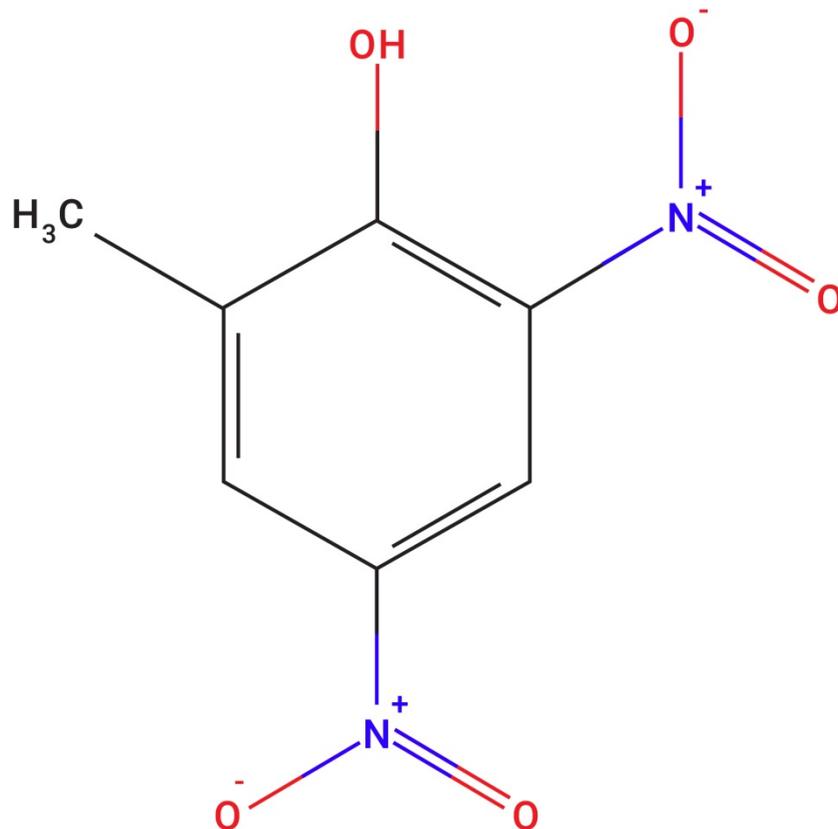


Update of Human Health Ambient Water Quality Criteria:

2-Methyl-4,6-dinitrophenol 534-52-1



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534-52-1

**Office of Science and Technology
Office of Water
U.S. Environmental Protection Agency
Washington, DC 20460**

Table of Contents

1	Introduction: Background and Scope of Update.....	2
2	Problem Formulation.....	3
3	Criteria Formulas: Analysis Plan	4
4	Exposure Factors	5
4.1	Body Weight.....	5
4.2	Drinking Water Intake.....	6
4.3	Fish Consumption Rate	6
4.4	Bioaccumulation Factor	7
4.4.1	Approach	7
4.4.2	Chemical-specific BAFs	9
5	Hazard Identification and Dose Response.....	10
5.1	Approach.....	10
5.2	Chemical-specific Toxicity Value.....	11
5.2.1	Reference Dose.....	11
5.2.2	Cancer Slope Factor.....	12
6	Relative Source Contribution.....	12
6.1	Approach.....	12
6.2	Chemical-specific RSC	14
7	Criteria Derivation: Analysis	15
7.1	AWQC for Noncarcinogenic Toxicological Effects	15
7.2	AWQC for Carcinogenic Toxicological Effects.....	16
7.3	AWQC Summary	16
8	Criteria Characterization.....	16
9	Chemical Name and Synonyms	18
10	References	20

1 Introduction: Background and Scope of Update

EPA's recommended ambient water quality criteria (AWQC) for human health are scientifically derived numeric values that EPA has determined will adequately protect human health from the adverse effects of pollutants in ambient water.

Section 304(a)(1) of the Clean Water Act (CWA) requires EPA to develop and publish, and from time to time revise, recommended criteria for the protection of water quality that accurately reflect the latest scientific knowledge. Water quality criteria developed under section 304(a) are based solely on data and scientific judgments on the relationship between pollutant concentrations and environmental and human health effects. Section 304(a) criteria do not reflect consideration of economic impacts or the technological feasibility of meeting pollutant concentrations in ambient water.

EPA's recommended section 304(a) criteria provide technical information for states and authorized tribes^a to consider and use in adopting water quality standards that ultimately provide the basis for assessing water body health and controlling discharges of pollutants into waters of the United States. Under the CWA and its implementing regulations, states and authorized tribes are required to adopt water quality criteria to protect the designated uses of waters (e.g., public water supply, aquatic life, recreational use, industrial use). EPA's recommended water quality criteria do not substitute for the CWA or regulations, nor are they regulations themselves. Thus, EPA's recommended criteria do not impose legally binding requirements. States and authorized tribes may adopt, where appropriate, other scientifically defensible water quality criteria that differ from these recommendations.

The water quality criteria that are the subject of this document are national AWQC recommendations for human health issued under CWA section 304(a). Unless expressly indicated otherwise, all references to "criteria," "water quality criteria," "ambient water quality criteria recommendations," or similar variants thereof are references to national AWQC recommendations for human health.

In this 2015 update, EPA has revised the human health criteria for 2-methyl-4,6-dinitrophenol to reflect the latest scientific information, including updated exposure factors (body weight [BW], drinking water intake [DI] rate, and fish consumption rate [FCR]), bioaccumulation factors (BAFs), and human health toxicity values (reference dose [RfD] multiplied by relative source contribution [RSC] or 10^{-6} divided by cancer slope factor [CSF]). The criteria continue to be based on EPA's *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health*, which is referred to as the "2000 Methodology" in this document (USEPA 2000a). EPA accepted written scientific views from the public on the draft updated human health criteria for this chemical (and 93 others) from May through August 2014.

^a Throughout this document, the term *states* means the 50 states, the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, Guam, American Samoa, and the Commonwealth of the Northern Mariana Islands. The term *authorized tribe* or *tribe* means an Indian tribe authorized for treatment in a manner similar to a state under CWA section 518 for the purposes of section 303(c) water quality standards.

It is important for states and authorized tribes to consider any new or updated section 304(a) recommended criteria as part of their triennial review process to ensure that state or tribal water quality standards reflect current science and protect applicable designated uses. These final 2015 updated section 304(a) human health criteria recommendations supersede EPA's previous recommendations.

2 Problem Formulation

Problem formulation provides a strategic framework for water quality criteria development by focusing on the most relevant endpoints and increasing the transparency of the effects assessment. The structure of this criteria document is intended to be consistent with general concepts of effects assessments as described in EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* (USEPA 2014a).

In developing AWQC, EPA currently follows the assessment method outlined in its 2000 Methodology (USEPA 2000a). The 2000 Methodology describes different approaches for addressing water and non-water exposure pathways to derive human health AWQC depending on the toxicological endpoint of concern, the toxicological effect (noncarcinogenic or carcinogenic), and whether toxicity is considered a linear or threshold effect. Water sources of exposure include both consuming drinking water and eating fish or shellfish from inland and nearshore waters that have been exposed to pollutants in the water body. For pollutants that exhibit a threshold of exposure before deleterious effects occur, as is the case for noncarcinogens and nonlinear carcinogens, EPA applies an RSC to account for other potential human exposures to the pollutant (USEPA 2000a). Other sources of exposure might include, but are not limited to, exposure to a particular pollutant from ocean fish or shellfish consumption (which is not included in the FCR), non-fish food consumption (e.g., consumption of fruits, vegetables, grains, meats, or poultry), dermal exposure, and inhalation exposure.

For substances for which the toxicity endpoint is carcinogenicity based on a linear low-dose extrapolation, only the exposures from drinking water and fish ingestion are reflected in human health AWQC; that is, non-water sources are not explicitly included and no RSC is applied (USEPA 2000a). In these situations, AWQC are derived with respect to the *incremental* lifetime cancer risk posed by the presence of a substance in water, rather than an individual's total risk from all sources of exposure. The resulting criterion represents the water concentration that is expected to increase an individual's lifetime risk of cancer from exposure to the particular pollutant by no more than one chance in one million for the general population. EPA calculates AWQC at a 10^{-6} (one in one million) cancer risk level for the general population (USEPA 2000a). The 2000 Methodology recommends that states set human health criteria cancer risk levels for the target general population at either 10^{-5} or 10^{-6} and also notes that states and authorized tribes can choose a more stringent risk level, such as 10^{-7} .

For substances that are carcinogenic, EPA takes an integrated approach and considers both cancer and noncancer effects when deriving AWQC (USEPA 2000a; USEPA 2000b). Where sufficient data are available, EPA derives AWQC using both carcinogenic and noncarcinogenic toxicity endpoints and recommends the lower value for the AWQC. The AWQC might not utilize

the value obtained from the cancer analysis if it is less protective than that derived from the noncancer endpoint.

3 Criteria Formulas: Analysis Plan

Human health AWQC for toxic pollutants are necessary to protect any designated uses related to ingestion of water and ingestion of aquatic organisms. These uses can include, but are not limited to, recreation in and on the water, consumption of fish or shellfish (including consumption associated with fishing or shellfish harvesting), and protection of drinking water supplies.

The derivation of human health AWQC requires information about both the toxicological endpoints of concern for water pollutants and the pathways of human exposure to those pollutants. EPA considers the following two primary pathways of human exposure to pollutants present in a particular water body when deriving human health 304(a) AWQC: (1) direct ingestion of drinking water obtained from the water body and (2) consumption of fish or shellfish obtained from the water body.

The equations for deriving human health AWQC for noncarcinogenic effects and carcinogenic effects are presented as Eqs. 1 and 2. EPA derives recommended human health AWQC based on the consumption of both water and aquatic organisms (Eq. 1) and based on the consumption of aquatic organisms alone (Eq. 2). The use of one criterion over the other depends on the designated use of a particular water body or water bodies (i.e., drinking water source and/or fishable waters). EPA recommends applying organism-only AWQC (Eq. 2) to a water body where the designated use includes supporting fishable uses under section 101(a) of the CWA but the water body is not a drinking water supply source (e.g., non-potable estuarine waters that support fish or shellfish for human consumption) (USEPA 2000a).

EPA recommends including the drinking water exposure pathway for ambient surface waters where drinking water is a designated use for the following reasons: (1) drinking water is a designated use for surface waters under the CWA, and therefore criteria are needed to ensure that this designated use can be protected and maintained; (2) although they are rare, some public water supplies provide drinking water from surface water sources without treatment; (3) even among the majority of water supplies that do treat surface waters, existing treatments might not be effective for reducing levels of particular contaminants; and (4) in consideration of the Agency's goals of pollution prevention, ambient waters should not be contaminated to a level where the burden of achieving health objectives is shifted away from those responsible for pollutant discharges and placed on downstream users that must bear the costs of upgraded or supplemental water treatment (USEPA 2000a).

The equations for deriving the criteria values are as follows (USEPA 2000a):

For consumption of water and organisms:

$$\text{AWQC } (\mu\text{g/L}) = \frac{\text{toxicity value (mg/kg-d)} \times \text{BW (kg)} \times 1,000 (\mu\text{g/mg})^b}{\text{DI (L/d)} + \sum_{i=2}^4 (\text{FCR}_i \text{ (kg/d)} \times \text{BAF}_i \text{ (L/kg)})} \quad (\text{Eq. 1})$$

For consumption of organisms only:

$$\text{AWQC } (\mu\text{g/L}) = \frac{\text{toxicity value (mg/kg-d)} \times \text{BW (kg)} \times 1,000 (\mu\text{g/mg})^c}{\sum_{i=2}^4 (\text{FCR}_i \text{ (kg/d)} \times \text{BAF}_i \text{ (L/kg)})} \quad (\text{Eq. 2})$$

Where:

AWQC = ambient water quality criteria

toxicity value = RfD x RSC (mg/kg-d) for noncarcinogenic effects

or

$10^{-6}/\text{CSF}$ (kg-d/mg) for carcinogenic effects^d

RSC = relative source contribution (applicable to only noncarcinogenic and nonlinear low-dose extrapolation for carcinogenic effects)

BW = body weight

DI = drinking water intake

$\sum_{i=2}^4$ = summation of values for aquatic trophic levels (TLs), where the letter *i* stands for the TLs to be considered, starting with TL2 and proceeding to TL4

FCR_{*i*} = fish consumption rate for aquatic TLs 2, 3, and 4

BAF_{*i*} = bioaccumulation factor for aquatic TLs 2, 3, and 4

EPA rounds AWQC to the number of significant figures in the least precise parameter as described in the 2000 Methodology (USEPA 2000a, section 2.7.3).

4 Exposure Factors

4.1 Body Weight

EPA updated the default BW assumption to 80.0 kg based on National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2006 as reported in Table 8.1 of EPA's *Exposure Factors Handbook* (USEPA 2011a). The updated BW represents the mean weight for adults ages 21 and older. EPA's previously recommended BW assumption for adults was 70 kg, which was based on the mean BW of adults from the NHANES III database (1988–1994) and a 1989 study conducted by the National Cancer Institute (USEPA 2000a).

^b 1,000 $\mu\text{g/mg}$ is used to convert the units of mass from milligrams to micrograms.

^c 1,000 $\mu\text{g/mg}$ is used to convert the units of mass from milligrams to micrograms.

^d 10^{-6} or 1 in 1,000,000 risk level for the general population.

4.2 Drinking Water Intake

EPA updated the default DI to 2.4 L/d, rounded from 2.414 L/d, based on NHANES data from 2003 to 2006 as reported in EPA's *Exposure Factors Handbook* (USEPA 2011a, Table 3-23). This rate represents the per capita estimate of combined direct and indirect community water^e ingestion at the 90th percentile for adults ages 21 and older. EPA selected the per capita rate for the updated DI because it represents the average daily dose estimates; that is, it includes both people who drank water during the survey period and those who did not, which is appropriate for a national-scale assessment such as CWA section 304(a) national human health criteria development (USEPA 2011a, section 3.2.1).

EPA's updated DI of 2.4 L/d is consistent with the 2000 Methodology. In that document, EPA recommended a default DI of 2 L/d, which represented the per capita community water ingestion rate at the 86th percentile for adults surveyed in the U.S. Department of Agriculture's 1994–1996 Continuing Survey of Food Intake by Individuals (CSFII) analysis (USEPA 2000a, section 4.3.2.1).

4.3 Fish Consumption Rate

The updated FCR for the general adult population is 22.0 g/d, or 0.0220 kg/d (USEPA 2014b, Table 9a). This FCR represents the 90th percentile per capita consumption rate of fish from inland and nearshore waters for U.S. adults ages 21 years and older based on NHANES data from 2003–2010. The 95 percent confidence interval (CI) of the 90th percentile per capita FCR is 19.1 g/d and 25.4 g/d. This updated FCR replaces EPA's previously recommended default FCR of 17.5 g/d, which represented an estimate of the 90th percentile per capita consumption rate of fish from inland and nearshore waters for U.S. adults ages 21 years and older. That default FCR was based on USDA's CSFII 1994–1996 data (USEPA 2002a).

As recommended in the 2000 Methodology, EPA updated the AWQC to reflect trophic level- (TL-) specific FCRs to better represent human dietary consumption of fish. An organism's trophic position in the aquatic food web can have an important effect on the magnitude of bioaccumulation of certain chemicals. The TL-specific FCRs are numbered 2, 3, and 4, and they account for different categories of fish and shellfish species based on their position in the aquatic food web: TL2 accounts for benthic filter feeders; TL3 accounts for forage fish; and TL4 accounts for predatory fish (USEPA 2000a).

EPA used the following TL-specific FCRs to derive the updated AWQC: TL2 = 7.6 g/d (0.0076 kg/d) (95 percent CI [6.4, 9.1] g/d); TL3 = 8.6 g/d (0.0086 kg/d) (95 percent CI [7.2, 10.2] g/d); and TL4 = 5.1 g/d (0.0051 kg/d) (95 percent CI [4.0, 6.4] g/d). Each TL-specific FCR represents the 90th percentile per capita consumption rate of fish and shellfish from inland and nearshore waters from that particular TL for U.S. adults ages 21 years and older (USEPA 2014b,

^e *Community water* includes direct and indirect use of tap water for household uses and excludes bottled water and other sources (USEPA 2011a, section 3.3.1.2). *Direct ingestion* is defined as direct consumption of water as a beverage, while *indirect ingestion* includes water added during food preparation (e.g., cooking, rehydration of beverages) but not water intrinsic to purchased foods (USEPA 2011a, section 3.1).

Tables 16a, 17a, and 18a). The sum of these three TL-specific FCRs is 21.3 g/d, which is within the 95 percent CI of the overall FCR of 22.0 g/d. EPA recommends using the TL-specific FCRs when deriving AWQC; however, the overall FCR rate (22.0 g/d) may be used if a simplified approach is preferred.

4.4 Bioaccumulation Factor

4.4.1 Approach

Several attributes of the bioaccumulation process are important to understand when deriving national BAFs for use in developing national recommended section 304(a) AWQC. First, the term *bioaccumulation* refers to the uptake and retention of a chemical by an aquatic organism from all surrounding media, such as water, food, and sediment. The term *bioconcentration* refers to the uptake and retention of a chemical by an aquatic organism from water only. For some chemicals (particularly those that are highly persistent and hydrophobic), the magnitude of bioaccumulation by aquatic organisms can be substantially greater than the magnitude of bioconcentration. Thus, an assessment of bioconcentration alone might underestimate the extent of accumulation in aquatic biota for those chemicals. Accordingly, the EPA guidelines presented in the 2000 Methodology emphasize using, when possible, measured or estimated BAFs, which account for chemical accumulation in aquatic organisms from all potential exposure routes (USEPA 2000a).

EPA estimated BAFs for this updated AWQC using EPA's 2000 Methodology (USEPA 2000a) and its *Technical Support Document, Volume 2: Development of National Bioaccumulation Factors* (Technical Support Document, Volume 2) (USEPA 2003a). Specifically, these documents provide a framework for identifying alternative procedures to derive national TL-specific BAFs for a chemical based on the chemical's properties (e.g., ionization and hydrophobicity), metabolism, and biomagnification potential (USEPA 2000a; USEPA 2003a).

EPA's approach for developing national BAFs represents the long-term average bioaccumulation potential of a pollutant in aquatic organisms that are commonly consumed by humans across the United States. National BAFs are not intended to reflect fluctuations in bioaccumulation over short periods (e.g., a few days) because human health AWQC are generally designed to protect humans from long-term (lifetime) exposures to waterborne chemicals (USEPA 2003a).

EPA followed the approach described in Figure 3-1 of the Technical Support Document, Volume 2 (USEPA 2003a). EPA used peer-reviewed, publicly available information to classify each chemical using this framework to derive the most appropriate BAFs according to EPA's 2000 Methodology (USEPA 2000a). The framework provides six alternatives, or procedures, resulting in up to four possible methods for each chemical, based on the chemical's properties. These four methods follow:

- **BAF Method.** This method uses measured BAFs derived from data obtained from field studies. Field-measured BAFs were normalized by adjusting for the water-dissolved portions of the chemical and the lipid fraction of fish tissue for each species, as well as the fraction of the total concentration of chemical in water that is freely dissolved. EPA averaged multiple field BAFs using a geometric mean of the normalized BAFs by species and TL; then EPA further averaged the BAFs across species to compute TL baseline BAFs. The national-level BAF adjusts the TL baseline BAFs by national default values for lipid content, dissolved and particulate organic carbon content, and the n-octanol-water partition coefficient (K_{ow}). EPA chose the recommended 50th percentile dissolved and particulate organic carbon content for the national-level default values, as described in section 6.3 of the Technical Support Document, Volume 2 (USEPA 2003a).
- **BSAF Method.** This method uses biota-sediment accumulation factors (BSAFs) to estimate BAFs. EPA did not use measured BSAFs to calculate national BAFs because the two major compilations of these data—EPA’s Biota-Sediment Accumulation Factor Data Set, Version 1.0 (USEPA 2015a), and the U.S. Army Corps of Engineers’ BSAF database (USACE 2015)—have not been peer-reviewed.
- **BCF Method.** This method uses BAFs estimated from laboratory-measured bioconcentration factors (BCFs) with or without adjustment by a food chain multiplier. Similar to field BAFs, laboratory-measured BCFs are normalized with the lipid fraction and the fraction of the total concentration of chemical in water that is freely dissolved, then multiplied by the food chain multiplier where applicable. Multiple values are averaged using a geometric mean across species and then across TL to compute baseline BAFs. The national-level BAF adjusts the TL baseline BAFs by national default values for lipid content, dissolved and particulate organic carbon content, and the K_{ow} . EPA chose the recommended 50th percentile dissolved and particulate organic carbon content for the national-level default values, as described in section 6.3 of the Technical Support Document, Volume 2 (USEPA 2003a).
- **K_{ow} Method.** This method predicts BAFs based on a chemical’s K_{ow} , with or without adjustment using a food chain multiplier, as described in section 5.4 of the Technical Support Document, Volume 2 (USEPA 2003a).

Following the decision framework presented in Figure 3-1 of the Technical Support Document, Volume 2 (USEPA 2003a), EPA selected one of the six procedures to develop a national-level BAF for this chemical. For a given procedure, EPA selected the method that provided BAF estimates for all three TLs (TL2–TL4) in the following priority:

1. BAF estimates using the BAF method (i.e., based on field-measured BAFs) if possible.
2. BAF estimates using the BCF method if (a) the BAF method did not produce estimates for all three TLs and (b) the BCF method produced national-level BAF estimates for all three TLs.
3. BAF estimates using the K_{ow} method if (a) Procedure 1 or 3 was applicable (see Figure 3-1 of the Technical Support Document, Volume 2 [USEPA 2003a]) and (b) the BAF and BCF methods did not produce BAF estimates for all three TLs.

In cases where the procedure called for the BAF method but there were fewer than three TL estimates and the K_{ow} method did not apply (i.e., Procedures 2, 4, 5, and 6), EPA used the BAF method estimate for the reported TLs by averaging the estimates using a geometric mean when there were two BAFs and using the single estimate when only one was available. EPA did not mix values from the BAF and BCF methods. If the BAF method did not have sufficient reliable data for any TLs, EPA used the BCF method estimates in the same manner. If none of the four methods provided sufficient data, or if none were appropriate for the procedure, EPA used the BCF from the previously recommended 2002/2003 criteria (USEPA 2002b; USEPA 2003b).

EPA primarily used field-measured BAFs and laboratory-measured BCFs available from peer-reviewed, publicly available databases (Arnot and Gobas 2006; Environment Canada 2006) to develop national BAFs. If field-measured BAFs and laboratory-measured BCFs were not available from those sources, EPA selected K_{ow} values from peer-reviewed sources (i.e., Agency for Toxic Substances and Disease Registry [ATSDR] preferentially, followed by U.S. Department of Health and Human Services' Hazardous Substances Data Bank) for use in calculating national BAFs using the K_{ow} method described in EPA's Technical Support Document, Volume 2 (USEPA 2003a). For those chemicals for which the K_{ow} method was not applicable based on the Technical Support Document, Volume 2 (USEPA 2003a), EPA performed open literature searches of peer-reviewed journal articles to find field-measured BAFs or laboratory-measured BCFs.

4.4.2 Chemical-specific BAFs

EPA selected national BAF values of 6.8 L/kg (TL2), 8.9 L/kg (TL3), and 10 L/kg (TL4) for 2-methyl-4,6-dinitrophenol. EPA followed the framework for selection of methods for deriving national BAFs in Figure 3-1 of the Technical Support Document, Volume 2 (USEPA 2003a) to select a procedure for estimating national BAFs for 2-methyl-4,6-dinitrophenol. Based on the characteristics of this chemical, EPA selected Procedure 3 for deriving a national BAF value. 2-Methyl-4,6-dinitrophenol has the following characteristics:

- Nonionic organic chemical (USDHHS 2013)
- Low hydrophobicity ($\log K_{ow} < 4$); $\log K_{ow} = 2.49$ (ATSDR 1995a)
- Low/unknown metabolism

EPA was not able to locate peer-reviewed, field-measured BAFs or lab-measured BCFs for TLs 2, 3, and 4. Therefore, EPA used the K_{ow} method to derive the national BAF values for this chemical:

TL2 = 6.8 L/kg

TL3 = 8.9 L/kg

TL4 = 10 L/kg

5 Hazard Identification and Dose Response

5.1 Approach

EPA considered all available toxicity values for both noncarcinogenic and carcinogenic toxicological effects to develop this updated AWQC for 2-methyl-4,6-dinitrophenol. As described in the 2000 Methodology (USEPA 2000a), where data are available EPA derives AWQC for both noncarcinogenic and carcinogenic effects and recommends the more protective value for the AWQC. (See section 7, Criteria Derivation: Analysis.)

For noncarcinogenic toxicological effects, EPA uses a chronic-duration oral RfD to derive human health AWQC. An RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure of the human population to a substance that is likely to be without an appreciable risk of deleterious effects during a lifetime. An RfD is typically derived from a laboratory animal dosing study in which a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or benchmark dose can be obtained. Uncertainty factors are applied to reflect the limitations of the data (USEPA 2000a).

For carcinogenic toxicological effects, EPA uses an oral CSF to derive human health AWQC. The oral CSF is an upper bound, approximating a 95 percent confidence limit, on the increased cancer risk from a lifetime oral exposure to a stressor.

For this update, EPA conducted a systematic search of eight peer-reviewed, publicly available sources to obtain the toxicity value (RfD or CSF) for use in developing AWQC. EPA's primary source of toxicity values for developing human health AWQC is its Integrated Risk Information System (IRIS) program (USEPA 2015b). EPA also systematically searched for toxicological assessments from the following EPA program offices, other national and international programs, and state programs:

- EPA, Office of Pesticide Programs (USEPA 2015c)
- EPA, Office of Pollution Prevention and Toxics (USEPA 2015d)
- EPA, Office of Water (USEPA 2015e)
- EPA, Office of Solid Waste and Emergency Response (USEPA 2015f)
- U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR 2015)
- Health Canada (HC 2015)
- California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (CalEPA 2014)

After identifying and documenting all available toxicity values, EPA followed a systematic process to select the toxicity values used to derive the AWQC for noncarcinogenic and carcinogenic effects. EPA selected IRIS toxicity values to derive the updated AWQC if *any* of the following conditions were met:

1. EPA's IRIS toxicological assessment was the only available source of a toxicity value.
2. EPA's IRIS toxicological assessment was the most current source of a toxicity value.
3. EPA's IRIS program was reassessing the chemical in question and had published the draft Toxicological Review for public review and comment, discussion at a public meeting, and subsequent expert peer review.^f
4. The toxicity value from a more current toxicological assessment from a source other than EPA IRIS was based on the same principal study and was numerically the same as an older EPA IRIS toxicity value.
5. A more current toxicological assessment from a source other than EPA IRIS was available, but it did *not* include the relevant toxicity value (chronic-duration oral RfD or CSF).
6. A more current toxicological assessment from a source other than EPA IRIS was available, but it did *not* introduce new science (e.g., the toxicity value was not based on a newer principal study) or use a more current modeling approach compared to an older EPA IRIS toxicological assessment.

EPA selected the toxicity value from a peer-reviewed, publicly available source other than EPA IRIS to derive the updated AWQC if *any* of the following conditions were met:

1. The chemical is currently used as a pesticide, and EPA Office of Pesticide Programs had a toxicity value that was used in pesticide registration decision-making.
2. A toxicological assessment from a source other than EPA IRIS was the only available source of a toxicity value.
3. A more current toxicological assessment from a source other than EPA IRIS introduced new science (e.g., the toxicity value was based on a newer principal study) or used a more current modeling approach compared to an older EPA IRIS toxicological assessment.

5.2 Chemical-specific Toxicity Value

5.2.1 Reference Dose

EPA selected an RfD of 3×10^{-4} mg/kg-d (0.0003 mg/kg-d) for 2-methyl-4,6-dinitrophenol based on a 2010 EPA Office of Solid Waste and Emergency Response (OSWER) Provisional Peer Reviewed Toxicity Value (PPRTV) (USEPA 2010). EPA OSWER identified Ibrahim et al. (1934) as the critical study and reduced BW, excessive perspiration and fatigue, elevated basal metabolic rate (BMR) and body temperature, and the development of greenish-yellow coloration of the conjunctivae as the critical effects in humans orally taking 2-methyl-4,6-dinitrophenol. The 5.5-week human study has a LOAEL of 0.8 mg/kg-d.

^f Equivalent to Step 4 in the July 2013 EPA Process for Developing IRIS Health Assessments. Available online at <http://www.epa.gov/iris/process.htm>.

Based on this human oral toxicity endpoint for 2-methyl-4,6-dinitrophenol, EPA OSWER developed a subchronic provisional RfD (subchronic p-RfD) and an oral *screening chronic value* (screening chronic p-RfD) (USEPA 2010). To derive the subchronic p-RfD, EPA OSWER applied a composite uncertainty factor of 1000 to account for intraspecies variation (10), use of a LOAEL instead of a NOAEL (10), and database deficiencies (10), resulting in a subchronic p-RfD of 8×10^{-4} mg/kg-d. EPA OSWER applied an additional uncertainty factor of 10 (i.e., composite uncertainty factor of 10,000) to account for subchronic-to-chronic extrapolation in deriving the *screening chronic p-RfD* of 8×10^{-5} mg/kg-d (0.00008 mg/kg-d) (USEPA 2010). Based on current EPA OSWER guidelines and standard operating procedures, composite uncertainty factors greater than 3000 cannot be considered for provisional reference value derivation.

For the purpose of updating the AWQC for 2-methyl-4,6-dinitrophenol, EPA Office of Water (OW) selected the OSWER subchronic p-RfD (8×10^{-4} mg/kg-d) and applied an additional uncertainty factor of 3 to account for subchronic-to-chronic extrapolation [i.e., composite uncertainty factor of 3000, consistent with EPA guidance (USEPA 2000a)]. The resulting chronic RfD for the purpose of AWQC development is 3×10^{-4} mg/kg-d (0.0003 mg/kg-d).

Due to low confidence in the database—particularly the lack of chronic toxicity studies—confidence in the subchronic p-RfD for 2-methyl-4,6-dinitrophenol is low (USEPA 2010). However, other available RfD sources report values that are similar to the RfD of 3×10^{-4} mg/kg-d. EPA identified two other RfD sources through the systematic search described in section 5: a 1980 EPA OW assessment (USEPA 1980) and a 1995 ATSDR assessment (ATSDR 1995b). The EPA OW assessment—which was based on a National Institute for Occupational Safety and Health (NIOSH) occupational exposure standard for inhalation of 2-methyl-4,6-dinitrophenol (NIOSH 1978)—has an RfD of 3.9×10^{-4} mg/kg-d. (ATSDR 1995b) published an intermediate-duration MRL of 4×10^{-3} mg/kg-d based on a human study with a LOAEL of 0.35 (Plotz 1936) and a composite uncertainty factor of 100; if an additional uncertainty factor of 10 was applied for subchronic-to-chronic duration, the chronic value would be 4×10^{-4} mg/kg-d. In the event that more current toxicity data or assessments become available for 2-methyl-4,6-dinitrophenol in the future, as with all chemicals, EPA will work to update the AWQC to reflect the latest information.

5.2.2 Cancer Slope Factor

EPA identified no CSF sources for 2-methyl-4,6-dinitrophenol through the systematic search described in section 5.

6 Relative Source Contribution

6.1 Approach

The RSC component of the AWQC calculation allows a percentage of the RfD's exposure to be attributed to the consumption of ambient water and fish and shellfish from inland and nearshore waters when there are other potential exposure sources. The RSC describes the portion of the RfD available for AWQC-related sources (USEPA 2000a); the remainder of the RfD is allocated to other sources of the pollutant. The rationale for this approach is that for

pollutants exhibiting threshold effects, the objective of the AWQC is to ensure that an individual's total exposure from all sources does not exceed that threshold level. Exposures outside the RSC include, but are not limited to, exposure to a particular pollutant from ocean fish and shellfish consumption (which is not included in the FCR), non-fish food consumption (e.g., fruits, vegetables, grains, meats, poultry), dermal exposure, and respiratory exposure.

EPA derived an RSC for each chemical included in this 2015 update by using the Exposure Decision Tree approach described in the 2000 Methodology (USEPA 2000a). To use that approach, EPA compiled information for each chemical on its uses, chemical and physical properties, occurrences in other potential sources (e.g., air, food), and releases to the environment, as well as regulatory restrictions on other sources that are specific to the chemical (e.g., air quality standards, food tolerance levels). The ATSDR "Toxicological Profiles" (ATSDR 2015) were the primary sources for this information. EPA used the Hazardous Substance Data Bank (HSDB) (USDHHS 2015) from the National Library of Medicine's Toxicology Data Network (TOXNET) as the primary source for chemicals without ATSDR Toxicological Profiles. Both sources are peer-reviewed compilations of chemical information.

EPA used additional references, including the following, to obtain specific types of information and to supplement the information from ATSDR and the HSDB:

- EPA's Six-Year Reviews (drinking water data) (USEPA 2009a; USEPA 2009b).
- FDA Total Diet Study (USFDA 2015).
- FDA Everything Added to Food in the United States (USFDA 2013).
- EPA National Lake Fish Tissue Study (USEPA 2009c).
- EPA Toxic Release Inventory (USEPA 2015g).
- International Bottled Water Association Standards of Quality (IBWA 2012).
- NOAA Mussel Watch (NOAA 2014).
- Additional sources as needed.

To determine the RSC to be used in the AWQC calculation, EPA then used the information compiled for each chemical to address the questions posed in the Exposure Decision Tree. Some of the important items evaluated in the Exposure Decision Tree follow:

- The adequacy of the data available for each relevant exposure source and pathway.
- The availability of sufficient information to characterize the likelihood of exposure to relevant sources.
- Whether there are significant known or potential uses/sources other than the source of concern (i.e., ambient water and fish/seafood from those waters).
- Whether information on each source is available to make a characterization of exposure.

In cases where there is a lack of environmental or exposure data, or both, the Exposure Decision Tree approach results in a recommended RSC of 20 percent. This 20 percent value for the RSC may be replaced where sufficient data are available to develop a scientifically

defensible alternative value. When appropriate, if scientific data demonstrating that sources and routes of exposure other than water and fish from inland and nearshore waters are not anticipated for the pollutant in question, the RSC may be raised to 80 percent based on the available data (USEPA 2000a).

6.2 Chemical-specific RSC

2-Methyl-4,6-dinitrophenol is produced for industrial chemical manufacturing and was formerly used to develop dinitrocresol pesticides. 2-Methyl-4,6-dinitrophenol is not currently registered as a pesticide (USEPA 2015c). ATSDR (1995b) reports that inhalation might be a principal route of exposure.

The vapor pressure of 2-methyl-4,6-dinitrophenol (0.00012 mm Hg at 25 °C) indicates that the chemical will exist solely in the vapor phase in the ambient atmosphere (USDHHS 2013). Recent data from EPA's Toxic Release Inventory (USEPA 2015g) indicate that 1 pound of 2-methyl-4,6-dinitrophenol was released to the air in 2013. 2-Methyl-4,6-dinitrophenol is listed as a hazardous air pollutant (USEPA 2013). Thus, based on the chemical's physical properties, air is a potentially significant source of exposure to it.

2-Methyl-4,6-dinitrophenol was not reported as being detected in food (ATSDR 1995b). More recent information regarding concentrations of 2-methyl-4,6-dinitrophenol in food could not be identified. Thus, the potential exposure to this chemical from food is unknown.

Monitoring data regarding 2-methyl-4,6-dinitrophenol in surface water or drinking water could not be identified. 2-Methyl-4,6-dinitrophenol is not regulated under the Safe Drinking Water Act (USEPA 2014c), and it was not a chemical of concern in EPA's Six-Year Reviews (USEPA 2009a; USEPA 2009b). There is no Standard of Quality for this chemical in bottled water (IBWA 2012). Therefore, the potential exposure to 2-methyl-4,6-dinitrophenol from drinking water ingestion is unknown.

The log K_{ow} for 2-methyl-4,6-dinitrophenol ranges from 2.12 to 2.85, with an average log K_{ow} of 2.49 (ATSDR 1995b). The national-level BAF estimates for 2-methyl-4,6-dinitrophenol range from 6.8 L/kg (TL2) to 10 L/kg (TL4), which indicates that 2-methyl-4,6-dinitrophenol has a low potential for bioaccumulation (USEPA 2011b). 2-Methyl-4,6-dinitrophenol was not a target chemical in EPA's National Lake Fish Tissue Study (USEPA 2009c), and it was not included as an analyte in NOAA's Mussel Watch Survey (NOAA 2014). Recent exposure information regarding concentrations of 2-methyl-4,6-dinitrophenol in fish and shellfish is lacking. Therefore, based on the chemical's low potential for bioaccumulation and available information, exposure to it from ingestion of fish and shellfish is not considered likely.

In summary, there is very limited exposure information for 2-methyl-4,6-dinitrophenol in all media, although the physical properties of the chemical indicate air might be a potentially significant source. Following the Exposure Decision Tree in EPA's 2000 Methodology (USEPA 2000a), a significant potential source other than fish and shellfish from inland and nearshore waters and water ingestion might exist (Box 8A in the Decision Tree); however, information is

not available to quantitatively characterize exposure from this source (Box 8B in the Decision Tree). Therefore, EPA recommends an RSC of 20 percent (0.20) for 2-methyl-4,6-dinitrophenol.

7 Criteria Derivation: Analysis

Table 1 summarizes the model inputs used to derive the 2015 updated human health AWQC that are protective of exposure to 2-methyl-4,6-dinitrophenol from consuming drinking water and eating fish and shellfish (organisms) from inland and nearshore waters. The criteria calculations are presented below. These updated criteria recommendations are based on the 2000 Methodology (USEPA 2000a) and the updated exposure assumptions described above. (See section 4, Exposure Factors; section 5, Hazard Identification and Dose Response; and section 6, Relative Source Contribution.)

Table 1. Summary of Input Parameters for 2015 Human Health AWQC for 2-Methyl-4,6-dinitrophenol

Input Parameter		Value
RfD		0.0003 mg/kg-d
CSF		No data
RSC		0.20
BW		80.0 kg
DI		2.4 L/d
FCR	TL2	0.0076 kg/d
	TL3	0.0086 kg/d
	TL4	0.0051 kg/d
BAF	TL2	6.8 L/kg
	TL3	8.9 L/kg
	TL4	10 L/kg

7.1 AWQC for Noncarcinogenic Toxicological Effects

For consumption of water and organisms:

$$\begin{aligned}
 \text{AWQC } (\mu\text{g/L}) &= \frac{\text{toxicity value (RfD [mg/kg-d])} \times \text{RSC} \times \text{BW (kg)} \times 1,000 (\mu\text{g/mg})}{\text{DI (L/d)} + \sum_{i=2}^4 (\text{FCR}_i \text{ (kg/d)} \times \text{BAF}_i \text{ (L/kg)})} \\
 &= \frac{0.0003 \text{ mg/kg-d} \times 0.20 \times 80.0 \text{ kg} \times 1,000 \mu\text{g/mg}}{2.4 \text{ L/d} + ((0.0076 \text{ kg/d} \times 6.8 \text{ L/kg}) + (0.0086 \text{ kg/d} \times 8.9 \text{ L/kg}) + (0.0051 \text{ kg/d} \times 10 \text{ L/kg)})} \\
 &= 1.86 \mu\text{g/L} \\
 &= 2 \mu\text{g/L (rounded)}
 \end{aligned}$$

For consumption of organisms only:

$$\begin{aligned} \text{AWQC } (\mu\text{g/L}) &= \frac{\text{toxicity value (RfD [mg/kg-d]} \times \text{RSC}) \times \text{BW (kg)} \times 1,000 (\mu\text{g/mg})}{\sum_{i=2}^4 (\text{FCR}_i (\text{kg/d}) \times \text{BAF}_i (\text{L/kg}))} \\ &= \frac{0.0003 \text{ mg/kg-d} \times 0.20 \times 80.0 \text{ kg} \times 1,000 \mu\text{g/mg}}{(0.0076 \text{ kg/d} \times 6.8 \text{ L/kg}) + (0.0086 \text{ kg/d} \times 8.9 \text{ L/kg}) + (0.0051 \text{ kg/d} \times 10 \text{ L/kg})} \\ &= 26.8 \mu\text{g/L} \\ &= 30 \mu\text{g/L (rounded)} \end{aligned}$$

7.2 AWQC for Carcinogenic Toxicological Effects

EPA identified no CSF sources through the systematic search described above. (See section 5, Hazard Identification and Dose Response.) Therefore, EPA was unable to derive AWQC for carcinogenic toxicological effects.

7.3 AWQC Summary

EPA derived the AWQC for 2-methyl-4,6-dinitrophenol using a noncarcinogenic toxicity endpoint. The updated human health AWQC for 2-methyl-4,6-dinitrophenol are **2 µg/L** for consumption of water and organisms and **30 µg/L** for consumption of organisms only (Table 2). These updated criteria replace EPA's previously published values (USEPA 2002b).

Table 2. Summary of EPA's Previously Recommended (2002) and Updated (2015) Human Health AWQC for 2-Methyl-4,6-dinitrophenol

	2002 Human Health AWQC	2015 Human Health AWQC
Water and Organism	13 µg/L	2 µg/L
Organism Only	280 µg/L	30 µg/L

These AWQC are intended to be protective of the general adult population from noncarcinogenic effects due to chronic (up to a lifetime) exposure to 2-methyl-4,6-dinitrophenol from ingesting water and/or consuming fish and shellfish from inland and nearshore waters.

8 Criteria Characterization

The updated 2015 human health AWQC for 2-methyl-4,6-dinitrophenol take into account current data on health effects and exposure input parameters, consistent with the 2000 Methodology (USEPA 2000a). The following paragraphs describe the individual influence of each of the revised inputs and exposure assumptions on the overall change in value.

Body Weight

EPA's updated AWQC assume a higher BW compared to the previously recommended 2002 criteria, reflecting a recent rise in average adult BW among the U.S. population. The updated BW assumption of 80.0 kg, based on recent survey data from the 1999–2006 NHANES data, is

10 kg greater than the previous assumption of 70 kg. Assuming all other input parameters remain constant, a higher average BW in the AWQC calculations (Eqs. 1 and 2 above) results in higher AWQC. That is, as BW increases, the level of a contaminant in water at or below which negative health effects are not anticipated from a lifetime of exposure also increases.

Drinking Water Intake

The updated DI assumption is 2.4 L/d, which is higher than the previously recommended rate of 2 L/d. Assuming all other input parameters remain constant, a higher DI assumption in the AWQC calculations (Eqs. 1 and 2 above) results in lower AWQC. That is, as DI increases, and thus overall exposure increases, the level of a contaminant in water at or below which negative health effects are not anticipated from a lifetime of exposure decreases.

Fish Consumption Rate

The updated FCR for fish and shellfish from inland and nearshore waters is 22.0 g/d; the TL-specific FCRs are 7.6 g/d, 8.6 g/d, and 5.1 g/d for TLs 2, 3, and 4, respectively. The previously recommended FCR was 17.5 g/d. Assuming all other input parameters remain constant, a higher FCR assumption in the AWQC calculations (Eqs. 1 and 2 above) results in lower AWQC. That is, as fish consumption increases, and thus overall exposure increases, the level of a contaminant in water at or below which negative health effects are not anticipated from a lifetime of exposure decreases.

Bioaccumulation Factor

The national lower (TL2), mid (TL3), and upper (TL4) TL BAFs used in the updated AWQC (Eqs. 1 and 2 above) are 6.8, 8.9, and 10 L/kg wet-weight, respectively. These BAFs were derived using EPA's 2000 Methodology (USEPA 2000a) and its Technical Support Document, Volume 2 (USEPA 2003a). These national TL BAFs replace EPA's previously recommended BCF of 5.5 L/kg.

As an additional line of evidence, EPA used model-estimated BAFs from the Estimation Program Interface (EPI) Suite (USEPA 2012) to support field-measured or predicted BAFs developed using the four methods described above. The BCFBAF program within EPI Suite estimates fish BAFs by using K_{ow} and biotransformation data from a model designed by Arnot and Gobas (2003). The model includes mechanistic processes for bioaccumulation, such as chemical uptake from the water at the gill surface and from the diet, chemical elimination at the gill surface, fecal egestion, growth dilution, and metabolic biotransformation. Other processes included in the calculations are bioavailability in the water column (only the freely dissolved fraction can bioconcentrate) and absorption efficiencies at the gill and in the gastrointestinal tract. The model requires the K_{ow} of the chemical and the normalized whole-body metabolic biotransformation rate constant as input parameters to predict BAF values. The EPI Suite model estimates are as follows:

$$TL2 = 4.757 \text{ L/kg}$$

$$TL3 = 4.771 \text{ L/kg}$$

$$TL4 = 4.485 \text{ L/kg}$$

Assuming all other input parameters remain constant, higher BAFs or BCFs result in lower AWQC. That is, as bioaccumulation or bioconcentration of a contaminant in fish and shellfish increases, the level of a contaminant in water at or below which negative health effects are not anticipated from a lifetime of exposure decreases.

The utilization of a national-level BAF rather than a BCF better represents the amount of a contaminant accumulating in an organism because it accounts not only for the organism's exposure to the pollutant in the water column, but also from the food chain and surrounding environment as well as biotransformation of the pollutant in the organism due to metabolic processes. The utilization of the three TLs of fish and shellfish consumed, as opposed to representing all TLs of fish and shellfish consumed by a single value, allows for better exposure representation.

Reference Dose

EPA selected an RfD of 0.0003 mg/kg-d for 2-methyl-4,6-dinitrophenol based on a 2010 EPA OSWER PPRTV (USEPA 2010). This RfD replaces the previous value of 0.00039 mg/kg-d (USEPA 1980; USEPA 2002c). EPA used the RfD of 0.0003 mg/kg-d to derive AWQC for noncarcinogenic effects. Assuming all other input parameters remain constant, a decrease in the RfD in the AWQC calculations (Eqs. 1 and 2) results in lower AWQC.

Cancer Slope Factor

EPA did not select a CSF for 2-methyl-4,6-dinitrophenol and therefore did not derive AWQC for carcinogenic effects. EPA did not derive AWQC for carcinogenic effects of 2-methyl-4,6-dinitrophenol in its previous criteria update (USEPA 2002c).

Relative Source Contribution

An RSC of 20 percent is included in the AWQC calculation. Previously, the AWQC did not include an RSC (or, in other words, the RSC was 100 percent) (USEPA 2002c). Assuming all other input parameters remain constant, a lower RSC in the AWQC calculations (Eqs. 1 and 2) results in lower AWQC.

9 Chemical Name and Synonyms

- 2-Methyl-4,6-dinitrophenol (CAS Number 534-52-1)
- o-Cresol,4,6-dinitro-
- Antinonin
- Antinonnin
- Arborol
- Degrassan
- Dekrysil
- Detal
- Dillex
- Dinitro

- Dinitro-o-cresol
- Dinitrocresol
- Dinitrodendtroxal
- Dinitrol
- Dinoc
- Dinurania
- Ditrosol
- Dn
- Dnoc
- Effusan
- Effusan 3436
- Elgetol
- Elgetol 30
- Elipol
- Extrar
- Hedolit
- Hedolite
- K III
- K IV
- Kresamone
- Krezotol 50
- Lipan
- Nitrofan
- Prokarbol
- Rafex
- Rafex 35
- Raphatox
- Sandolin
- Sandolin A
- Selinon
- Sinox
- Winterwash
- 2,4-Dinitro-6-methylphenol
- 3,5-Dinitro-2-h

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