDR's *Guidance for Developing Toxicological Profiles* (ATSDR, 2003a,b). So far, the guidance has served as an internal document and has not been released to the public. However, parts of the guidance related to neurological, developmental, and respiratory effects and respective MRLs based on these effects were previously published (Chou and Williams-Johnson, 1998; Pohl et al., 1998; Wilbur, 1998).

2. Materials and methods

The MRLs were based on vast databases compiled in the toxicological profiles for acrylonitrile (ATSDR, 1990), atrazine (ATSDR, 2003a,b), cyanide (ATSDR, 1997), RDX [1,3,5,-triaza-1,3,5-trinitrocyclohexane] (ATSDR, 1995a,b,c), di(2-ethylhexyl)phthalate (ATSDR, 2002a,b,c,d), diethyl phthalate (ATSDR, 1995a,b,c), hexachlorobenzene (ATSDR, 2002a,b,c,d), methoxychlor (ATSDR, 2002a,b,c,d), dibromochloropropane (ATSDR, 1992a,b), 1,3-dinitrobenzene and 1,3,5-trinitrobenzene (ATSDR, 1995a,b,c), chlorophenols (ATSDR, 1999), 2,4- and 2,6-dinitrotoluene (ATSDR, 1998a,b), iodine (ATSDR, 2001a,b), pentachlorophenol (ATSDR, 2001a,b), and polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs) (ATSDR, 2002a,b,c,d). Toxicological profiles (final and draft documents) can be found on ATSDR's website (www.atsdr.cdc.gov). The MRLs were derived according to the current ATSDR methodology (Chou et al., 1998; Pohl and Abadin, 1995). A list of all current MRLs (updated on May 11, 2004) is available on ATSDR's website (www.atsdr.cdc.gov).

3. Results

3.1. Reproductive effects and related MRLs

Reproductive toxicity is defined as a dysfunction induced by a chemical, physical, and or other agent that affects the process of gametogenesis from its earliest stage to implantation of the conceptus in the endometrium. Reproductive studies were conducted for numerous chemicals. The studies differ not only in their quality, but also in the sensitivity of parameters measured. These include pathological and histopathological changes in organ and cellular structures together with pathophysiological changes in male and female reproductive systems, and reproductive outcomes for both sexes. Examples of reproductive effect end points are listed and classified as less serious or serious according to the ATSDR guidance document (ATSDR, 2003a,b) in Table 1. It is recognized that for some effects, there is a continuum in the severity and the whole clinical

Table 1
Reproductive effect end points

Effect	Less serious	Serious
Abnormal sperm[a] (morphology, count, motility)		+
Abortion		+
Atrophy		+
Decreased fertility[b]	+	+
Decreased litters		+
Decreased spermatogenesis[a]	+	+
Degeneration of epididymides[b]	+	+
Disrupted spermatogenesis		+
Females: no reproduction		+
Maternal toxicity		+
Increased estrus		+
Irreversible histological change in testes		+
Ovarian dysfunction		+
Ovary weight change	+	
Postimplantation loss		+
50% reduction in number of offspring		+
Sterility		+
Testicular atrophy		+
Testicular degeneration	+	+
Granuloma epididymides[c]	+	+
Tubular degeneration		+
Tubule edema	+	
Vaginal bleeding	+	

[a] Variability exists among normal/less serious/serious; e.g., a normal human semen specimen has a volume of 3-4 mL, a sperm count of 30×10^6, and 80% morphologically normal and motile spermatozoa.
[b] The effect can be less serious or serious depending upon the degree.
[c] This condition can be considered serious because it can lead to progressive fibrosis.

picture has to be evaluated. for the correct classification. For example, organ weight changes for ovaries or testes are considered less-serious effects. A definitive organ dysfunction along with the atrophy (weight change) of ovaries or testes is a serious effect.

Although the ovaries and testes have endocrine functions, for reasons of consistency among the toxicological profiles ATSDR's guidance recommends categorization of effects involving these functions as reproductive effects.

As of May 2004, ATSDR listed 14 MRLs based on reproductive effects. These MRLs and the specific endpoints that served as the bases for their derivation are listed in Table 2. As an example, some MRLs that are no longer valid, because they were supplanted by new MRLs based on updated information, are also listed in the table. They are further discussed in the text.

Because of its noninvasive nature, collection of sperm is one of the easiest way to evaluate the male reproductive system in humans. Sperm number, structure, maturation, motility, viability, and function (i.e., cervical-mucus penetrations and sperm–oocyte interactions) also are the tests most often performed in laboratory animals. They are, therefore, also the basis for MRL derivation for a number of chemicals (e.g., acrylonitrile, cyanide, di(2-ethyl-hexyl)phthalate, 1,2-dibromo-3-chloropropane, and 1,3-dinitrobenzene).

In some instances, the sperm tests were supplemented with data from evaluation of histopathological changes in testes and epididymis (e.g., acrylonitrile and 1,3-dinitrobenzene). Evaluation of testicular degeneration varied across the studies from crude measurements of testicular and epididymal weights (cyanide), to light-microscopic examination revealing tubular degeneration (1,3-dinitrobenzene), and more advanced electron-microscopic examination describing Leydig cell mitochondrial swelling, focal dilatation, and vesiculation of the smooth endoplasmic reticulum (diethyl phthalate). In addition, hormonal changes served as end points for deriving MRLs for the methoxychlor and 1,2-dibromo-3-chloropropane. In fact, for some chemicals that are known toxicants to the male reproductive system, such as 1,2-dibromo-3-chloropropane, changes in hormonal levels provide early warnings of the chemically induced toxicity (ATSDR, 1992a,b). MRLs for atrazine, hexachlorobenzene, and methoxychlor were based on effects in the female reproductive system. The chemicals caused hormonal changes, histopathological changes (degeneration of primordial follicles), and early onset of puberty (early estrus), respectively.

Effects on the developing embryo are important in the evaluation of reproductive in utero effects. Fertilization, implantation of blastocyst, and gastrulation can be evaluated. Chemical insult in this stage is expressed mostly as embryonic death and resorption. Developmental effects are distinguished from reproductive effects by evaluation of the conceptus after implantation. MRLs for di(2-ethylhexyl) phthalate, white phosphorus, and 2,4,6-trichlorophenol were based on the measurement of actual reproductive outcome.

For the derivation of MRLs, standard default uncertainty factors (UF) of 10 were used to extrapolate from a LOAEL to a NOAEL, from animals to humans, and for human susceptibility (for more information about the methodology, see Pohl and Abadin, 1995). There were several exceptions to this procedure. ATSDR used an UF of 3 to extrapolate from a LOAEL to a NOAEL in deriving an acute oral exposure MRL for diethyl phthalate. The LOAEL was deemed "minimal" because the testicular changes in rats were observable only under the electron microscope. Similarly, ATSDR used an UF of 3 for a "minimal" LOAEL for ultrastructural changes in ovaries confirmed by electron microscopy in monkeys exposed to hexachlorobenzene by oral route for intermediate duration. In case of the MRL for atrazine, a UF of 3 instead of 10 was used for human variability because the critical effect was identified in a sensitive population (young, developing female pigs). In contrast, ATSDR added a modifying factor (MF) of 3 for an MRL derived for RDX because of the lack of relevant neurological studies in the database. This step actually increased the uncertainty associated with the derived MRL.

4. Endocrine effects and related MRLs

As of May 2004, ATSDR's MRL Workgroup derived five MRLs based on endocrine effects (excluding reproductive hormones changes). MRLs based on changes of reproductive hormones (FSH and prolactin in case of 1,2,-dibromo-3-chloropropane and methoxychlor, respectively) are described under reproductive effects above. Pathological and pathophysiological changes of thyroid gland and related upper regulatory hormones (i.e., TSH [thyroid stimulating hormone] from anterior pituitary gland) are often the subject of investigation of injury caused by endocrine disruptors. Table 3 lists MRLs that were based on thyroid effects. Relevant studies on endocrine effects other than those pertaining to thyroid and reproductive hormones are less frequent. No MRLs were based on these studies. The only notable deviation from applying the default uncertainty factors are the MRLs for iodine. UF of 1 was used for human susceptibility because of the robust database and available studies in children who are considered to be a sensitive population.

5. Discussion and conclusion

In recent years, attention has focused on the potential for a wide range of xenobiotic chemicals to interact with

Table 2
MRLs based on reproductive effects

Substance	Route	Duration	MRL value	UF	End point	Reference
Acrylonitrile	Oral	Intermediate	0.01 mg/kg/day	1000	LOAEL in mice; decreased sperm count, tubular degeneration	Tandon et al. (1988)
Atrazine	Oral	Intermediate	0.003 mg/kg/day	300	LOAEL in pigs; serum 17 β-estradiol, changes in estrus cycle	Gojmerac et al. (1999)
Cyanide	Oral	Intermediate	0.05 mg/kg/day	100	NOAEL in rats; decreased epididymis, testis weight, spermatid heads, spermatid counts at higher dose	NTP (1993)
RDX	Oral	Intermediate	0.03 mg/kg/day	300	NOAEL in rats; testicular degeneration at higher dose	Army (1983)
Di(2-ethylhexyl)phthalate[a]	Oral	Acute	1 mg/kg/day	100	NOAEL in rats; reduced testicular weight, delayed spermatid maturation at higher dose	Dostal et al. (1988)
Di(2-ethylhexyl)phthalate	Oral	Intermediate	0.1 mg/kg/day	100	NOAEL in mice; decreased fertility at higher doses	Lamb et al. (1987)
Di(2-ethylhexyl)phthalate	Oral	Chronic	0.06 mg/kg/day	100	NOAEL in rats; aspermatogenesis at higher doses	David et al. (2000)
Diethyl phthalate	Oral	Acute	7 mg/kg/day	300	LOAEL in rats; Leydig cell mitochondrial swelling, focal dilatation, and vesiculation of the smooth endoplasmic reticulum	Jones et al. (1993)
Hexachloro-benzene	Oral	Intermediate	0.0001 mg/kg/day	90	LOAEL in monkeys; decreased number of oocytes; ultrastructural degeneration of ovarian primordial follicles	Bourque et al. (1995), Jarell et al. (1993)
Pentachlorophenol	Oral	Intermediate	0.001 mg/kg/day	1000	LOAEL in mink; deceased mating	Beard et al. (1997)
Methoxychlor[a]	Oral	Acute	0.02 mg/kg/day	1000	LOAEL in rats; accelerated onset of puberty in females	Gray et al. (1989)
Methoxychlor	Oral	Intermediate	0.005 mg/kg/day	1000	LOAEL in rats; precocious vaginal opening, more severe effects at higher doses	Chapin et al. (1997)
1,2-Dibromo-3-chloropropane	Inhal	Intermediate	0.0002 ppm	100	NOAEL in rabbits; sperm abnormalities, increased serum FSH, reversible decreased spermatogenesis at higher dose	Rao et al. (1982)
1,2-Dibromo-3-chloropropane	Oral	Intermediate	0.002 mg/kg/day	1000	LOAEL in rabbits; abnormal sperm morphology, decreased spermatogenesis	Foote et al. (1986a,b)
1,3-Dinitro-benzene	Oral	Acute	0.008 mg/kg/day	100	NOAEL in rats; damaged testicular epithelium, decreased spermatozoa, morphological changes in spermatozoa, histological changes in epididymis at higher dose	Linder et al. (1990)
2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin[a]	Oral	Intermediatechronic	1 pg/kg/day	1000	LOAEL in rats; changes in gestational index	Murray et al. (1979)
2,4,6-Trichloro-phenol[a]	Oral	Intermediate	0.04 mg/kg/day	100	NOAEL in rats; reduced mean litter size at higher dose	Exon and Koller (1985)
White phosphorus	Oral	Intermediate	0.0002 mg/kg/day	100	NOAEL in rats; increased number of stillborn pups	IRDC (1985)

LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor. Acute exposure = up to 14 days; intermediate-duration exposure = 15 days to 365 days; chronic exposure = more than 1 year.
[a] MRLs that were supplanted by new MRLs based on updated information or withdrawn.

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Table 3
MRLs based on endocrine effects

Substance	Route	Duration	MRL value (mg/kg/day)	UF	End point	Reference
Iodine	Oral	Acute	0.01	1	LOAEL in humans; subclinical hypothyroidism	Paul et al. (1988)
Iodine	Oral	Chronic	0.005	1	LOAEL in humans; subclinical hypothyroidism with gland enlargement	Boyages et al. (1989)
Pentachlorophenol	Oral	Chronic	0.001	1000	LOAEL in mink; decreased serum thyroxine and decreased relative thyroid weight	Beard and Rawlings (1998)
Polybrominated biphenyls	Oral	Acute	0.01	100	NOAEL in rats; decreased serum levels of thyroid T_4 hormone	Allen-Rowlands et al. (1981)
Polybrominated diphenyl ethers	Oral	Acute	0.03	30	LOAEL in rats; reduced serum T_4 in fetuses	Zhou et al. (2002)

LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; NOAEL = no-observed-adverse-effect level; UF= uncertainty factor. Acute exposure = up to 14 days; intermediate-duration exposure = 15 days to 365 days; chronic exposure = more than 1 year.

and disrupt the endocrine systems of humans and animals (De Rosa et al., 1998, 2001a,b). ATSDR's Priority List of Hazardous Substances lists about 300 substances found at hazardous waste sites. The substances are ranked by priority based on the frequency of occurrence at waste sites, toxicity, and potential for human exposure (ATSDR, 2003a,b). Well over half of those substances are metals and organochlorine compounds, two major classes of chemicals associated with disruption of the endocrine system. Many of these chemicals cause a wide range of health effects including endocrine, reproductive, and developmental effects (De Rosa et al., 1998, 2001a,b).

Health guidance values reflect the application of a range of default assumptions that are conservative (i.e., protective) and which are believed, in aggregate, to result in protective health guidance values. As explained previously, to account for recognized areas of uncertainty regarding species variability in effect(s) and effect levels, sensitive human populations, and low-dose extrapolation, UF are used in developing health guidance values. The application of such UF contributes to the protective nature of health guidance values. The limitations, assumptions, and uncertainties inherent in health risk assessment are addressed in the National Academy of Sciences report "Science and Judgment in Risk Assessment" (NRC, 1994). In this report, the Academy states that "uncertainty analysis should be an iterative process, moving from the identification of generic uncertainties" to more refined analyses of uncertainties. Further uncertainties include differences in bioavailability of chemicals, background exposures, background prevalence of diseases (health effects), possible misclassification of effects, etc. Some examples of uncertainties and limitations are discussed here.

To understand the mechanisms by which chemicals cause reproductive effects, it is necessary to have a basic understanding of the physiologic interrelationships of the various components of the endocrine and reproductive systems, the multiple control mechanisms, and the pathology (gross and histological) of the targeted organs. It is easy to make an erroneous conclusion regarding the cause of a reproductive effect based on limited observations at a single time point. Therefore, a battery of tests often is recommended (WHO, 1984).

All MRLs presented in this paper, except those for iodine, were based on effects observed in animals. Even for chemicals well known to target human reproductive system, such as 1,2-dibromo-3-chloropropane, a health-based guidance value related to observed effects in humans is difficult to derive. Most available data came from occupational settings, in case of 1,2-dibromo-3-chloropropane, from cohorts of workers exposed to this nematocide during production at factories (Potashnik et al., 1978; Whorton et al., 1979), and from cohorts of applicators and farmers (Glass et al., 1979; Sandifer et al., 1979) and actual levels of exposure were not established. Animal studies intended to investigate reproductive effects should follow certain protocols that were outlined elsewhere (EPA, 1991, 1996, 1998; FDA, 1993). Hence, animal studies in laboratory settings provide more reliable information for risk assessment. However, a detailed description of protocols relevant to the assessment of reproductive and endocrine outcomes is beyond the scope of this paper (ATSDR, 2003a,b).

Basing the health guidance values on animal studies brings another set of problems. Despite controlled laboratory conditions and rigid protocols, the animal data have several confounding factors. Some of the concerns are related to actual delivered dose, end point classification, windows of susceptibility, and relevance of animal data to humans. For example, the preimplantation and early postimplantation background losses in rats are low, less than 10% (Fritz et al., 1978; Frohberg, 1977; Perraud, 1976), whereas the spontaneous fetal abortions in humans may be as high as 50% (Edmonds et al., 1982; Lopata et al., 1982; Miller et al., 1980). Evaluation of interspecies differences always should play an important role in the derivation of MRLs. From our data set, an intermediate-duration oral MRL for 2,4,6-trichlorophenol was based on a NOAEL for reduced litter size

($p < 0.10$) observed in rats at higher doses. Another study with chlorophenols indicated an increased trend in percentage of preimplantation loss in rats. Although no data on reproductive effects of chlorophenols in humans are available, this end point is considered relevant for consideration in human risk assessment. The statistical increase in losses linked to the exposure similarly could be reflected in humans by a further increase in losses above the already high background levels.

Although many chemicals are considered endocrine disruptors and/or reproductive toxicants, other end points in their database were more sensitive and appropriate for MRL derivations. A chronic oral MRL for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) can illustrate deliberations to select a proper end point (ATSDR, 1998a,b). TCDD exposure in rats and mice enhanced surgically induced endometriosis. Significant increases in the diameter of the endometriotic site and an acceleration of growth were observed in rats (Cummings et al., 1996) and mice (Cummings et al., 1996; Johnson et al., 1997), respectively. However, Foster et al. (1997) noted that preexposure to TCDD resulted in endometriosis development due to immune suppression rather than an estrogen-responsive disease. Rier et al. (1993) found a dose-related increase in the incidence and severity of endometriosis in monkeys chronically exposed to TCDD in a diet. However, monkeys appear to be more susceptible to endometriosis, based on a 30% background incidence of endometriosis in monkeys (Rier et al., 1993) compared with a 10% background incidence in humans (Wheeler, 1992). Thus, if the derivation of a chronic oral MRL were based on endometriosis would necessitate using an uncertainty factor of less than 1 (or, at most, 1) to account for the higher sensitivity of monkeys to endometriosis as compared to humans. This would result in a computed MRL essentially the same as the chronic oral MRL of 1 pg/kg/day based on developmental toxicity (Schantz et al., 1992) as described in the toxicological profile (ATSDR, 1998a,b). Moreover, (1) the clinical history for these rhesus monkeys during the period between the Schantz et al. (1992) study and the Rier et al. (1993) examination conducted 10 years later is unknown (not reported); (2) Boyd et al. (1995) did not find an association between exposure to chlorinated dibenzo-*p*-dioxins (CDDs), chlorinated dibenzofurans (CDFs), or polychlorinated biphenyls (PCBs) and endometriosis in a clinical study in women; (3) the U.S. Environmental Protection Agency (EPA) (1997) concluded that "the evidence for supporting the hypothesis that CDDs and PCBs are causally related to human endometriosis via an endocrine-disruption mechanism is very weak." Therefore, even though information indicates that endometriosis also may be a sensitive toxicological end point for TCDD exposure, the neurobehavioral developmental end point (altered social behavior) reported in the Schantz et al. (1992) study was determined to be the most appropriate end point for deriving an MRL for chronic oral exposure to TCDD.

Table 2 also lists some of the MRLs that have been supplanted by new MRLs based on more recent evaluations of the updated database (i.e., new data being published on the profiled chemicals). For example, ATSDR has withdrawn the previous MRL of 0.02 mg/kg/day for acute-duration exposure derived in the 1994 Toxicological Profile for Methoxychlor. This MRL was based on precocious opening (early puberty) observed in rats exposed to 25 mg/kg/day (Gray et al., 1989). This study did not test doses as low as the current intermediate-duration MRL study (Chapin et al., 1997), which demonstrated the same effect from 5 mg/kg/day administered from gestation day 14 to postnatal day 42. Another example is the MRL for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. In 1989, the LOAEL of 0.001 μg/kg/day was considered for derivation of the intermediate-duration oral MRL of 1 pg/kg/day. At this exposure level, dilated pelvises and changes in gestational index were observed in rats (Murray et al., 1979). A UF of 10 was used for extrapolation from animals to humans, a factor of 10 for human variability, and a factor of 10 for the use of a LOAEL. The intermediate-duration exposure MRL was adopted for chronic exposure. No UF was used to extrapolate across durations. In 1998, the chronic MRL of 1 pg/kg/day was based on a LOAEL of 0.12 ng/kg/day in monkeys administered in a diet for a total exposure of 16.2 ± 0.4 months (Schantz et al., 1992). An uncertainty factor of 3 was used for extrapolation from animals to humans, a factor of 10 for human variability, and a factor of 3 for the use of a LOAEL. In summary, although based on a lower LOAEL, the final value is the same because of the decreased uncertainty. The uncertainty was decreased because of the greater knowledge about dioxins based on 10 years of intensive research featured in a vast literature database. From that resulted a greater confidence in the new value (De Rosa et al., 1999; Pohl et al., 2002).

Health-based guidance values are derived by other agencies around the world. We have compared the MRLs with the reference concentrations (RfCs) and reference doses (RfDs) derived by U.S. EPA. The RfCs and RfDs values were found posted on the Integrated Risk Information System site at www.epa.gov/iris. In July 2004, a total of 69 RfCs and 358 RfDs was listed on the IRIS web site. Of all the RfCs listed, five were based on reproductive effects. Four of the chemicals were not evaluated by ATSDR. Only one chemical, 1,2,-dibromo-3-chloropropane was evaluated by both agencies. The RfC of 0.0002 mg/m^3 (ppm) is identical to the ATSDR's derived MRL for intermediate-duration inhalation exposure. Of all the RfDs listed, 18 were based on reproductive effects. Eleven chemicals were not evaluated by ATSDR. Of the remaining seven chemicals with RfDs based on reproductive effects, only two

corresponding chemicals have MRLs based on reproductive effects. Both agencies have the same value of 0.005 mg/kg/day for methoxychlor. The RfD for RDX is 0.003 mg/kg/day, the intermediate-duration oral MRL is 0.03 mg/kg/day. However, considering that the RfD value is for chronic exposure and this MRL is for intermediate-duration exposure, the value would be virtually the same after extrapolation across duration. MRLs for the remaining chemicals are based on different end points but also are derived for durations other than chronic (ATSDR, 1996). A valid comparison cannot be made.

In conclusion, because of interspecies variability and multifactorial control mechanisms, it is often difficult to predict reproductive toxicity in humans based on animal studies. For example, fertility studies, especially in rodents, are relatively insensitive indicators of chemical toxicity. Normal male rodents produce numbers of sperm that greatly exceed the minimum requirements for fertility studies, while in humans, the sperm counts in many individuals approach the threshold for infertility (Kimmel et al., 1992). In contrast, fertility in rodents remains unchanged, even after a 90% reduction in sperm count (Meistrich, 1982; Robaire et al., 1984). Interspecies differences between fertility of female rodents and humans in regard to sensitivity to chemicals reflected as implantation losses were discussed above. Although this relative insensitivity of laboratory animals may have contributed to overall databases for individual chemicals, other end points proved to be more sensitive indicators of toxicity. This, in turn, accounts for fewer ATSDR's MRLs and EPA's RfCs and RfDs based on reproductive effects. Nevertheless, careful evaluation of the whole database for each chemical, enabled ATSDR to derive several MRLs on the basis of reproductive and endocrine effects. The MRLs were based on solid scientific information and current methodology for risk assessment of noncancer end points. They are subject to change if new information becomes available (ATSDR, 1996, 2003a,b; EPA, 1998).

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