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Journal of Toxicology and Pharmacology

Research Article | Open Access

Evaluation of ATSDR's Inhalation and Oral MRLs and EPA's RfCs/RfDs: Similarities, Differences, and Rationales

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Received: 08 June 2020; **Accepted:** 30 July 2020; **Published:** 03 August 2020

Abstract

Objectives: The Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA) derive minimal risk levels (MRLs) and reference concentrations and doses (RfCs and RfDs), respectively, for environmental contaminants to help identify potential health risks to exposed populations. MRLs, RfDs, and RfCs involve similar derivation methods, but the values sometimes differ for the same chemical. The objectives of this manuscript are to quantitatively assess similarities and differences between MRLs, RfCs, and RfDs, qualitatively describe how a number of factors can influence the development of the health guidance values (HGVs) and identify ongoing collaborations and opportunities for increased coordination of efforts.

Materials and Methods: We collected MRLs and RfCs/RfDs, assessment date, and description of the derivation process from ATSDR's toxicological profiles and EPA's Integrated Risk Information System (IRIS) and Office of Pesticide Program (OPP) and identified reasons for differences between MRLs and RfCs/RfDs.

Results: The most frequent types of differences in values that we found in our analysis included use of different methodologies, use of different studies, and/or completion of a more recent chemical evaluation. These can stem from differences in scientific judgement.

Conclusion: To avoid confusion when disparate HGVs occur between government agencies, a keen understanding of these differences can be helpful for appropriate risk characterization and communication when applying HGVs.

Keywords: Agency for Toxic Substances and Disease Registry; ATSDR; Environmental Protection Agency; EPA; Minimal Risk Levels; MRLs; Reference Concentration; RfC; Reference Dose; RfD; derivation; comparison

Abbreviations

ATSDR: Agency for Toxic Substances and Disease Registry; BMD: Benchmark Dose; BMCL: Benchmark Concentration Lower Limit; CERNS: National Science & Technology Council's Committee on Environment, Natural Resources, and Sustainability; EPA: Environmental Protection Agency; GAO: Government Accountability Office; HC: Health Canada; HEC: Human Equivalent Concentration; HGV: Health Guidance Value; IRIS: EPA's Integrated Risk Information System; ITC: Interagency Testing Committee; LOAEL: Lowest Observed Adverse Effect Level; MCL: Maximum Contaminant Level; MF: Modifying Factor; MOU: Memorandum of Understanding; MRL: Minimal Risk Level; NIEHS: National Institute of Environmental Health Science; NIOSH: National Institute for Occupational Safety and Health; NOAEL: No Observed Adverse Effect Level; NTP: National Toxicology Program; OPP: EPA's Office of Pesticide Program; OSHA: Occupational Safety and Health Administration; PBPK: Physiologically based pharmacokinetic models; POD: Point of Departure; R&D: Research and Development; RfC: Reference Concentration; RfD: Reference Dose; RFI: Request for Information; RIVM: Netherland's National Institute for Public Health and the Environment; TASARC: Tri-Agency Superfund Applied Research Committee; T&R: Toxics and Risks; TSCA: Toxic Substances Control Act; UF: Uncertainty Factor

Introduction

Federal and state agencies derive reference levels (e.g., health guidance values (HGVs)) for environmental contaminants to help identify potential exposure-related health risks in communities. We define HGVs as values used by different agencies that estimate levels of chemical exposure for a specific duration and exposure route that are likely to pose little or no risk to human health. Among the most frequently used HGVs are EPA's Reference Concentrations (RfCs), Reference Doses (RfDs) and ATSDR's Minimal Risk Levels (MRLs). In general, public health officials often compare RfCs/RfDs and MRLs because of EPA's and ATSDR's complementary chemical assessment activities. In short, ATSDR derives MRLs as risk screening levels to determine if exposures at hazardous waste sites or in emergency response situations have the potential to harm human health. MRLs are estimates of daily human exposure that are likely to be without appreciable risk of adverse effect over a specified duration of exposure (acute, intermediate, or chronic). EPA derives RfCs and RfDs to be used in combination with exposure information for specific pathways to characterize public health risks. These risk characterizations can form the basis for risk-based decision-making, regulatory activities, and other risk management decisions. Derivation processes for RfCs, RfDs, and MRLs are described in detail elsewhere [1-4]. Both agencies review the available literature, which includes a quality assessment of studies considered for HGV derivation. Study quality review and weight of evidence analysis is conducted as part of the hazard identification phase. Deficiencies in study quality may be addressed using modifying or uncertainty factors when necessary. In this paper, chronic-duration inhalation and oral MRLs are compared to RfCs/RfDs.

Previous studies have compared HGVs between federal and state agencies [5-7], however only 2 have directly compared EPA's reference values and ATSDR's MRLs [8,9]. Risher and DeRosa did not quantify differences between EPA's reference values but did identify methodological differences stemming from programmatic differences based on legislative mandates, and in some cases different interpretations of scientific data, as reasons for dissimilarities in HGVs between EPA and ATSDR [9]. Holman and colleagues [8] systematically compared non-cancer oral human health risk assessment values from ATSDR and EPA, along with values from Health Canada (HC), and the Netherlands's National Institute for Public Health and the Environment (RIVM). The authors determined that disagreements in the total uncertainty factors (UFs) applied were the most frequent reason for differences between RfDs and chronic oral MRLs evaluated. In a 2014 report, the Government Accountability Office (GAO) assessed the chemical toxicity assessment activities of ATSDR, EPA, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), and the Occupational Safety and Health Administration (OSHA) and compared 10 values between the agencies. GAO determined that each agency has its own programmatic goals charged by statutory directives for deriving HGVs, often resulting in different but complementary values [10].

We aimed to expand upon previously published research by completing the following objectives:

- Quantify the frequency of equal and divergent RfCs/RfDs and MRLs, and

- Qualitatively analyze factors that may result in differences between MRLs and RfCs/RfDs by including examples from recent assessments.

By quantitatively and qualitatively describing the factors that result in differences between inhalation/oral MRLs and RfC/RfDs respectively, we demonstrate the necessity for each agency's assessments and emphasize that many different factors often drive each agency's risk assessment activities. These factors can be scientific practices, differences in interpretation of data, or programmatic differences such as agency-specific drivers of scientific decision-making; these may include goals, protocols, priorities, and legislative mandates that are explicit to risk assessment activities. By identifying chemicals that have data needs we highlight opportunities for future collaboration while also emphasizing ongoing interagency coordination efforts aimed at addressing these data needs.

Methods

In February 2018, we screened ATSDR's Toxicological Profiles and MRL list for chronic (≥365 days) inhalation and oral MRLs, as well as subchronic MRLs when the toxicological profiles explicitly deemed them protective of chronic exposure. We established these criteria because chronic inhalation and oral MRLs are comparable to RfCs and RfDs respectively, which examine health effects from lifetime exposure. Once identified, we collected the following information: HGV, date of toxicological profile release, and description of the derivation of each MRL. Next, we screened EPA's Integrated Risk Information System (IRIS) for any substance for which ATSDR developed a toxicological profile; for pesticides we cross-referenced with EPA's Office of Pesticide Program (OPP). Then we extracted RfC/RfD values, date of assessment, and description of RfC/RfD derivation process. Our comparative analysis focused on the following:

- Frequency of equivalent versus distinct RfCs/RfDs and inhalation/oral chronic MRLs.
- Justification for the differences between values using an author derived coding scheme (Table 1), based on qualitative analysis of abstracted data and source documents. A chemical could have multiple justifications for differences between values. For example, justifications for one chemical could include both use of different studies and the selection of different health effects as the critical effect. Three independent reviewers validated the codes and resolved coding inconsistencies during group meetings.
- Identification of substances where an HGV was not derived.

It should be noted that both ATSDR and EPA round to one significant digit. When comparing values, care was taken to ensure differences were not due to rounding differences by evaluating each step in the derivation process. When values differed by one significant digit, authors discussed derivation methods/choices and came to a consensus as to whether values should be considered different or equivalent.

Results/Discussion

Quantitative Evaluation

Table 2 presents the number of cases where the chronic inhalation or oral MRL was greater than, less than, or equal to the RfC/RfD. Nineteen chemicals had a higher oral MRL compared to the RfD, and 14 chemicals had a higher inhalation MRL compared to the RfC. Additionally, 12 and 11 substances had lower MRLs compared to RfDs and RfCs, respectively. Twenty-six chemicals had equivalent oral MRLs and RfDs, and six had equivalent inhalation MRLs and RfCs. Often ATSDR and EPA derive equivalent HGVs using the same methodology (Supplemental Table 1). For example, both agencies derived oral HGVs of 0.002 mg/kg/day for beryllium using the same primary study and same derivation methods; similarly, both agencies derived inhalation HGVs of 0.03 ppm for 1,4-dioxane based on the same study and same methodology. Though equivalent, the derivation of these values does not constitute duplication given that these agencies target different audiences and public health applications with their HGVs. As the authors of the GAO noted, while EPA derives RfCs/RfDs for use by EPA Programs (e.g., land, air, water) and regional offices to inform "regulatory and risk management decisions," ATSDR targets state and local health departments and mostly focuses on hazardous waste sites [10].

In some cases, programmatic difference resulted in the use of differing derivation methods or studies, but the resulting HGVs were equivalent. For instance, ATSDR and EPA derived an equivalent chronic oral MRL and RfD of 0.02 mg/kg/day for bromoform despite using different studies reported in the NTP Technical Report Series No. 350 [11]. ATSDR chose a chronic study that exposed rats to bromoform via gavage for 103 weeks [12], while EPA chose a subchronic study with exposure to rats via gavage for 13 weeks [13]. EPA extrapolated from subchronic to chronic duration. Consequently, EPA used an additional uncertainty factor to account for extrapolation from subchronic to chronic exposure in the 13-week study, resulting in equivalent HGVs. ATSDR derives separate acute and intermediate duration HGVs. Our quantitative evaluation of chronic MRLs and RfCs/RfDs indicates that many hazardous substances have equivalent HGVs. Even when diverse derivation methods can be employed, sometimes resulting values are equivalent.

Table 1. Coding Scheme for Observed Inconsistencies between MRLs and RfCs/RfDs.

Code	Criteria
1	EPA subchronic to chronic extrapolation
2	Different studies used
3	Different use of assessment factors (e.g. modifying or uncertainty factors)
4	Different health effects
5	MRL not derived when RfC/RfD was derived
6	RfC/RfD not derived/not evaluated when MRL was derived
7	Different methods used (e.g. used of BMD modeling, different conversion factors, etc.)
8	EPA used unpublished study[a]
9	ATSDR conducted a more recent assessment (≥ 5 years from time of EPA's HGV derivation)
10	EPA conducted a more recent assessment (≥ 5 years from time of ATSDR's HGV derivation)
11	ATSDR adopted an acute and intermediate value for a chronic value

[a] IRIS uses only publicly available information and doesn't have access to CBI data. Thus, IRIS Tox Reviews do not routinely use unpublished studies as the basis for reference values. Pesticide assessments by the Office of Pesticide Programs frequently benefit from submitted large Good Laboratory Practices (GLP) reports that may not be fully available to the public. The toxicity information is provided in Data Evaluation Records (DERs) due to confidential business information (CBI) data.

Table 2: Description of Quantitative Comparison of MRLs and RfCs/RfDs, Including a Frequency Count of Reasons for Discrepancies.

Oral		Inhalation	
Description	**N (%)[a]**	**Description**	**N (%)[a]**
MRL = RfD	26	MRL = RfC	6
MRL > RfD	19	MRL > RfC	14
Different methods employed	11	Different methods employed	11
Different UF or MF	9	Different UF or MF	6
ATSDR's assessment ≥ 5 years older than EPA's assessment	7	Different studies used	5
Different studies used	6	Different health effects	3
EPA subchronic to chronic	2	ATSDR's assessment ≥ 5 years older than EPA's assessment	3
Different health effects	2	EPA's assessment ≥ 5 years older than ATSDR's assessment	2
EPA's assessment ≥ 5 years older than ATSDR's assessment	2	EPA subchronic to chronic	1
EPA used unpublished study	1	EPA used unpublished study	0
MRL < RfD	12	MRL < RfC	11
Different studies used	8	Different methods employed	6
Different methods employed	5	Different UF or MF	6
ATSDR's assessment ≥ 5 years older than EPA's assessment	4	Different studies used	5
Different UF or MF	3	ATSDR's assessment ≥ 5 years older than EPA's assessment	4
Different health effects	3	Different health effects	1
EPA used unpublished study	1	EPA's assessment ≥ 5 years older than ATSDR's assessment	1
ATSDR adopts shorter duration MRL	2		
EPA subchronic to chronic	0	EPA subchronic to chronic	0
EPA's assessment ≥ 5 years older than ATSDR's assessment	0	EPA used unpublished study	0
Guidance value(s) not derived		Guidance value(s) not derived	
Neither derived	85	Neither derived	167
MRL not derived, RfD derived	77	RfC not derived, MRL derived	21
RfD not derived, MRL derived	20	MRL not derived, RfC derived	21

Reasons for Differences

Supplemental Table 1 provides an overview of chemicals that had no differences between MRLs and RfDs/RfCs. Supplemental Tables 2 and 3 provide an overview of the substances that had higher or lower MRLs compared to RfCs/RfDs, respectively. Table 1 presents the coding scheme for the multiple reasons for variation. Table 2 provides a count of the reasons for discrepancies. The most common reason found was the use of different methodologies (33 instances), followed by nearly identical frequencies of using different studies (24), applying different UFs or modifying factors (MFs) (24), and conducting a more recent chemical evaluation (23).

Different methods include but are not limited to the use of different conversion factors, use of physiologically based pharmacokinetic models (PBPK), the use of benchmark dose (BMD) modeling techniques, or the selection of models within BMD. Many of the differences in methods stem from differences in the dates of the assessment where the later assessment may have had access to newer information such as PBPK models, BMD techniques and/or models, or different reference values for conversion (e.g., different values for water intake or body weight). For example, EPA utilized BMD for chlordecone RfD, 1,1-dichloroethene RfD, carbon tetrachloride RfC, and nitrobenzene RfC while ATSDR did not; on the other hand, ATSDR utilized BMD while EPA did not for chromium (VI) oral MRL, 2,4-dinitrotoluene oral MRL, 1,2,4-trichlorobenzene oral MRL, and manganese inhalation MRL. In nearly all these examples, the agency (EPA or ATSDR) that did not utilize BMD conducted their assessment before the introduction of these BMD analysis. Another common methodological concept that underpinned many of the differences in HGVs is the use of different conversion factors. These include, but are not limited to, use of a human equivalent concentration (e.g., chlordane and chloroethane RfCs), different adjustments for intermittent to continuous exposure (e.g., mercury inhalation HGVs), or different exposure calculations (e.g., disulfoton and nitrate oral HGVs).

On some occasions both agencies chose the same critical study, but differences in scientific decisions throughout the evaluation process lead to use of distinct methods that resulted in different HGVs. For example, when deriving an inhalation HGV for toluene, ATSDR and EPA both identified a series of studies evaluating neurological effects in workers occupationally exposed to toluene. In deriving the HGVs, both agencies utilized no observed adverse effect levels (NOAELs) as the point of departure (POD). However, EPA selected the arithmetic mean of the NOAELs (34 ppm) from the group of studies while ATSDR selected the highest NOAEL (45 ppm) from the same group of studies. Both agencies adjusted for intermittent occupational exposure, but they utilized slightly different adjustment factors. Both agencies divided their respective adjusted PODs by a total UF of 10, resulting in an MRL of 1 ppm (3.8 mg/m^3) compared to EPA's RfC of 1.33 ppm (5 mg/m^3).

We also found that use of differing UFs was a common co-reason for divergent HGVs when agencies employed different derivation methods. For example, ATSDR and EPA based their inhalation HGVs for ammonia on the same occupational study but used different methodologies to define the POD and applied different UFs [14]. EPA used the 95% lower confidence bound of the mean exposure concentration in the high-exposure group as the POD while ATSDR used the mean time-weighted average (TWA) exposure concentration for the whole population as the POD. Both agencies adjusted for intermittent exposure but employed slightly different adjustment methods. In the end, ATSDR utilized an additional MF of 3 for database uncertainty on top of the UF of 10 for human variability that both agencies used. Because application of varying methods and adjustments can impact the need to account for uncertainties inherent to toxicity assessment, it makes sense that agencies may choose different UFs if they employ one or more of these methods and adjustments.

In some cases, where the choice of a different critical study resulted in divergent HGVs, agencies chose not only different studies but also different types of studies (animal vs epidemiological). Similarly, the use of the same type of study in the derivation process did not always result in the same HGV as exemplified when determining the oral HGVs for

methyl mercury. While both agencies agreed on neurotoxicity as the most important health outcome, however unique scientific judgements led the agencies to use different critical studies. EPA derived a RfD of 0.001 mg/kg/day and ATSDR derived a chronic oral MRL of 0.0001 mg/kg/day [15,16]. Sometimes, the age of the assessment affects availability of data and/or methodologies used. In fact, out of the 30 instances when the agencies used different methodologies to derive their respective HGVs, nearly half (13/30) involved chemical assessments conducted at least five years apart. For instance, ATSDR has a lower inhalation MRL (0.97 mg/m^3) for 2-butoxyethanol based on a 1998 assessment as compared to the 2010 EPA assessment (RfC of 1.6 mg/m^3). ATSDR identified a POD of 0.6 ppm (3 mg/m^3) in humans exposed occupations to 2-butoxyethanol for 1 to 6 years [17]. EPA's more recent assessment that identified a newer study that had not been published when ATSDR conducted its assessment [18]. In addition, EPA conducted a BMD analysis. EPA's POD was based on human equivalent concentrations (HEC) derived from a human PBPK model. A benchmark concentration limit ($BMCL_{10}$) of 133 µmol/L, was back calculated using PBPK modeling to a benchmark concentration limit human equivalent concentration ($BMCL_{HEC}$) of 16 mg/m^3 based on hemosiderin staining in the liver of male rats after 2 years of exposure.

On the other hand, ATSDR derived a higher chronic oral MRL for methylene chloride in the year 2000 compared to EPA's 2011 RfD (0.06 vs. 0.006 mg/kg/day) [19]. Both agencies used the same study; however, when EPA updated its RfD, eleven years after ATSDR published its MRL, EPA was able to utilize a PBPK model that was not available at the time of ATSDR's assessment. Moreover, EPA utilized BMD in its RfD derivation. Therefore, EPAs POD was a $BMDL_{HEC}$ of 17.2 mg/m^3 compared to ATSDR's POD of 173.5 mg/m^3 based on liver histopathology in female rats. In this case, the newer evaluation did not result in substantial addition of new data but did lead to the use of more modern risk assessment methods for extrapolating between species.

The age of the assessment also had a strong influence on the choice of critical studies used to calculate the POD. Conducting a more recent literature evaluation was the reason for 54% (13/24) of the differences involving use of different studies. Thus, the availability of new literature may have influenced study choice more than differences in data access or study selection policies. From the examples above, one can see that by conducting a more recent chemical assessment, new literature can inform different PODs or advances in risk assessment methodology such as PBPK modeling can explain differences between agency values.

Moreover, an agency's ability to access sufficient data from unpublished studies can also account for some of the HGV distinctions [10]. We found 18 cases where EPA/OPP utilized unpublished studies to derive RfCs/RfDs; ATSDR was only able to derive 2 MRLs locating published data for 2,4-D and pentachlorophenol. In the other 16 cases, ATSDR did not derive inhalation or oral chronic MRLs, due to insufficient publicly available data. The examples above highlight the diverse reasons for HGV differences.

An example of a programmatic difference that resulted in different HGV between agencies is EPA's practice to extrapolate from subchronic to chronic exposure as needed, when deriving RfCs/RfDs. ATSDR does not generally use such an extrapolation; instead, ATSDR chooses to derive separate acute (≤ 14 days) and/or intermediate (15-365 days) duration MRLs when sufficient data are available. In addition to some of the programmatic differences (i.e., EPA's use of subchronic studies) that resulted in different HGVs between EPA and ATSDR, the intended end use of the HGVs may result in different derivation choices. One of the uses of RfCs/RfDs is to derive EPA's Regional Screening Levels (RSLs), which inform remediation decisions. On the other hand, MRLs are intended to be used by health assessors as screening levels for potential chemicals that may cause adverse health effects. Each agency may use the other agency's HGV for its purpose (i.e. EPA using an MRL for derivation of an RSL). It is likely that the end use of HGV influences decisions during the derivation process. It should also be noted that additional discretion may be used by a health assessor/remediation professional to further modified the RfC/RfD or MRL when they are applied based on-site specific needs. Further transparency associated with decisions at each step of the process may help health assessors modify HGVs when needed [20].

Identification of Data Needs

In several cases, ATSDR did not derive MRLs even though EPA considered the data sufficient to derive a reference value (Supplemental Table 4). Programmatic difference may influence the presence of data needs. As mentioned above, EPA extrapolates from subchronic to chronic exposure, while ATSDR does not typically use subchronic studies to derive MRLs. ATSDR may classify these shorter duration MRLs as protective of chronic exposure if the existing data permit. EPA will extrapolate across exposure durations, which may help explain the greater number of RfCs/RfDs derived for substances without chronic MRLs. For example, EPA derived a RfC for 2-hexanone using a subchronic inhalation study in monkeys resulting in decrements in sciatic-tibial nerve motor conduction velocity [21]. ATSDR acknowledged this study in its discussion of literature for its intermediate MRL duration but ultimately did not use this study to derive an intermediate MRL because the endpoint was deemed a serious lowest observed adverse effect level (SLOAEL) [22]. ATSDR does not use serious health effects (e.g. effects that prevent an organism from functioning normally, such as death, coma, seizures, extensive necrosis, abortion, and birth defects) for MRL derivation [2,23]. EPA may use serious effects (called frank effects) when such effects occur at low doses and the selection of an alternative endpoint may underestimate toxicity [4]. EPA's use of freestanding NOAELs as PODs when applicable may also explain some of the data gaps. By contrast, ATSDR requires a NOAEL to be accompanied by a LOAEL, thus limiting the number of suitable studies for HGV derivation relative to EPA practice.

Each agency prioritizes chemicals to evaluate based on programmatic differences, which can result in differences in databases between agencies. For instance, the overwhelming majority of MRL candidate substances are chosen from chemicals found at NPL sites. However, ATSDR also selects non-NPL substances nominated by other agencies, states, and the public. ATSDR further prioritizes chemicals based on frequency of detection, human exposure, and toxicity [24]. EPA, on the other hand, derives RfCs/RfDs for a larger portfolio of chemicals, based on their broader mission and jurisdiction.

Consequently, the flexibility that comes with exposure duration extrapolation, use of serious health effects or freestanding NOAELs, and choice of substances for evaluation may result in a larger pool of data for EPA to choose from when deriving RfCs/RfDs that does not meet ATSDR's criteria.

In other cases, both agencies may choose not to derive an HGV (Supplemental Table 4). Reasons for not deriving a chronic HGV include having a limited database on the suspected critical health effects or because the available literature has not identified thresholds for critical effects (e.g. lead, asbestos). ATSDR may have also derived acute and/or intermediate MRLs for some of these substances.

In order to address some of these data needs and/or coordinate HGV activities, agencies have established formal collaborative agreements. A number of federal agencies have Congressional mandates related to protecting human health and the environment from chemical exposures – namely EPA, ATSDR, the National Institute of Environmental Health Sciences' National Toxicology Program (NIEHS/NTP), NIOSH, and OSHA. As documented in the GAO's 2014 Chemical Assessments report, many of these agencies already coordinate HGV activities through at least one of four mechanisms – memorandum of

understanding (MOU), interagency workgroups, data-sharing (e.g. literature search results), and case-by-case coordination for specific chemicals [10]. ATSDR and EPA have established an MOU to facilitate increased communication and coordination of efforts to develop human health assessment products [25]. Various interagency committees have been established to monitor and directly communicate these needs to other agencies. For instance, the Toxic Substances Control Act (TSCA) established the TSCA Interagency Testing Committee (ITC) to independently advise the EPA administrator on "prioritizing and selecting chemicals for testing or information reporting" [26]. To coordinate Federal science and technology efforts regarding environmental exposures to toxic chemicals, the National Science & Technology Council's Committee on Environment, Natural Resources, and Sustainability (CENRS) established the Toxics and Risks (T&R) Subcommittee. One of the functions of the T&R subcommittee was to help communicate across federal agencies the research needs around chemical exposure health risks, to help identify cross-cutting national research and development (R&D) priorities [27]. In addition, ATSDR, EPA, and NTP established the Tri-Agency Superfund Applied Research Committee (TASARC) to share data needs research efforts and review protocols of voluntary research studies submitted to ATSDR's voluntary research program [28]. Federal agencies can also publish Requests for Information (RFIs) in the Federal Register to solicit information regarding ongoing or completed research pertaining to data gaps, as OSHA has recently done [29].

Based on our HGV analysis, we can propose a number of recommendations. Agencies can consider continuing to harmonize their toxicity assessment activities to ensure HGVs remain independent yet complementary. Additionally, more engagement with end-users and stakeholders in public meetings on how they use HGVs for different exposure scenarios can be helpful. This would enable agencies to better communicate the implications and applications of HGVs for various public health activities (i.e. adequate reporting of HGV derivation methods). To improve the usability of their MRLs, ATSDR recently added concise summary statements and indications for when a subchronic value could be used (e.g. when they could not derive a chronic MRL) at the beginning of their MRL Worksheets, based on suggestions from public health practitioners. Furthermore, agencies may continue to leverage and sustain their collaborative efforts to plan HGV development and/or research activities around different data needs. These cross-cutting initiatives offer opportunities to share and maximize resources across many data needs while catering to their respective public health missions. Finally, agencies can consider using the findings of our data gap analysis as a baseline to monitor progress towards fulfilling outstanding data needs.

Conclusions

This paper builds on previous research by quantitatively evaluating HGVs from two US federal agencies, determining how the agencies' unique missions may influence HGV differences, and identifying data needs. Key findings from this exercise indicate that although similar, the motivations and methods for deriving the two agencies' values can sometimes differ enough to confuse practitioners and the public about which value to use for a given risk assessment [9]. ATSDR and EPA have distinct toxicity assessment activities that contribute to different public health decisions when deriving HGVs and address different exposure scenarios. Clear risk communication is an important tool that should be used to explain these differences, particularly when divergent HGVs are available.

Our evaluation contributes to the current body of literature in several important ways. First, we were able to include a quantitative analysis not performed by Risher and DeRosa [9], and unlike Holman et al. [8], our quantitative analysis included additional and modified coding categories. Second, we included an assessment of EPA's RfC and ATSDR's chronic inhalation MRLs and also compared assessments that were more than one year apart, leading to an evaluation of an additional 52 values compared to Holman et al [8]. Finally, we identified current data needs. Data needs are defined as instances when one or both agencies did not derive a value.

Similar to the GAO report, our exercise indicated that each agency's work is unique but complementary because the HGVs are aimed at different audiences and public health applications. For instance, ATSDR uses MRLs as non-regulatory screening levels at hazardous wastes sites and in emergency response activities to quickly but safely rule out exposures that do not pose human health risks. EPA derives RfCs and RfDs to provide consistent values for use throughout the agency, such as deriving maximum contaminant levels (MCLs) [30]. Federal agencies and researchers have established partnerships to address data needs, avoid duplicative activities, share expertise and other resources, and ensure derivation of appropriately protective HGVs based on the best available science. Understanding agencies' programmatic differences and scientific practices can help public health officials decide the suitability of HGVs to their particular exposure situation. Risk communication regarding these differences is critical to reducing confusion and misapplication of HGVs. Overall, the differing HGVs complement each other in their agencies' missions to protect public health.

Acknowledgements

We would like to thank Selene Chou of ATSDR (retired) for reviewing this manuscript and providing insightful feedback.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Supplemental Table 1: Chemicals with the same MRL and RfC/RfD Values.

Chemical (CAS)	Value	MRL Date	RfC/RfD Date
Oral			
Aldrin (309-00-2)	0.00003 mg/kg/day[a]	2002	2002
Arsenic (7440-38-2)	0.0003 mg/kg/day	2007	1991
Barium, soluble salts (7440-39-3)	0.2 mg/kg/day	2007	2003
Beryllium (7440-41-7)	0.002 mg/kg/day	2002	1998
Boron (7440-42-8)	0.2 mg/kg/day	2010	2004
Bromodichloromethane (75-27-4)	0.02 mg/kg/day	1989	1988
Bromoform (75-25-2)	0.02 mg/kg/day	2005	1987
Chlordane (57-74-9)	0.0006 mg/kg/day[a]	1994	1998
Chloroform (67-66-3)	0.01 mg/kg/day	1997	1987
1,3-Dichloropropene (542-75-6)	0.03 mg/kg/day	2008	2000
Dichlorvos (62-73-7)	0.0005 mg/kg/day[b]	1997	1993
Dieldrin (60-57-1)	0.00005 mg/kg/day[a]	2002	1988
Endrin (Endrin aldehyde) (72-20-8)	0.0003 mg/kg/day[a]	1996	1988
Formaldehyde (50-00-0)	0.2 mg/kg/day	1999	1990
Isophorone (78-59-1)	0.2 mg/kg/day	1989	1989
Malathion (121-75-5)	0.02 mg/kg/day[b]	2013	1987
Methyl Parathion (298-00-0)	0.0003 mg/kg/day[b]	2001	1987
Nitrite (84145-82-4)	0.1 mg/kg/day	2017	1987
Perchlorates (10034-81-8, 7778-74-7, 7790-98-9, 7601-89-0, 7791-03-9)	0.0007 mg/kg/day	2008	2005
Polychlorinated Biphenyls (PCBs) (11097-69-1)	0.02 µg/kg/day	2000	1994
Selenium (7782-49-2)	0.005 mg/kg/day	2003	1991
Tin and Other Compounds (56-36-9; 683-18-1; 7440-31-5)	0.0003 mg/kg/day (Tributyltin oxide)	2005	1997
Trichloroethylene (TCE) (79-01-6)	0.0005 mg/kg/day	2014	2011
Vinyl Chloride (75-01-4)	0.003 mg/kg/day	2006	2000
Xylene (1330-20-7)	0.2 mg/kg/day	2007	2003
Zinc (7440-66-6)	0.3 mg/kg/day	2005	2005
Inhalation			
1,4-Dioxane (123-91-1)	0.03 ppm	2012	2013
Dichlorvos (62-73-7)	0.00006 ppm[b]	1997	1994
Naphthalene (91-20-3)	0.0007 ppm (0.003 mg/m3)	2005	1998
Styrene (100-42-5)	0.2 ppm	2010	1992
Tetrachloroethylene (PERC) (127-18-4)	0.006 ppm	2014	2012
Trichloroethylene (TCE) (79-01-6)	0.0004 ppm (0.002 mg/m3)	2014	2011

[a]Not evaluated by OPP
[b]No value reported by OPP

Supplemental Table 2: Chemicals that have higher MRLs compared with RfDs/RfCs.

Chemical (CAS)	MRL	Date	RfD/RfC	Date	Code
Oral					
Chlordecone (143-50-0)	0.0005 mg/kg/day	1995	0.0003 mg/kg/day[a]	2009	7,10
Chlorinated Dibenzo-p-dioxins (CDDs) (1746-01-6)	0.000000001 mg/kg/day (2,3,7,8-TCDD)	1998	7 E 10 mg/kg/day (2,3,7,8-TCDD)	2012	2,3,7,10
Cresols (1319-77-3)	0.1 mg/kg/day	2008	0.05 mg/kg/day (m- and o-cresol)	1988	1,2,9
Di(2-ethylhexyl) phthalate (DEHP) (117-81-7)	0.06 mg/kg/day	2002	0.02 mg/kg/day	1987	2,3,9
Dibromochloromethane (124-48-1)	0.09 mg/kg/day	2005	0.02 mg/kg/day	1987	3,7,9
1,2-Dichlorobenzene (95-50-1)	0.3 mg/kg/day	2006	0.09 mg/kg/day	1989	3
2,4-Dichlorophenoxyacetic Acid (2,4-D) (94-75-7)	0.009 mg/kg/day (intermediate protective of chronic)	2017	0.005 mg/kg/day[b]	2005	2,8
Diisopropyl Methylphosphonate (DIMP) (1445-75-6)	0.6 mg/kg/day	1998	0.08 mg/kg/day	1989	1,9
1,4-Dioxane (123-91-1)	0.1 mg/kg/day	2012	0.03 mg/kg/day	2010	3
Disulfoton (298-04-4)	0.00006 mg/kg/day	1995	0.00004 mg/kg/day	1987	7,9
2-Hexanone (591-78-6)	0.02 mg/kg/day	2018 (draft for public comment)	0.005 mg/kg/day	2009	7,9
Mercury (7439-97-6)	0.0003 mg/kg/day (MeHg)	1999	0.0001 mg/kg/day (MeHg)	2001	2,7
Methylene Chloride (75-09-2)	0.06 mg/kg/day	2000	0.006 mg/kg/day[a]	2011	7,10

2-Methylnaphthalene (91-57-6)	0.04 mg/kg/day	2005	0.004 mg/kg/day	2003	3
Mirex (2385-85-5)	0.0008 mg/kg/day	1995	0.0002 mg/kg/day[c]	1992	3
Nitrate (84145-82-4)	4 mg/kg/day	2017	1.6 mg/kg/day	1991	7,9
RDX (Cyclonite) (121-82-4)	0.1 mg/kg/day	2012	0.003 mg/kg/day	1988	4,7,9
Tetrachloroethylene (PERC) (127-18-4)	0.008 mg/kg/day	2014	0.006 mg/kg/day	2012	3,7
1,2,4-Trichlorobenzene (120-82-1)	0.1 mg/kg/day	2014	0.01 mg/kg/day	1992	2,3,4,7,9
Inhalation					
Bromomethane (74-83-9)	0.005 ppm (0.019 mg/m3)	1992	0.005 mg/m3	1992	2,4
Carbon Disulfide (75-15-0)	0.3 ppm (0.78 mg/m3)	1996	0.7 mg/m3	1995	7
Carbon Tetrachloride (56-23-5)	0.03 ppm (~0.19 mg/m3)	2005	0.1 mg/m3	2010	3,7,10
Chlordane (57-74-9)	0.00002 mg/m3	1994	0.0007 mg/m3[a]	1998	7
Chloroethane (75-00-3)	15 ppm (~40 mg/m3) (acute protective of chronic)	1998	10 mg/m3	1991	3,7,9
Chloromethane (74-87-3)	0.05 ppm (~0.1 mg/m3)	1998	0.09 mg/m3	2001	2
1,3-Dichloropropene (542-75-6)	0.007 ppm	2008	0.02 mg/m3 (0.004 ppm)	2000	7
Hexamethylene Diisocyanate (822-06-0)	0.00001 ppm (0.000069 mg/m3)	1999	0.00000145 ppm (0.00001 mg/m3)	1994	3,4,7,9
N-Hexane (110-54-3)	0.6 ppm (2.12 mg/m3)	1999	0.7 mg/m3	1998	2,3,7
Manganese (7439-96-5)	0.0003 mg/m3	2012	0.00005 mg/m3	1993	7,9
Methylene Chloride (75-09-2)	0.3 ppm	2000	0.6 mg/m3 (0.17 ppm ~ 0.2 ppm)[a]	2011	3,7,10
Methylenediphenyl Diisocyanate (MDI) (101-68-8)	0.001 mg/m3	2015	0.0006 mg/m3	1998	3,7,9
Xylene (1330-20-7)	0.05 ppm	2007	0.02 ppm	2003	1,2,4

[a]Not evaluated by OPP
[b]Same value reported by both IRIS and OPP
[c]No value reported by OPP

Supplemental Table 3: Chemicals that have lower MRLs compared with RfDs/RfCs.

Chemical (CAS)	MRL	Date	RfD/RfC	Date	Code
Oral					
Acrylamide (79-06-1)	0.001 mg/kg/day	2012	0.002 mg/kg/day	2010	2,7
Benzene (71-43-2)	0.0005 mg/kg/day	2007	0.004 mg/kg/day	2003	2,3
Cadmium (7440-43-9)	0.0001 mg/kg/day	2012	0.0005 mg/kg/day	1989	2,9
Chromium (VI) (18540-29-9)	0.0009 mg/kg/day	2012	0.003 mg/kg/day (soluble salts)	1998	2,7,9
1,1-Dichloroethene (75-35-4)	0.009 mg/kg/day	1994	0.05 mg/kg/day	2002	7
2,4-Dinitrotoluene (121-14-2)	0.001 mg/kg/day	2016	0.002 mg/kg/day	1992	7
Endosulfan (115-29-7)	0.005 mg/kg/day	2015	0.006 mg/kg/day[c]	1994	2,4,11
Ethion (563-12-2)	0.0004 mg/kg/day	2000	0.0005 mg/kg/day[c]	1989	3
Ethylene Glycol (107-21-1)	0.8 mg/kg/day (acute protective of chronic)	2010	2 mg/kg/day	1987	2,9,11
Fluorides, Hydrogen Fluoride, and Fluorine (7681-49-4)	0.05 mg/kg/day	2003	0.06 mg/kg/day (fluorine [soluble fluoride])	1987	2,4,9
Hexachlorobenzene (118-74-1)	0.00007 mg/kg/day	2015	0.0008 mg/kg/day[c]	2003	3,7,9
Pentachlorophenol (87-86-5)	0.001 mg/kg/day	2001	0.005 mg/kg/day[c]	2010	2,4,8
Inhalation					
Ammonia (7664-41-7)	0.1 mg/m3	2004	0.5 mg/m3	2004	3,7
Benzene (71-43-2)	0.003 ppm (0.0096 mg/m3)	2007	0.03 mg/m3	2003	2,3
2-Butoxyethanol (111-76-2) (111-76-2)	0.2 ppm (0.97 mg/m3)	1998	1.6 mg/m3	2010	2,7,10
Chromium (VI), aerosols and mists (18540-29-9)	0.000005 mg/m3	2012	0.000008 mg/m3	1998	3,7,9
1,4-Dichlorobenzene (106-46-7)	0.01 ppm	2006	0.8 mg/m3 (0.1 ppm)	1994	2,9
Ethylbenzene (100-41-4)	0.06 ppm	2010	1 mg/m3 (0.23 ppm)[b]	1991	2,9
Mercury (7439-97-6)	0.0002 mg/m3 (metallic)	1999	0.0003 mg/m3 (elemental)	1995	7
Methyl-t-Butyl Ether (1634-04-4)	0.7 ppm	1996	0.8 ppm	1993	3
Toluene (108-88-3)	1ppm (3.8 mg/m3)	2017	5 mg/m3 (1.33 ppm)	2005	7,9
Toluene Diisocyanate (TDI) (26471-62-5)	0.000003 ppm (0.00002 mg/m3)	2015	0.00007 mg/m3 (0.00001 ppm)	1995	2,3,9

[a]Same value reported by both IRIS and OPP
[b]Not evaluated by OPP
[c]No value reported by OPP

Supplemental Table 4. Lists of Substances (CAS) for which one or more values were not derived.

Substance	Oral		Inhalation	
	MRL not derived	RfD not derived	MRL not derived	RfC not derived
Acenapthene (83-29-9)	X		X	X
Acetone (67-64-1)	X			X
Acrolein (107-02-8)	X		X	
Acrylamide (79-06-1)			X	
Acrylonitrile (107-13-1)		X	X	
Aldrin (309-00-2)			X	X
Aluminum (7429-90-5)		X	X	X
Americium (7440-35-9)		X	X	X
Ammonia (7664-41-7)	X	X		
Anthracene (120-12-7)	X		X	X
Antimony (7440-36-0)	X			X
Arsenic (7440-38-2)			X	X
Asbestos (1332-21-4, 12172-73-5, 12001-29-5, 14567-73-8, 13768-00-8, 17068-78-9, 12001-28-4)	X	X	X	X
Atrazine (1912-24-9)	X		X	X
Barium, soluble salts (7440-39-3)			X	X
Baythroid/Cyfluthrin (68359-37-5)	X		X	X
Benzidine (92-87-5)	X		X	X
Benzo[a]pyrene (50-32-8)	X		X	
2,3-Benzofuran (271-89-6)	X	X	X	X
Beryllium (7440-41-7)			X	
Biphenthrin (82657-04-3)	X		X	X
Bis(2-Chloroethyl) ether (111-44-4)	X	X	X	X
Bis(2-Chloromethyl) ether (542-88-1)	X	X	X	X
Boron (7440-42-8)				X
Bromodichloromethane (75-27-4)			X	X
Bromoform (75-25-2)			X	X
Bromomethane (74-83-9)	X			
1-Bromopropane (106-94-5)	X	X		X
1,3-Butadiene (106-99-0)	X	X	X	
2-Butanone (MEK) (78-93-3)	X		X	
2-Butoxyethanol (111-76-2) (111-76-2)	X			
Cadmium (7440-43-9)				X
Carbon Disulfide (75-15-0)	X			
Carbon Tetrachloride (56-23-5)	X			
Cesium (7440-46-2)		X	X	X
Chlordecone (143-50-0)			X	X
Chlorfenvinphos (470-90-6)		X	X	X
Chlorinated Dibenzo-p-dioxins (CDDs) (1746-01-6)			X	X
Chlorine (7782-50-5)	X			X
Chlorine Dioxide/Chlorite (10049-04-4/7758-19-2)	X		X	
Chlorobenzene (108-90-7)	X		X	X
Chloroethane (75-00-3)	X	X		
Chloroform (67-66-3)				X
Chloromethane (74-87-3)	X	X		
2,4,5-Trichlorophenol (95-95-4)	X		X	X
2,4-Dichlorophenol (120-83-2)	X		X	X
2-Chlorophenol (95-57-8)	X		X	X
Chlorpyrifos (2921-88-2)			X	X
Chromium (III), insoluble particulates (16065-83-1)	X		X	X
Chromium (III), soluble particulates (16065-83-1)	X	X	X	X
Chromium (VI), particulates (18540-29-9)	X	X	X	
Cobalt (7440-48-4)		X		X
Copper (7440-50-8)	X	X	X	X
Creosote (8021-39-4, 8001-58-9, 8007-45-2)	X	X	X	X

Substance	Oral		Inhalation	
	MRL not derived	RfD not derived	MRL not derived	RfC not derived
Cresols (1319-77-3)			X	X
Cyanide (143-33-9)	X		X	
Cyhalothrin/Karate (68085-85-8)	X		X	X
Cypermethrin (52315-07-8)	X		X	X
Danitol/Fenpropathrin (64257-84-7 (racemic), 39515-41-8 (stereochemistry))	X		X	X
DDT, DDE, DDD (50-29-3, 72-55-9, 72-54-8, 789-02-6, 3424-82-6, 53-19-0)	X		X	X
DEET (N,N-Diethyl-Meta-Toluamide) (134-62-3)		X	X	X
Di(2-ethylhexyl) phthalate (DEHP) (117-81-7)			X	X
Diazinon (33-41-5)		X	X	X
1,2-Dibromo-3-Chloropropane (96-12-8)	X	X	X	
Dibromochloromethane (124-48-1)			X	X
1,2-Dibromoethane (106-93-4)	X		X	
1,2-Dichlorobenzene (95-50-1)			X	X
1,3-Dichlorobenzene (541-73-1)	X	X	X	X
1,4-Dichlorobenzene (106-46-7)		X		
3,3'-Dichlorobenzidine (91-94-1)	X	X	X	X
1,1-Dichloroethane (75-34-3)	X	X	X	X
1,2-Dichloroethane (107-06-2)	X	X		X
1,1-Dichloroethene (75-35-4)			X	
1,2-Dichloroethene (cis-/trans-) (156-59-2/156-60-5)	X		X	X
2,4-Dichlorophenoxyacetic Acid (2,4-D) (94-75-7)			X	X
1,2-Dichloropropane (78-87-5)		X	X	
1,1-Dichloropropene (563-58-6)	X	X	X	X
1,2-Dichloropropene (563-54-2)	X	X	X	X
2,3-Dichloropropene (78-88-6)	X	X	X	X
3,3-Dichloropropene (563-57-5)	X	X	X	X
Dieldrin (60-57-1)			X	X
Diethyl phthalate (DEP) (84-66-2)	X		X	X
Diisopropyl Methylphosphonate (DIMP) (1445-75-6)			X	X
Di-n-butyl Phthalate (84-74-2)	X		X	X
1,3-Dinitrobenzene (99-65-0)	X		X	X
Dinitrocresols (616-73-9, 534-52-1, 497-56-3, 609-93-6)	X	X	X	X
Dinitrophenols (66-56-8, 51-28-5, 329-71-5, 573-56-8, 577-71-9, 586-11-8, 25550-58-7)	X		X	X
2,3-Dinitrotoluene (602-01-7)	X	X	X	X
2,4-Dinitrotoluene (121-14-2)			X	X
2,5-Dinitrotoluene (619-15-8)	X	X	X	X
2,6-Dinitrotoluene (606-20-2)	X	X	X	X
3,4-Dinitrotoluene (610-39-9)	X	X	X	X
3,5-Dinitrotoluene (618-85-9)	X	X	X	X
Di-n-octylphthalate (DNOP) (117-84-0)	X	X	X	X
1,2-Diphenylhydrazine (122-66-7)	X	X	X	X
Disulfoton (298-04-4)			X	X
Endosulfan (115-29-7)			X	X
Endrin (Endrin aldehyde) (72-20-8)			X	X
Ethion (563-12-2)			X	X
Ethylbenzene (100-41-4)	X			
Ethylene Glycol (107-21-1)			X	X
Ethylene Oxide (75-21-8)	X	X	X	X
Fluoranthene (206-44-0)	X		X	X
Fluorene (86-73-7)	X		X	X
Fluorides, Hydrogen Fluoride, and Fluorine (7681-49-4)			X	X
Fluvalinate (69409-94-5)	X		X	X
Formaldehyde (50-00-0)				X
Fuel Oils/Kerosene (68476-30-2 (Fuel oil no 2))	X	X	X	X
Gasoline, Automotive (8006-61-9)	X	X	X	X
Glutaraldehyde (111-30-8)		X		X

Substance	Oral		Inhalation	
	MRL not derived	RfD not derived	MRL not derived	RfC not derived
Guthion (86-50-0)		X		X
Heptachlor/Heptachlor Epoxide (76-44-8)	X		X	X
Hexachlorobenzene (118-74-1)			X	X
Hexachlorobutadiene (87-68-3)	X	X	X	X
alpha-Hexachlorocyclohexane (319-84-6)		X	X	X
beta-Hexachlorocyclohexane (319-85-7)	X	X	X	X
gamma-Hexachlorocyclohexane (58-89-9)	X		X	X
Hexachlorocyclopentadiene (77-47-4)	X			X
Hexachloroethane (67-72-1)	X		X	
Hexamethylene Diisocyanate (822-06-0)	X	X		
n-Hexane (110-54-3)	X	X		
2-Hexanone (591-78-6)			X	
HMX (Cyclotetramethylene Tetranitramine) (2691-41-0)	X		X	X
Hydraulic Fluids (28777-70-0, 68937-40-6, 55957-10-3, 66594-31-8, 63848-94-2, 10702-44-4, 50815-84-4, 55962-27-1, 291-37-2)	X	X	X	X
Hydrazines (302-01-2, 57-14-7, 540-73-8)	X	X	X	X
Hydrogen Sulfide (7783-06-4)	X	X	X	X
Iodide (7553-56-2)		X	X	X
Isophorone (78-59-1)			X	X
Jet A (8008-20-6, 70892-10-3)	X	X	X	X
JP-4 (50815-00-4)	X	X	X	X
JP-5 (8008-20-6, 70892-10-3)	X	X	X	X
JP-7 (HZ0600-22-T)	X	X		X
JP-8 (8008-20-6, 70892-10-3)	X	X	X	X
Lead (7439-92-1)	X	X	X	X
Malathion (121-75-5)			X	X
Manganese (7439-96-5)	X			
Mercuric Chloride (7487-94-7)	X		X	X
Methoxychlor (72-43-5)	X		X	X
Methyl Mercaptan (74-93-1)	X	X	X	X
Methyl Parathion (298-00-0)			X	X
4,4'-Methylenebis(2-Chloroaniline) (101-14-4)		X	X	X
4,4'-Methylenedianiline (101-77-9)	X	X	X	X
Methylenediphenyl Diisocyanate (MDI) (101-68-8)	X	X		
1-Methylnaphthalene (90-12-0)		X	X	X
2-Methylnaphthalene (91-57-6)			X	X
Methyl-t-Butyl Ether (1634-04-4)	X	X		
Mirex (2385-85-5)			X	X
Molybdenum (7439-98-7)	X			X
Naphthalene (91-20-3)	X			
Nickel (7440-02-0)	X			X
Nitrate (84145-82-4)			X	X
Nitrite (84145-82-4)			X	X
Nitrobenzene (98-95-3)	X		X	
Nitrophenols (88-75-5; 100-02-7)	X	X	X	X
n-Nitrosodimethylamine (62-75-9)	X	X	X	X
n-Nitrosodi-n-Propylamine (621-64-7)	X	X	X	X
n-Nitrosodiphenylamine (86-30-6)	X	X	X	X
Otto Fuels (106602-80-6)	X	X		X
Parathion (56-38-2)	X	X	X	X
Pentachlorophenol (87-86-5)			X	X
Perchlorates (10034-81-8, 7778-74-7, 7790-98-9, 7601-89-0, 7791-03-9)			X	X
Perfluorohexane sulfonic acid (PFHxS) (355-46-4)	X	X	X	X
Perfluorononanoic acid (PFNA) (375-95-1)	X	X	X	X
Perfluorooctane sulfonic acid (PFOS) (1763-23-1)	X		X	X
Perfluorooctanoic acid (PFOA) (355-67-1)	X		X	X

Substance	Oral		Inhalation	
	MRL not derived	RfD not derived	MRL not derived	RfC not derived
Permethrin (52645-53-1)	X		X	X
Phenol (108-95-2)	X		X	X
Phosphate Ester Flame Retardants				
Tributyl phosphate (TnBP) (126-73-8)		X	X	X
Tricresyl phosphate (TCP) (1330-78-5)		X	X	X
Tris(1,2-dichloro-2-propyl) phosphate (TDCP) (13674-87-8)		X	X	X
Tris(2-chloroethyl) phosphate (TCEP)(115-96-8)		X	X	X
Plutonium (2023631)	X	X	X	X
Polybrominated Biphenyls (PBBs) (36355-01-8)	X	X	X	X
Polybrominated Diphenyl Ethers (BDEs)				
2,2',4,4'-tetrabromodiphenyl ether (BDE-47) (40088-47-9)	X		X	X
2,2',4,4',5-pentabromodiphenyl ether (BDE-99) (32534-81-9)	X		X	X
2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153) (36483-60-0)	X		X	X
2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether (BDE-209) (67774-32-7)	X		X	X
p,p'-Dibromodiphenyl ether (2050-47-7)	X	X	X	X
Hexabromodiphenyl ether (36483-60-0)	X	X	X	X
Nonabromodiphenyl ether (63936-56-1)	X	X	X	X
Octabromodiphenyl ether (32536-52-0)	X		X	X
Pentabromodiphenyl ether (32534-81-9)	X		X	X
Tetrabromodiphenyl ether (40088-47-9)	X	X	X	X
Tribromodiphenyl ether (49690-94-0)	X	X	X	X
Polychlorinated Biphenyls (PCBs) (11097-69-1)			X	X
Propylene Glycol (57-55-6)	X	X	X	X
Pydrin/Fenvalerate (51630-58-1)	X		X	X
Pyrene (129-00-00)	X		X	X
Pyridine (110-86-1)	X		X	X
Radium (7440-14-4)	X	X	X	X
Radon (10043-92-2, 14859-67-7)	X	X	X	X
RDX (Cyclonite) (121-82-4)			X	X
Resmethrin (10453-86-8)	X		X	X
Selenium (7782-49-2)			X	X
Silica (7631-86-9, 14808-60-7, 14464-46-1, 15468-32-3, 61790-53-2, 68855-54-9, 60676-86-0, 91053-39-3, 112945-52-5, 112926-00-8, 63231-67-4)	X	X	X	X
Silver (7440-22-4)	X		X	X
Stoddard Solvent (8052-41-3)	X	X	X	X
Strontium (7440-24-6)	X		X	X
Styrene (100-42-5)	X			
Sulfur Dioxide (7446-09-05)	X	X	X	X
Sulfur Mustard (505-60-2)	X	X	X	X
Sulfur Trioxide/Sulfuric Acid (7446-11-9, 7664-93-9)	X	X	X	X
Synthetic Vitreous Fibers (HZ0900-26-T)	X	X		X
1,1,2,2-Tetrachloroethane (79-34-5)	X		X	X
Tetryl (479-45-8)	X	X	X	X
Thallium (7440-28-0)	X	X	X	X
Thorium (7440-29-1)	X	X	X	X
Tin and Other Compounds (56-36-9; 683-18-1; 7440-31-5)			X	X
Titanium Tetrachloride (7550-45-0)	X	X		X
Toluene (108-88-3)	X			
Toluene Diisocyanate (TDI) (26471-62-5)	X	X		
Toxaphene (800-35-2)	X	X	X	X
Tralomethrin (66841-25-6)	X		X	X
1,2,4-Trichlorobenzene (120-82-1)			X	X
1,1,1-Trichloroethane (71-55-6)	X		X	
1,1,2-Trichloroethane (79-00-5)	X		X	X
1,2,3-Trichloropropane (96-18-4)	X		X	
1,3,5-Trinitrobenzene (99-35-4)	X		X	X

Substance	Oral		Inhalation	
	MRL not derived	RfD not derived	MRL not derived	RfC not derived
2,4,6-Trinitroltoluene (118-96-7)	X		X	X
Tungsten (7440-33-7)	X	X	X	X
Uranium, insoluble (7440-61-1)	X	X		X
Uranium, soluble (7440-61-1)	X			X
Used Mineral-based Crankcase Oil (8002-05-9)	X	X	X	X
Vanadium (740-62-2)	X			X
Vinyl Acetate (108-05-4)	X	X	X	
Vinyl Chloride (75-01-4)			X	
White Phosphorus (7723-14-0)	X		X	X
Zinc (7440-66-6)			X	X