Six-Year Review

Chemical Contaminants

Health Effects Technical Support Document

Office of Water
Office of Science and Technology
EPA 822-R-03-008
June 2003

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United States Environmental Protection Agency
Office of Water
Office of Science and Technology
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Abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark dose
bw	Body weight
CCRIS	Chemical Carcinogenesis Research Information System
DART	Developmental and Reproductive Toxicology
DEHA	Di(2-ethylhexyl)adipate
EC	European Commission
EPA	U.S. Environmental Protection Agency
FQPA	Food Quality Protection Act
HSDB	Hazardous Substances Data Bank
I	Daily drinking water intake
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
kg	Kilogram
LOAEL	Lowest-observed-adverse-effect level
MCL	Maximum contaminant level
MCLG	Maximum contaminant level goal
MF	Modifying factor
MFL	Million fibers per liter
mg	Milligram
MRL	Minimal risk level
NA	Not available
NAS	National Academy of Sciences
NDWAC	National Drinking Water Advisory Council
NIEHS	National Institute of Environmental Health Sciences
NOAEL	No-observed-adverse-effect level
NPDWR	National Primary Drinking Water Regulation
NTP	National Toxicology Program
OPP	Office of Pesticide Programs
OST	Office of Science and Technology
OW	Office of Water
RfD	Reference dose
RSC	Relative source contribution
SDWA	Safe Drinking Water Act
TT	Treatment technology
UF	Uncertainty factor
UL	Tolerable upper intake level
WHO	World Health Organization

1. INTRODUCTION

The Environmental Protection Agency (EPA) has developed a *Protocol for the Review of Existing National Primary Drinking Water Regulations* (USEPA, 2003a) based on recommendations of the National Drinking Water Advisory Council (NDWAC, 2000), through consultations with stakeholders representing a wide variety of interest groups, and internal Agency deliberations. The Protocol outlines the approach to be used to review and identify national primary drinking water regulations (NPDWRs) that warrant revision to maintain, or provide for greater, public health protection. The key elements of the review process are health effects, analytical and treatment technology, other regulatory revisions (e.g., monitoring and reporting requirements), occurrence and exposure analysis and, as appropriate, economic considerations.

The purpose of the health effects component of the review process is to identify, within the limitations of the Agency's available resources, new health risk assessments that indicate possible change to the maximum contaminant level goal (MCLG) and, perhaps, to the maximum contaminant level (MCL).

A total of 68 regulated chemical contaminants are being considered during this first Six-Year Review cycle. These are inorganic and organic contaminants regulated prior to the Safe Drinking Water Act (SDWA) 1996 Amendments, except arsenic, radionuclides, disinfectant residuals, and disinfection by-products, which are being or have already been reviewed in separate actions.

2. MAXIMUM CONTAMINANT LEVEL GOAL

Because the identification of contaminants for potential revision based on health effects is dependent on whether or not the MCLG could change, a brief explanation of the derivation of the MCLG is warranted. The MCLG is the maximum level of a contaminant in drinking water at which no known or anticipated adverse health effects occur, allowing for an adequate margin of safety. MCLGs are non-enforceable health goals. EPA establishes the MCL based on the MCLG. The MCL is the maximum permissible level of a contaminant in water that is delivered to any user of a public water system. Prior to the 1996 Amendments to the SDWA, the MCL was set as close to the MCLG as was feasible. The 1996 Amendments to the SDWA permit consideration of costs and benefits in establishing an MCL. MCLs are enforceable standards.

2.1. Reference Dose

For chemicals exhibiting a threshold for toxic effects, EPA establishes the MCLG on the basis of an oral reference dose (RfD). A change in the RfD could lead to a change in the MCLG and thus in the MCL. The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The RfD is derived as follows:

$$\text{RfD (mg/kg/day)} = \frac{\text{NOAEL or LOAEL or BMD}}{\text{UF} \times \text{MF}}$$

where:

NOAEL	=	no-observed-adverse-effect level (mg/kg/day)
LOAEL	=	lowest-observed-adverse-effect level (mg/kg/day)
BMD	=	benchmark dose (mg/kg/day)
UF	=	uncertainty factor
MF	=	modifying factor

The UF is used to account for the extrapolation uncertainties (e.g., interindividual variation, interspecies differences, duration of exposure, use of a LOAEL in place of a NOAEL), and database adequacy. The MF is used as a judgment factor to account for the confidence in the critical study (or studies) used in the derivation of the RfD (USEPA, 2000).

The MCLG is then derived from the RfD as follows:

$$\text{MCLG (mg/liter)} = \frac{\text{RfD} \times \text{bw} \times \text{RSC}}{\text{I}}$$

where:

bw	=	body weight (70 kg for adults, 10 kg for children, 4 kg for infants);
RSC	=	relative source contribution, the fraction of the RfD allocated to drinking water (to take into account exposure from other sources);
I	=	daily drinking water intake (2 liters for adults, 1 liter for children, 0.64 liter for infants).

EPA generally assumes that the relative source contribution from drinking water is 20 percent of the RfD, unless other exposure data for the chemical are available. This allows 80 percent of the total exposure to come from sources other than drinking water, such as exposure from food, inhalation, or dermal contact. The RSC is one factor that will determine whether or not a change in the RfD will lead to a change in the MCLG.

It has also been the Agency policy to apply an additional safety factor to the RfD for chemicals with limited evidence of carcinogenicity (Section 2.2). This practice is another factor that must be evaluated to determine the impact of a change in RfD on the MCLG.

2.2. Assessment of Carcinogenicity

For drinking water contaminants regulated prior to the 1996 SDWA, OW followed a three-category regulatory cancer classification system (Categories I, II, or III). These categories specify decisions as to degree of concern for an agent's carcinogenic potential as a contaminant of drinking water, and define to some extent the approach to risk management that is taken for establishing MCLGs. Categories I, II, and III are designations not defined in guidelines but that reflect Office of Water (OW) policy.

EPA also used the six alphanumeric categories (A, B1, B2, C, D, E) of the 1986 cancer guidelines (USEPA, 1986) in establishing the MCLG. The six-group classification system is often equated to the three-category system in the NPDWR Federal Register announcements. Table 1 describes the three categories and, with few exceptions (e.g., beryllium), their usual

equivalent alphanumeric classification. If a chemical is a known or probable human carcinogen (Category I, generally Group A or B), the MCLG is generally set at zero because it is assumed, in the absence of other data, that there is no known threshold for carcinogenicity. If a chemical falls in Group C, a RfD approach along with an additional safety factor is used in deriving the MCLG. The methodology used for establishing MCLGs for chemicals with varying degrees of evidence of carcinogenicity is briefly described in Table 1.

Recent Agency assessments also use the 1996 Proposed Guidelines for Carcinogen Risk Assessment (USEPA, 1996) or the draft revised Guidelines for Carcinogen Risk Assessment (USEPA, 1999). The proposed and revised Guidelines use standard descriptors as part of the hazard narrative to express the weight of evidence for carcinogenic hazard potential. These hazard descriptors are given in the text whenever appropriate.

3. IDENTIFYING CANDIDATES FOR POSSIBLE REGULATORY REVISION

EPA will identify regulated chemical contaminants for which there have been changes in the RfD and/or in cancer risk assessment from oral exposure. Such changes could result in a change in the MCLG and MCL. Chemicals thus identified are potential candidates for regulatory revision.

Health risk assessments completed under the following programs will be examined:

- EPA Integrated Risk Information System (IRIS)
- EPA Office of Pesticide Programs (OPP)
- National Academy of Sciences (NAS)
- Agency for Toxic Substances and Disease Registry (ATSDR)

Table 2 lists the 68 chemicals included in the Six-Year Review process, the RfDs and cancer groups on which the MCLGs are based, those established by IRIS and OPP, and assessment dates. The uses of certain pesticides are currently "banned" or "severely restricted." These pesticides are indicated as "canceled" under OPP columns. Updated risk assessments of canceled pesticides are usually done by EPA's offices other than OPP. IRIS dates are difficult to determine with any precision because of numerous sequential revisions described in the "Revision History" for each substance. Dates of IRIS assessments are approximate and refer to the most recent year when significant revisions were made to the RfD or cancer assessment. Risk assessments conducted by IRIS and OPP can be found at www.epa.gov/iris/index.html and www.epa.gov/pesticides/reregistration/status.htm, respectively.

IRIS and OPP do not use the three-category approach for cancer hazard characterization, but use the 1986 Guidelines for carcinogen risk assessment and, recently, the 1996 and 1999 proposed cancer Guidelines (USEPA, 1986; USEPA, 1996; USEPA, 1999). For easy comparison, Categories I, II, and III on which the MCLGs are based have been replaced by the equivalent cancer groups of the 1986 cancer guidelines (Table 1). If the oral and inhalation cancer groups differ, the cancer groups given in Table 2 are those for oral exposure. Whenever appropriate, the cancer hazard descriptors of the 1996 or 1999 proposed cancer Guidelines are also given in Table 2.

As indicated in Table 2, NAS established in 1997 a tolerable upper intake level (UL) for fluoride of 10 mg/day for children older than eight years and for adults, based on protection against skeletal fluorosis (NAS, 1997). The 1997 NAS evaluation of fluoride does not have an impact on the MCLG. In addition, recent assessments of copper and selenium by NAS (NAS, 2000a; NAS, 2000b) do not have an impact on the MCLGs for these two chemicals.

ATSDR establishes oral minimal risk levels (MRLs) for non-neoplastic endpoints for acute, intermediate, and chronic exposure durations. MRLs for oral chronic exposure are similar to EPA's RfDs. The chronic MRL for cadmium of 1999 is the only one among the chemicals under consideration that is more recent than and different from the RfD established in 1991. As such, cadmium would qualify for possible revision. However, a new IRIS assessment of cadmium is due in 2003 or 2004 (Table 3). Further review and revision of cadmium is therefore not appropriate until completion of the Agency's ongoing assessment. In summary, ATSDR completed assessments do not have an impact on the selection of chemicals for potential revision during this first Six-Year Review cycle.

Nine chemicals given in bold in Table 2 potentially qualify for revision, because of different RfD and/or cancer assessments postdating the MCLG. These are alachlor, beryllium, chromium, 1,1-dichloroethylene, diquat, glyphosate, lindane, oxamyl and picloram. However, as of December 31, 2002, updated assessments for alachlor (IRIS), diquat (OPP), and glyphosate (IRIS) are expected in 2003 or 2004 (Table 3). In addition, the National Toxicology Program has initiated subchronic and chronic toxicity studies for hexavalent chromium (NTP, 2002). Therefore, further review and assessment of these four chemicals is not appropriate until completion of the Agency's ongoing assessments, and NTP studies. The remaining five chemicals are potential candidates for revision and are listed below together with the latest assessment date.

Beryllium (IRIS 1998)	Oxamyl (OPP 2000)
1,1-Dichloroethylene (IRIS 2002)	Picloram (OPP 1998)
Lindane (OPP 2002)	

This tentative identification of chemicals potentially qualifying for revision was conducted independently of other considerations (e.g., analytical and treatment technology, occurrence data), which may influence the final selection of contaminants to be revised.

For some chemicals with an MCLG of zero (chlordane, vinyl chloride), a change in RfD postdating the regulation occurred in 1998 or later without a change in cancer group. These chemicals do not potentially qualify for revision because, following Agency policy, the MCLG for these chemicals will remain at zero, irrespective of any change in RfD.

4. NOMINATION OF CHEMICALS FOR NEW RISK ASSESSMENT

In order to identify chemicals for which current risk assessments need updating, the Office of Science and Technology conducted a full toxicological literature search, including developmental and reproductive toxicity, for a number of chemicals with current risk assessments conducted prior to 1997. The toxicological literature search included at a minimum the following databases: TOXLINE, MEDLINE, Developmental and Reproductive Toxicology (DART), Chemical Carcinogenesis Research Information System (CCRIS), NTP, and Hazardous

Substances Data Bank (HSDB). In addition, recent risk assessments conducted by several national and international institutions were also examined for toxicological information. These organizations/institutions included the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), the European Commission, Health Canada, California Environmental Protection Agency, ATSDR, NAS and NIEHS.

4.1. Priority Chemicals of Potential Reproductive/Developmental Concern

With the passage of the 1996 SDWA Amendments and FQPA of 1996, a concerted effort was made by EPA to take into account reproductive and developmental effects, and effects of chemicals on sensitive subpopulations. However, contaminants under consideration in this first Six-Year Review cycle were regulated in 1992 or earlier and might not have received adequate scrutiny for reproductive and developmental effects. Accordingly, a literature search was conducted by EPA's Office of Science and Technology (OST) to identify contaminants for which developmental and/or reproductive effects might now appear to be the critical effects[1]. Contaminants thus identified will be nominated as high priority for new Agency assessments.

New assessments by IRIS or OPP are ongoing for several chemicals included in this first Six-Year Review cycle. Any reproductive or developmental effects of these chemicals will be taken fully into consideration as part of these new assessments. Therefore, a literature search for reproductive/developmental effects was not considered useful for the 31 chemicals listed below with ongoing IRIS (USEPA, 2002; USEPA, 2003b) or OPP assessments, as of December 31, 2002. Expected completion years of these assessments are indicated below. If, upon completion of these new assessments, it is determined that there is a potential impact on the MCLG, the chemicals in question will be considered candidates for possible revision in the next Six-Year Review cycle, unless a compelling reason exists to accelerate the review of that NPDWR.

[1] Critical effect is defined as the biologically significant adverse effect expected to occur at the lowest dose.

Acrylamide (IRIS, 2003/2004)
Alachlor (IRIS, 2003/2004)
Antimony (IRIS, 2003/2004)
Asbestos (IRIS, 2005)
Atrazine (OPP, 2003) *
Benzo[a]pyrene (IRIS, 2003/2004)
Cadmium (IRIS, 2003/2004)
Carbofuran (OPP, 2003/2004)
Carbon tetrachloride (IRIS, 2003/2004)
Copper (IRIS, 2003/2004)
2,4-D (OPP, 2004)
Di(2-ethylhexyl)phthalate (IRIS, 2003/2004)
1,2-Dichlorobenzene (IRIS, 2003/2004)
1,4-Dichlorobenzene (IRIS, 2003/2004)
1,2-Dichloroethane (IRIS, 2003/2004)
Diquat (OPP, 2003)
Endothall (OPP, 2003/2004)
Ethylbenzene (IRIS, 2003/2004)
Ethylene dibromide (IRIS, 2003/2004)
Glyphosate (IRIS, 2003/2004)
Methoxychlor (OPP, 2003)
Pentachlorophenol (IRIS, 2003/2004)
Polychlorinated biphenyls (IRIS, 2003/2004)
Simazine (OPP, 2003/2004)
Styrene (IRIS, 2003/2004)
2,3,7,8-TCDD (IRIS, 2003/2004)
Tetrachloroethylene (IRIS, 2003/2004)
Toluene (IRIS, 2003/2004)
1,1,1-Trichloroethane (IRIS, 2003/2004)
Trichloroethylene (IRIS, 2003/2004)
Xylenes (IRIS, 2003/2004)

* Amended OPP Interim Reregistration Eligibility Decision (IRED) scheduled for release October 2003

Twelve chemicals are not under review by IRIS or OPP but have an MCLG of zero. These are listed below, together with the year of the most recent Agency cancer assessments (see also Table 2).

Benzene (00)
Chlordane (98)
1,2-Dibromo-3-chloropropane (91)
Dichloromethane (92)
1,2-Dichloropropane (91)
Epichlorohydrin (92)
Heptachlor (92)
Heptachlor epoxide (92)
Hexachlorobenzene (92)
Lead (91)
Toxaphene (91)
Vinyl chloride (00)

For these chemicals, an MCLG of zero will remain at zero, irrespective of new information on reproductive or developmental effects, unless new information indicates that the dose-response relationship for tumorigenesis is nonlinear. EPA reviewed recent IRIS, ATSDR and IARC carcinogenicity assessments for these 12 chemicals to determine whether these assessments may now indicate a mode of action that implies nonlinearity of the dose-response, in which case an MCLG of zero would no longer be appropriate and might be based instead on threshold effects such as reproductive or developmental effects. EPA did not find any data to support such a nonlinear mode of action (IARC, 1999; IARC, 2001; ATSDR, 1999). Therefore, revision of the MCLG of zero for these 12 chemicals is not appropriate at this time.

Information on potential reproductive and developmental effects for chemicals with MCLGs of zero may have an impact on risk management strategies, such as monitoring frequency, to control peak occurrence. This aspect of the assessment will be considered during subsequent Six-Year Review cycles, in conjunction with available occurrence data, to determine whether changes in risk management strategies might provide for better public health protection.

For chemicals with nonzero MCLGs, evaluation of the literature search for reproductive and developmental effects was not considered necessary if new Agency assessments were finalized in 1997 or later. These assessments are recent enough to have considered reproductive and developmental toxicity as a part of the evaluation. Agency assessments finalized in 1997 or later are available for nine chemicals. These are barium (1998), beryllium (1998), chromium

(1998), 1,1-dichloroethylene (2002), hexachlorocyclopentadiene (2001), lindane (2002), inorganic mercury (1997), oxamyl (2000), and picloram (1998).

The literature search for reproductive and developmental effects for the remaining 16 chemicals listed in Table 4 was evaluated. For various reasons briefly described in Table 4, RfDs for three chemicals—cyanide, di(2-ethylhexyl)adipate, thallium—could be affected by new information on developmental and/or reproductive toxicity. The small number of chemicals thus identified is not surprising, as EPA's selection of contaminants for new IRIS or OPP assessment is biased toward chemicals for which there is an indication that reproductive or developmental effects may be of concern. In conclusion, three chemicals are high priority and, at the request of OST, new IRIS risk assessments have been initiated for these chemicals. The new risk assessments are expected to be completed in the 2005 time frame for cyanide, 2003/2004 for di(2-ethylhexyl)adipate, and 2005 for thallium (USEPA, 2003b).

4.2. Other Nominations for New Risk Assessment

As described above, the literature search for reproductive and developmental effects for 16 chemicals was evaluated. Three of these chemicals were identified as of potential reproductive or developmental concern, and IRIS risk assessments were initiated in 2002. It was considered desirable to determine, through a literature search for all other toxicological endpoints, if new health effects information had become available for any of the remaining 13 chemicals, in which case the chemical would be nominated for a new assessment.

Of the 13 chemicals under consideration, NAS conducted a recent assessment of selenium and no new information was identified which may have an impact on the current MCLG (NAS, 2000b). Therefore, selenium was eliminated from further consideration and a toxicological literature search was conducted by OST for the remaining 12 chemicals. These are:

Dalapon	Endrin	Nitrite
cis-1,2-Dichloroethylene	Fluoride	2,4,5-TP (Silvex)
trans-1,2-Dichloroethylene	Monochlorobenzene	1,2,4-Trichlorobenzene
Dinoseb	Nitrate	1,1,2-Trichloroethane

There is new information on the effects of fluoride on bone and on the contribution of various sources to total fluoride exposure (dental health products, water, food, beverages) (WHO, 2002). At the request of EPA, NAS has agreed to review the toxicological data on fluoride for all toxicological endpoints, including effects on bone. NAS will also examine the data on relative fluoride exposure from drinking water compared to fluoride exposure from the diet and fluoride-containing dental products. It is anticipated that the NAS review will be completed in 2004.

No new information was found for any of the remaining chemicals that could have an impact on the MCLG. Accordingly, and for the time being, these contaminants will not be nominated for new IRIS assessments.

Because of considerable stakeholder interest in nitrate and nitrite, a more detailed rationale for not considering these two chemicals as potential candidates for new IRIS assessments is provided here. At the request of EPA, NAS evaluated the 1991 MCLGs and MCLs for nitrate and nitrite. NAS evaluated the epidemiological and toxicological studies available for these

chemicals and concluded that EPA's current MCLGs and MCLs for nitrate and nitrite are adequate to protect human health. NAS also concluded that exposure to nitrate/nitrite concentrations found in drinking water in the United States is unlikely to contribute to human cancer risk (NAS, 1995). In 1997, California established Public Health Goals for nitrate and nitrite in drinking water identical to EPA's MCLGs and concluded that recent epidemiological studies do not support an association between nitrate and nitrite exposure from drinking water and increased cancer rates in humans (Cal/EPA, 1997). More recently, the World Health Organization (WHO) evaluated nitrate and nitrite and established the same "guideline values" for these two chemicals as EPA's MCLGs, to protect against methemoglobinemia in bottle-fed infants below three months of age, the most susceptible segment of the population. WHO also concluded that there is no evidence for an association between nitrite and nitrate exposure in humans and the risk of cancer (WHO, 1998).

A number of studies on nitrate and nitrite have become available since WHO's assessment of 1998. Some of these studies that could possibly have an impact on the MCLGs are discussed here. In an epidemiological study in Iowa, Weyer et al. (2001) found a positive relationship between nitrate levels in drinking water and risk of bladder and ovarian cancers, and an inverse relationship for cancer of the uterine corpus and rectum. The authors recognized that additional studies were needed before confirming these trends. Several limitations of the study were also pointed out by the authors, including lack of information on individual water consumption and poor characterization of the magnitude of exposure to nitrate, relatively small sample size for bladder cancer, lack of information on occurrence of bladder infections, lack of information on concomitant exposure to other contaminants in drinking water, including disinfection by-products. No clear and consistent associations were found between increasing nitrate in drinking water and non-Hodgkin's lymphoma, leukemia, or cancers of the colon, breast, lung, pancreas, or kidney (Weyer et al., 2001). Other epidemiological studies of nitrate and/or nitrite and non-Hodgkin's lymphoma (Ward et al., 1996), gastric, esophageal or brain cancer (Van Loon et al., 1998, Barrett et al., 1998) are also inconclusive. Several epidemiological studies of maternal ingestion of nitrate in drinking water failed to confirm an association between nitrate exposure and developmental effects in offspring (e.g., Croen et al., 1997).

There are differing views on the role of nitrate/nitrite versus gastrointestinal infections as the cause of infant methemoglobinemia (Avery, 1999; Knobeloch et al., 2000). It is recognized that bottle-fed infants have a high probability of developing gastrointestinal infections because of their low gastric acidity. It is also recognized that gastrointestinal infections and low acidity enhance the conversion of nitrate to nitrite and methemoglobin formation in infants. This is an additional reason for considering these infants as a high-risk group for developing methemoglobinemia from exposure to nitrate/nitrite (WHO, 1998).

NTP carried out toxicology and carcinogenesis studies of sodium nitrite (NTP, 2001). There was no evidence of carcinogenic activity of sodium nitrite in male or female rats, nor in male mice. There was equivocal evidence of carcinogenic activity in female mice based on a positive trend in the incidences of squamous cell papilloma or carcinoma (combined) of the forestomach. Given these conclusions, a change in the cancer assessment of nitrite is not warranted at this time.

The outcome of the review of nitrate and nitrite indicates that the basis of the current MCLGs for these two chemicals remain appropriate and, therefore, nitrate and nitrite are not nominated for new IRIS assessments at this time.

5. SUMMARY

Five chemicals have been identified as potentially qualifying for revision on the basis of new IRIS or OPP health assessments that could impact the MCLG. These are beryllium, 1,1-dichloroethylene, lindane, oxamyl, and picloram. This tentative identification of chemicals potentially qualifying for revision was conducted independently of other considerations (e.g., analytical and treatment technology, occurrence data), which may influence the final selection of contaminants to be revised.

Three chemicals - cyanide, di(2-ethylhexyl)adipate and thallium - are high priority for reevaluation because of reproductive and/or developmental concerns. New IRIS risk assessments of these chemicals have been initiated. The new risk assessments are expected to be completed in the 2004/2005 time frame for cyanide, 2003/2004 for di(2-ethylhexyl)adipate, and 2004/2005 for thallium (USEPA, 2003b).

New data have become available regarding the effect of fluoride on bone, and the contribution of various sources to total fluoride exposure (WHO, 2002). At the request of EPA, NAS has initiated a review of the toxicological data on fluoride, including effect on bone, as well as the relative contribution of various sources to the overall exposure to fluoride.

Hexavalent chromium is under study by the National Toxicology Program (NTP, 2002). Once the subchronic and chronic studies are completed, the Agency will evaluate the toxicological data with regard to their impact on the present MCLG.

Table 5 summarizes the review process applied to each of the 68 chemicals under consideration.

Table 1. Cancer classification systems used by EPA (USEPA, 1986; USEPA, 1989; USEPA, 1992)

Three-category approach for establishing MCLGs	Corresponding five-group classification system of 1986 cancer guidelines
MCLG generally set at zero	
Category I: **Known or probable human carcinogens: Strong evidence of carcinogenicity** Sufficient human or animal evidence of carcinogenicity.	**Generally Group A or B:** **A: Human carcinogen** Sufficient evidence from epidemiological studies to support a causal association. **B: Probable human carcinogen** ***B1****:* Limited evidence of carcinogenicity from epidemiological studies. ***B2****:* Inadequate evidence or no data from epidemiological studies; sufficient evidence from animal studies.
MCLG based on the RfD with an additional safety factor of up to 10 to account for possible carcinogenicity, or is based on excess cancer risk range of 10^{-5} to 10^{-6}	
Category II: **Limited evidence of carcinogenicity** Some limited but insufficient evidence of carcinogenicity from animal data.	**Generally Group C:** **Possible human carcinogen** Limited evidence of carcinogenicity in animals in the absence of human data.
MCLG established using the RfD approach	
Category III: **Inadequate or no evidence of carcinogenicity in animals**	**Group D or Group E:** **D: Not classifiable as to human carcinogenicity** Inadequate human and animal evidence of carcinogenicity, or no data available. **E: Evidence of non-carcinogenicity for humans** No evidence of carcinogenicity in two different animal species, or in both epidemiological and animal studies.

Table 2. Chemicals considered under the first Six-Year Review cycle
(New RfD and/or cancer assessment have become available for nine chemicals given in **bold**).

Chemical	Regulation (month/year)				IRIS (year)		OPP (month/year)	
	MCLG mg/L	***MCL mg/L***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***
1. Acrylamide	0 (1/91)	TT	0.0002	B2	0.0002 (91)	B2 (91)		
2. Alachlor	**0 (1/91)**	**0.002**	**0.01**	**B2**	**0.01 (93)**	**NA**	**0.01 (9/98)**	**— [1] (9/98)**
3. Antimony	0.006 (7/92)	0.006	0.0004	D	0.0004 (91)	NA		
4. Asbestos (fibers > 10 μm in length)	7 MFL (1/91)	7 MFL	—	C [2]	NA	— [3] (88)		
5. Atrazine	0.003 (1/91)	0.003 (1/91)	0.005	C	0.035 (93)	NA		
6. Barium	2 (7/91)	2	0.07	D	0.07 (98)	D[4] (98)		
7. Benzene	0 (7/87)	0.005	—	A	0.004	A [5] (00)		
8. Benzo[a]pyrene	0 (7/92)	0.0002	—	B2	NA	B2 (92)		

[1] Under the 1996 proposed cancer guidelines, alachlor is characterized as likely to be carcinogenic to humans at high doses, but not likely at low doses.

[2] Asbestos: Group C based on limited evidence of carcinogenicity by the oral route; Group A by inhalation exposure (USEPA, 1989).

[3] Asbestos: Limited animal evidence for carcinogenicity via ingestion, and epidemiologic data in this regard are inadequate. Group A by inhalation exposure.

[4] Under the 1996 proposed cancer guidelines, barium is characterized as not likely to be carcinogenic to humans following oral exposure.

[5] Under the 1996 proposed cancer guidelines, benzene is characterized as a known human carcinogen for all routes of exposure.

Table 2 (continued)

Chemical	Regulation (month/year)				IRIS (year)		OPP (month/year)	
	MCLG mg/L	***MCL mg/L***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***
9. Beryllium	**0.004 (7/92)**	**0.004**	**0.005**	**B2** [6]	**0.002 (98)**	**B1** [7] **(98)**		
10. Cadmium	0.005 (1/91)	0.005	0.0005	D	0.0005 (91)	— [8] (91)		
11. Carbofuran	0.04 (1/91)	0.04	0.005	E	0.005 (87)	NA		
12. Carbon tetrachloride	0 (7/87)	0.005	0.0007	B2	0.0007 (91)	B2 (91)		
13. Chlordane	0 (1/91)	0.002	0.00006	B2	0.0005 (98)	B2 [9] (98)	Canceled	
14. Chromium (total)	**0.1 (1/91)**	**0.1**	**0.005**	**D**				
Cr (VI)					**0.003 (98)**	**D** [10] **(98)**		
Cr (III)					**1.5 (98)**	**D** [11] **(98)**		

[6] EPA classified beryllium in Group B2, probable human carcinogen, based on clear evidence of its carcinogenicity via inhalation or injection in several animal species. However, EPA also placed beryllium in drinking water Category II for regulation (limited evidence of carcinogenicity considering the weight of evidence for carcinogenicity via ingestion, potency, exposure, and pharmacokinetics). The MCLG was derived using the RfD and applying an additional safety factor of 10 for possible carcinogenic potential.

[7] B1 based on inhalation exposure. Under the 1996 proposed cancer guidelines, inhaled beryllium is characterized as a likely carcinogen in humans, and the human carcinogenic potential of ingested beryllium cannot be determined.

[8] Carcinogenicity studies of cadmium administered orally to animals have shown no evidence of carcinogenic response. B1 based on inhalation exposure.

[9] Under the 1996 proposed cancer guidelines, chlordane is characterized as a likely human carcinogen by all routes of exposure.

[10] Under the 1996 proposed cancer guidelines, the oral carcinogenicity of Cr VI cannot be determined.

[11] Under the 1996 proposed cancer guidelines, there are inadequate data to determine the potential carcinogenicity of Cr III.

Table 2 (continued)

Chemical	Regulation (month/year)				IRIS (year)		OPP (month/year)	
	MCLG mg/L	***MCL mg/L***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***
15. Copper	1.3 [12] (6/91)	TT [12]	—	D	NA	D (88)		
16. Cyanide	0.2 (7/92)	0.2	0.02	D	0.02 (87)	D		
17. 2,4-D (2,4-Dichloro phenoxyacetic acid)	0.07 (1/91)	0.07	0.01	D	0.01 (87)	NA		D (7/96)
18. Dalapon (2,2-di chloropropionic acid)	0.2 (7/92)	0.2	0.03	D	0.03 (88)	NA	Canceled	
19. Di(2-ethylhexyl) adipate	0.4 (7/92)	0.4	0.6	C	0.6 (92)	C (92)		
20. Di(2-ethylhexyl) phthalate	0 (7/92)	0.006	0.02	B2	0.02 (88)	B2 (88)		
21. 1,2-Dibromo-3-chloropropane (DBCP)	0 (1/91)	0.0002	—	B2	NA (91)	NA	Canceled	
22. Dichlorobenzene o-(1,2-Dichlorobenzene)	0.6 (1/91)	0.6	0.09	D	0.09 (90)	D (90)	Canceled	
23. Dichlorobenzene p-(1,4-Dichlorobenzene)	0.075 (7/87)	0.075	0.1	C	NA (94)	NA		
24. Dichloroethane(1,2-) (Ethylene dichloride)	0 (7/87)	0.005	—	B2	NA	B2 (91)	Canceled	
25. Dichloroethylene (1,1-)	**0.007 (7/87)**	**0.007**	**0.009**	**C**	**0.046 (02)**	**C[13] (02)**		
26. Dichloroethylene (cis-1,2-)	0.07 (1/91)	0.07	0.01	D	NA	D (90)		
27. Dichloroethylene (trans-1,2-)	0.1 (1/91)	0.1	0.02	D	0.02 (88)	NA		
28. Dichloromethane (methylene chloride)	0 (7/92)	0.005	0.06	B2	0.06 (91)	B2 (91)	Canceled	
29. Dichloropropane (1,2-)	0 (1/91)	0.005	—	B2	NA (91)	NA		

[12] NAS (2000a) considered that the MCLG for copper was appropriate. Copper action level: 1.3 mg/L.

[13] Under the draft revised guidelines for carcinogen risk assessment (USEPA, 1999), the data for 1,1-DCE are *inadequate for an assessment of human carcinogenic potential* by the oral route.

Table 2 (continued)

Chemical	Regulation (month/year)				IRIS (year)		OPP (month/year)	
	MCLG mg/L	***MCL mg/L***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***
30. Dinoseb	0.007 (7/92)	0.007	0.001	D	0.001 (89)	D (89)	Canceled	
31. Diquat	**0.02 (7/92)**	**0.02**	**0.0022**	**D**	**0.0022 (87)**	**NA**	**0.005 (3/95)**	**E (3/95)**
32. Endothall	0.1 (7/92)	0.1	0.02	D	0.02 (87)	NA		
33. Endrin	0.002 (7/92)	0.002	0.0003	D	0.0003 (89)	D (89)	Canceled	
34. Epichlorohydrin	0 (1/91)	TT	NA	B2	NA	B2 (92)		
35. Ethylbenzene	0.7 (1/91)	0.7	0.1	D	0.1 (91)	D (91)		
36. Ethylene dibromide (EDB; 1,2-Dibromoeth-ane)	0 (1/91)	0.00005	—	B2	NA	B2 (91)	Canceled	
37. Fluoride [14]	4.0 (11/85)	4.0 (4/86)	0.11 [15]	—	0.06[16] 0.12[17] (87)	NA		
38. Glyphosate	**0.7 (7/92)**	**0.7**	**0.1**	**D**	**0.1 (89)**	**D (89)**	**2 (9/93)**	**E (9/93)**
39. Heptachlor	0 (1/91)	0.0004	0.0005	B2	0.0005 (91)	B2 (91)	0.0005 (92)	B2 (92)
40. Heptachlor epoxide	0 (1/91)	0.0002	0.000013	B2	0.000013 (91)	B2 (91)	0.000013 (92)	B2 (92)

[14] NAS (1997) established a tolerable upper intake level (UL) for fluoride of 10 mg/day for children older than 8 years and for adults, based on protection against skeletal fluorosis. The 1997 NAS evaluation of fluoride does not affect the MCLG.

[15] This is the RfD calculated from the MCLG assuming 70kg body weight and intake of 2L/day. The MCLG was developed from a lowest effect level for crippling skeletal fluorosis of 20 mg/day with continuous exposures over a 20-year or longer period. The LOAEL was divided by an uncertainty factor of 2.5 and a drinking water intake of 2L/day to obtain the MCLG.

[16] For objectionable dental fluorosis, a cosmetic effect.

[17] For crippling skeletal fluorosis in humans.

Table 2 (continued)

Chemical	Regulation (month/year)				IRIS (year)		OPP (month/year)	
	MCLG mg/L	***MCL mg/L***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***
41. Hexachlorobenzene	0 (7/92)	0.001	0.0008	B2	0.0008 (91)	B2 (91)	Canceled	
42. Hexachlorocyclo-pentadiene	0.05 (7/92)	0.05	0.007	D	0.006 [18] (01)	— [19] (01)		
43. Lead	0 (6/91)	TT [20]	—	B2	NA	B2 (88)		
44. Lindane (γ-hexa-chlorocyclohexane)	**0.0002 (1/91)**	**0.0002**	**0.0003**	**C**	**0.0003 (88)**	**NA**	**0.0047 [21] (7/02)**	**— [22] (7/02)**
45. Mercury (Inorganic)	0.002 (1/91)	0.002	0.0003	D	0.0003 [23] (97)	— [23] (97)		
46. Methoxychlor	0.04 (1/91)	0.04	0.005	D	0.005 (90)	D (90)		
47. Monochlorobenzene (Chlorobenzene)	0.1 (1/91)	0.1	0.02	D	0.02 (90)	D (90)		
48. Nitrate (as N)	10 (1/91)	10	1.6 [24]	D	1.6 [24] (91)	NA		

[18] RfD of HCCP based on the same toxicological study as that of the MCLG but using benchmark dose modeling for the dose-response analysis.

[19] HCCP: E by inhalation exposure; the potential for carcinogenicity by the oral route is unknown.

[20] Lead action level: 0.015 mg/L.

[21] Lindane: An additional safety factor of three was applied to the RfD to take into account the evidence for increased susceptibility of the young demonstrated in developmental neurotoxicity and reproductive toxicity studies in rats, giving a population adjusted dose (PAD) of 0.0016 mg/kg/day.

[22] Under the draft revised guidelines for carcinogen risk assessment (USEPA, 1999), the data for lindane show *suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential*.

[23] Mercury Study Report to Congress assessment (USEPA, 1997): RfD for inorganic Hg of 0.0003 mg/kg/day retained. Under the 1996 proposed cancer guidelines, inorganic mercury is not likely to be a human carcinogen at levels found in water.

[24] RfDs for nitrate and nitrite, in mg N/kg/day, back-calculated from epidemiological studies on the basis of 0.64 L/day and a 4-kg infant.

Table 2 (continued)

Chemical	Regulation (month/year)				IRIS (year)		OPP (month/year)	
	MCLG mg/L	***MCL mg/L***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***
49. Nitrite (as N)	1 (1/91)	1	0.16 [24]	D	0.1[25] (87)	NA		
Nitrate + Nitrite (as N)	10 (1/91)	10	—	—	—	—		
50. Oxamyl (Vydate)	**0.2 (7/92)**	**0.2**	**0.025**	**E**	**0.025 (87)**	**NA**	**0.001 (10/00)**	**E (10/00)**
51. Pentachlorophenol	0 (1/91)	0.001	0.03	B2	0.03 (91)	B2 (91)		
52. Picloram	**0.5 (7/92)**	**0.5**	**0.07**	**D**	**0.07 (87)**	**NA**	**0.2 (4/98)**	**E (4/98)**
53. Polychlorinated biphenyls (Aroclors)	0 (1/91)	0.0005	—	B2	2 - 7 $x10^{-5}$ (96)	B2 (96)		
54. Selenium [26]	0.05 (1/91)	0.05	0.005	D	0.005 (91)	D (91)		
55. Simazine	0.004 (7/92)	0.004	0.005	C	0.005 (93)	NA		
56. Styrene	0.1 (1/91)	0.1	0.2	C	0.2 (90)	NA		
57. 2,3,7,8-TCDD (Dioxin)	0 (7/92)	$3x10^{-8}$	10^{-9}	B2				
58. Tetrachloroethylene ("perc")	0 (1/91)	0.005	0.01	B2	0.01 (88)	NA	Canceled	
59. Thallium	0.0005 (7/92)	0.002	0.00007	D	0.00008 (90)	D (90)	Canceled	
60. Toluene	1 (1/91)	1	0.2	D	0.2 (90)	D (90)		
61. Toxaphene	0 (1/91)	0.003	NA	B2	NA	B2 (91)	Canceled	

[25] RfD for nitrite, in mg N/kg/day, back-calculated from epidemiological studies on the basis of 1 L/day and a 10-kg child. It is equivalent to a RfD of 0.16 mg/kg/day if 0.64 L/day and a 4-kg infant were used.

[26] NAS (2000b) tolerable upper intake level (UL) for selenium for adolescents and adults is 0.4 mg/day, a value equivalent to the RfD of 0.005 mg/kg/day established in 1991.

Table 2 (continued)

Chemical	Regulation (month/year)				IRIS (year)		OPP (month/year)	
	MCLG mg/L	***MCL mg/L***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***	***RfD mg/kg/d***	***Cancer group***
62. 2,4,5-TP (Silvex; 2,4,5-Trichlorophenoxy propionic acid)	0.05 (1/91)	0.05	0.008	D	0.008 (88)	D (88)	Canceled	
63. Trichlorobenzene (1,2,4-)	0.07 (7/92)	0.07	0.01	D	0.01 (92)	D (91)		
64. Trichloroethane (1,1,1-)	0.20 (7/87)	0.20	0.035	D	NA (91)	D (90)		
65. Trichloroethane (1,1,2-)	0.003 (7/92)	0.005	0.004	C	0.004 (91)	C (91)	Canceled	
66. Trichloroethylene	0 (7/87)	0.005	—	B2	NA (89)	NA (89)	Canceled	
67. Vinyl chloride	0 (7/87)	0.002	—	A	0.003 (00)	A [27] (00)		
68. Xylenes (total)	10 (1/91)	10	2	D	2 (88)	D (88)		

[27] Under the 1996 proposed cancer guidelines, vinyl chloride is a known human carcinogen by the inhalation route of exposure, based on human epidemiological data, and by analogy the oral route because of positive animal bioassay data as well as pharmacokinetic data allowing dose extrapolation across routes.

Table 3. Assessment by IRIS, OPP, ATSDR, and NAS of chemicals considered under the first Six-Year Review cycle

Chemical, Year Regulated	*90/91*	*92/93*	*94/95*	*96*	*97*	*98*	*99*	*00*	*01*	*02*	*≥03*
Acrylamide ’91	IRIS										IRIS
Alachlor ’91		IRIS				OPP					IRIS
Antimony ’92	IRIS	ATSDR									IRIS
Asbestos ’91									ATSDR		IRIS
Atrazine ’91		IRIS									OPP ATSDR
Barium ’91		ATSDR				IRIS					
Benzene ’87					ATSDR			IRIS			
Benzo[a]pyrene ’92		IRIS	ATSDR								IRIS
Beryllium ’92						IRIS				ATSDR	
Cadmium ’91	IRIS						ATSDR				IRIS
Carbofuran ’91											OPP
Carbon tetrachloride ’87	IRIS		ATSDR								IRIS
Chlordane ’91			ATSDR			IRIS					
Chromium ’91						IRIS		ATSDR		NTP [1]	
Copper ‘91								NAS			ATSDR IRIS
Cyanide ’92					ATSDR						IRIS

[1] Subchronic and chronic toxicological studies of Cr VI initiated by NTP.

Table 3 (continued)

Chemical, Year Regulated	*90/91*	*92/93*	*94/95*	*96*	*97*	*98*	*99*	*00*	*01*	*02*	*≥03*
2,4-D ’91											OPP
Dalapon ’92											
Di (2-ethylhexyl)adipate ’92		IRIS									IRIS
Di (2-ethylhexyl)phthalate ’92										ATSDR	IRIS
1,2-DBCP ’91	IRIS	ATSDR									
1,2-Dichlorobenzene ’91	IRIS										IRIS
1,4-Dichlorobenzene ’87			IRIS			ATSDR					IRIS
1,2-Dichloroethane ’87	IRIS								ATSDR		IRIS
1,1-Dichloroethylene ’87			ATSDR							IRIS	
cis-1,2-Dichloroethylene ’91	IRIS			ATSDR							
trans-1,2-Dichloroethylene ’91				ATSDR							
Dichloromethane ’92	IRIS							ATSDR			
1,2-Dichloropropane ’91	IRIS										
Dinoseb ’92											
Diquat ’92			OPP								OPP
Endothall ’92											OPP
Endrin ’92				ATSDR							
Epichlorohydrin ’91		IRIS									

Table 3 (continued)

Chemical, Year Regulated	*90/91*	*92/93*	*94/95*	*96*	*97*	*98*	*99*	*00*	*01*	*02*	*≥03*
Ethylbenzene ’91	IRIS							ATSDR			IRIS
Ethylene dibromide ’91	IRIS	ATSDR									IRIS
Fluoride ’86		NAS			NAS						ATSDR NAS
Glyphosate ’92		OPP									IRIS
Heptachlor ’91	IRIS	OPP ATSDR									
Heptachlor epoxide ’91	IRIS	OPP ATSDR									
Hexachlorobenzene ’92	IRIS									ATSDR	
Hexachlorocyclopentadiene ’92							ATSDR		IRIS		
Lead ’91							ATSDR				
Lindane ’91							ATSDR			OPP	
Mercury ’91 (Inorganic)			IRIS		EPA [2]		ATSDR				
Methoxychlor ’91	IRIS									ATSDR	OPP
Monochlorobenzene ’91	IRIS ATSDR										

[2] Mercury Study Report to Congress (USEPA, 1997).

Table 3 (continued)

Chemical, Year Regulated	*90/91*	*92/93*	*94/95*	*96*	*97*	*98*	*99*	*00*	*01*	*02*	*≥03*
Nitrate ’91	IRIS		NAS								
Nitrite ’91			NAS								
Oxamyl ’92								OPP			
Pentachlorophenol ’91	IRIS								ATSDR		IRIS
Picloram ’92						OPP					
PCBs ’91				IRIS				ATSDR			IRIS
Selenium ’91	IRIS							NAS			ATSDR
Simazine ’92		IRIS									OPP
Styrene ’91	IRIS	ATSDR									IRIS [3]
2,3,7,8-TCDD ’92						ATSDR					IRIS
Tetrachloroethylene ’91					ATSDR						IRIS
Thallium ’92	IRIS	ATSDR									IRIS
Toluene ’91	IRIS							ATSDR			IRIS
Toxaphene ’91	IRIS			ATSDR							
2,4,5-TP ’91											

[3] Joint IRIS/ Styrene Information and Research Council.

Table 3 (continued)

Chemical, Year Regulated	*90/91*	*92/93*	*94/95*	*96*	*97*	*98*	*99*	*00*	*01*	*02*	*≥03*
1,2,4-Trichlorobenzene ’92		IRIS									
1,1,1-Trichloroethane ’87	IRIS		ATSDR								IRIS
1,1,2-Trichloroethane ’92	IRIS										
Trichloroethylene ’87					ATSDR						IRIS
Vinyl chloride ’87					ATSDR			IRIS			
Xylenes ’91			ATSDR								IRIS

Table 4. Evaluation of the literature search for reproductive and developmental toxicity
(New IRIS assessments initiated for chemicals given in **bold**)

Chemical	*Comments*
Cyanide	Based on NTP (1993) 13-week study, ATSDR (1997) identified a NOAEL of 4.5 mg/kg/day for reproductive effects in male rats (decreases in epididymis and testis weights and reduction in spermatid head size and count). The current 1992 NPDWR RfD of 0.02 mg/kg/day is based on a NOAEL of 10.8 mg/kg/day in a 2-year study for weight loss, thyroid effects and myelin degeneration in rats. New IRIS assessment initiated.
Dalapon	Literature search performed for the Six-Year Review did not identify any information to support consideration of a revision to the RfD (and therefore the MCLG).
Di(2-ethylhexyl)adipate	Current RfD/MCLG of 1992 based on a developmental toxicity study in rats that identified a NOAEL of 170 mg/kg/day. WHO (1996) and the European Commission (EC 1999) considered the LOAEL to be 170 mg/kg/day and the NOAEL to be the next lower dose of 28 mg/kg/day. Similarly, IARC (2000) indicated effects at 170 mg/kg/day. New IRIS assessment initiated to reevaluate the available developmental and reproductive studies, and to evaluate new studies that have become available on the toxicity of DEHA and its metabolites.
cis-1,2-Dichloroethylene	Literature search performed for the Six-Year Review did not identify any information to support consideration of a revision to the RfD (and therefore the MCLG).
trans-1,2-Dichloroethylene	Literature search performed for the Six-Year Review did not identify any information to support consideration of a revision to the RfD (and therefore the MCLG).
Dinoseb	Current RfD based on three-generation reproductive study in rats. Developmental effects seen at higher doses than are reproductive effects. New information does not support need to revise RfD/MCLG.
Endrin	Reproductive and developmental effects occur at doses above those causing hepatotoxicity, the critical effect. New information does not support need to revise RfD/MCLG.
Fluoride [1]	No new studies identified in the literature search indicating that fluoride adversely affects reproductive or developmental endpoints. Epidemiological studies show no evidence of an association between the consumption of fluoridated drinking water by mothers and increased risk of spontaneous abortion or congenital malformation (WHO, 2002).
Monochlorobenzene	Literature search performed for the Six-Year Review did not identify any information to support consideration of a revision to the RfD (and therefore the MCLG).

[1] NAS assessment of fluoride initiated

Table 4 (continued)

Chemical	*Comments*
Nitrate	Current RfD/MCLG established to protect infants, the most susceptible segment of the population. Epidemiological studies of maternal nitrate exposure from drinking water and developmental effects in offspring or spontaneous abortion are inconclusive (Croen et al., 1997). Reproductive and developmental effects in experimental animals are not the critical effects. Epidemiological studies of nitrate in drinking water and cancer incidence, including non-Hodgkin's lymphoma, a childhood cancer, and bladder cancer are inconclusive (Weyer et al., 2001; Ward et al., 1996). New information does not support need to revise RfD/MCLG.
Nitrite	Current RfD/MCLG is protective of methemoglobinemia in infants, the most susceptible segment of the population. Sodium nitrite was tested in mice by NIEHS (Chapin et al., 1997) using the Reproductive Assessment by Continuous Breeding protocol; reproductive effects are not the critical effects and did not occur at doses as high as 425 mg nitrite/kg/day. New information does not support need to revise RfD/MCLG.
Selenium	NAS (2000b) assessment of Se confirms the current RfD of 1991 based on epidemiological studies of selenosis in humans. Epidemiological studies of Se deficiency and male infertility, pregnancy-induced hypertension and congenital heart disease, are inconclusive (ATSDR, 1996). In experimental animals, reproductive and developmental toxicity are not the critical effects (NTP, 1996). New information does not support need to revise RfD/MCLG.
Thallium	ATSDR (1992) identified LOAELs in rats for developmental effects (impairment of learning ability) and reproductive effects (histological alteration of testis) of 0.08 and 0.7 mg/kg/day, respectively, compared to the NOAEL of 0.2 mg/kg/day, the highest dose tested and the basis of the NPDWR. Also, the present NOAEL of 0.2 mg/kg/day is debatable: Cal/EPA (1999) considers the NOAEL to be the next lower dose tested of 0.04 mg/kg/day for changes in blood chemistry, alopecia and lacrimation in rats. Evaluation of developmental neurological effects of TI by the oral route need to be assessed. New IRIS assessment initiated.
2,4,5-TP (Silvex)	Current RfD protective of chronic liver effects would also protect against fetotoxicity and teratogenicity. New information does not support need to revise RfD/MCLG.
1,2,4-Trichlorobenzene	Current RfD based on a multigeneration reproductive study in rats. New information does not support need to revise RfD/MCLG.
1,1,2-Trichloroethane	Literature search performed for the Six-Year Review did not identify any information to support consideration of a revision to the RfD (and therefore the MCLG).

Table 5. Overall review of chemicals

Chemical	*RfD/Cancer group changed*	*Ongoing IRIS or OPP assessment*	*MCLG = 0*	*Recent (≥97) EPA assessment available*	*Evaluate Literature search for repro/develop endpoints*	*High priority, nominate for new IRIS assessment*	*Evaluate Literature search for other tox endpoints*	*Nominate for new assessment*
Acrylamide		Yes			No		No	
Alachlor	Yes	Yes			No		No	
Antimony		Yes			No		No	
Asbestos		Yes			No		No	
Atrazine		Yes			No		No	
Barium				Yes	No		No	
Benzene			Yes	Yes	No		No	
Benzo[a]pyrene		Yes			No		No	
Beryllium	Yes			Yes	No		No	
Cadmium		Yes			No		No	
Carbofuran		Yes			No		No	
Carbon tetrachloride		Yes			No		No	
Chlordane			Yes	Yes	No		No	
Chromium	Yes	NTP [1]		Yes	No		No	
Copper		Yes			No		No	

[1] Ongoing NTP subchronic and chronic toxicological studies for Cr VI (NTP, 2002).

Table 5 (continued)

Chemical	*RfD/Cancer group changed*	*Ongoing IRIS or OPP assessment*	*MCLG = 0*	*Recent (≥97) EPA assessment available*	*Evaluate Literature search for repro/develop endpoints*	*High priority, nominate for new IRIS assessment*	*Evaluate Literature search for other tox endpoints*	*Nominate for new assessment*
Cyanide					**Yes**	**Yes**	No	
2,4-D		Yes			No		No	
Dalapon					**Yes**	No	**Yes**	**No**
Di(2-ethylhexyl) adipate					**Yes**	**Yes**	No	
Di(2-ethylhexyl) phthalate		Yes			No		No	
1,2-DBCP			Yes		No		No	
1,2-Dichlorobenzene		Yes			No		No	
1,4-Dichlorobenzene		Yes			No		No	
1,2-Dichloroethane		Yes			No		No	
1,1-Dichloroethylene	Yes			Yes	No		No	
Dichloroethylene (cis-1,2-)					**Yes**	No	**Yes**	**No**
Dichloroethylene (trans-1,2-)					**Yes**	No	**Yes**	**No**
Dichloromethane			Yes		No		No	
1,2-Dichloropropane			Yes		No		No	

Table 5 (continued)

Chemical	*RfD/Cancer group changed*	*Ongoing IRIS or OPP assessment*	*MCLG = 0*	*Recent (≥97) EPA assessment available*	*Evaluate Literature search for repro/develop endpoints*	*High priority, nominate for new IRIS assessment*	*Evaluate Literature search for other tox endpoints*	*Nominate for new assessment*
Dinoseb					**Yes**	No	**Yes**	**No**
Diquat	Yes	Yes			No		No	
Endothall		Yes			No		No	
Endrin					**Yes**	No	**Yes**	**No**
Epichlorohydrin			Yes		No		No	
Ethylbenzene		Yes			No		No	
Ethylene dibromide		Yes			No		No	
Fluoride					**Yes**	No	**Yes**	**Yes (NAS)**
Glyphosate	Yes	Yes			No		No	
Heptachlor			Yes		No		No	
Heptachlor epoxide			Yes		No		No	
Hexachlorobenzene			Yes		No		No	
Hexachlorocyclopenta-diene				Yes	No		No	
Lead			Yes		No		No	
Lindane	Yes			Yes	No		No	

Table 5 (continued)

Chemical	*RfD/Cancer group changed*	*Ongoing IRIS or OPP assessment*	*MCLG = 0*	*Recent (≥97) EPA assessment available*	*Evaluate Literature search for repro/develop endpoints*	*High priority, nominate for new IRIS assessment*	*Evaluate Literature search for other tox endpoints*	*Nominate for new assessment*
Mercury (inorganic)				Yes	No		No	
Methoxychlor		Yes			No		No	
Monochlorobenzene					**Yes**	No	**Yes**	**No**
Nitrate					**Yes**	No	**Yes**	**No**
Nitrite					**Yes**	No	**Yes**	**No**
Oxamyl	Yes			Yes	No		No	
Pentachlorophenol		Yes			No		No	
Picloram	Yes			Yes	No		No	
PCBs		Yes			No		No	
Selenium					**Yes**	No	No (NAS, 2000)	
Simazine		Yes			No		No	
Styrene		Yes			No		No	
2,3,7,8-TCDD		Yes			No		No	
Tetrachloroethylene		Yes			No		No	
Thallium					**Yes**	**Yes**	No	
Toluene		Yes			No		No	

Table 5 (continued)

Chemical	*RfD/Cancer group changed*	*Ongoing IRIS or OPP assessment*	*MCLG = 0*	*Recent (≥97) EPA assessment available*	*Evaluate Literature search for repro/develop endpoints*	*High priority, nominate for new IRIS assessment*	*Evaluate Literature search for other tox endpoints*	*Nominate for new assessment*
Toxaphene			Yes		No		No	
2,4,5-TP (Silvex)					**Yes**	No	**Yes**	**No**
Trichlorobenzene (1,2,4-)					**Yes**	No	**Yes**	**No**
Trichloroethane (1,1,1-)		Yes			No		No	
Trichloroethane (1,1,2-)					**Yes**	No	**Yes**	**No**
Trichloroethylene		Yes			No		No	
Vinyl chloride			Yes	Yes	No		No	
Xylenes		Yes			No		No	

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EPA 822-R-03-008

Six-Year Review - Chemical Contaminants Health Effects Technical Support Document