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Assignment of Toxicity Values to a Standardized Framework of Non-Cancer Toxicity Target Organs and Systems for Use in Chemical Mixtures Health Risk Assessment

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1. PURPOSE

This document provides a method for assigning toxicity values to a standardized framework of toxicity target organs and systems (TTOS). A comprehensive, standardized framework does not yet exist within published health risk assessment methods.

A standard approach to TTOS assignments allows for a consistent approach to the calculation of noncancer hazard indices (HIs) that are segregated by the type of toxic effect. A site-specific risk assessment that estimates a total, non-segregated HI greater than 1.0 indicates the possibility of a multiple chemical exposure concern. The segregation of HI estimates is a basic risk assessment screening-level method for determining if simultaneous exposure to multiple chemicals may actually require further investigation before risk-based decisions are made.

2. BACKGROUND

Environmental health risk assessments often involve assessing the potential health effects of exposure to more than one chemical (i.e., mixtures). Because the possible number of chemical combinations is large, very few toxicological studies with chemical mixtures have been performed. To address the uncertainty in evaluating the risk of cumulative chemical exposures, a conservative risk assessment approach is used where hazard quotients (HQs) for each chemical are summed into a single HI for the receptor. The original U.S. Environmental Protection Agency (EPA) method assumes that simultaneous exposure to multiple chemicals of concern will adversely affect (target) the body without regard to tissue or organ specificity and will act in an additive manner. The EPA recognized this assumption and provided guidance that a HI for toxicity specific to the target could be calculated (EPA 1989). The EPA later elaborated on this guidance by providing slightly more detailed approaches based on the level of data available for the mixture of interest (EPA 2000). However, the EPA has not prescribed a standardized methodology that delineates specific target organs or systems and how precisely to assign target organ/system toxicity in regards to critical effect. The Agency for Toxic Substances and Disease Registry (ATSDR) provided further guidance in mixture-specific interaction profiles (ATSDR 2001). While these profiles provide data pertaining to common mixtures of interest, they are not readily applied to other, less common, mixtures. This technical guide (TG) supplement presents a phased approach using a standardized hierarchy to assign targets of toxicity specific to route and duration of exposure.

2.1 The Traditional Risk Assessment Guidance for Superfund (Part A) Approach

The EPA Risk Assessment Guidance for Superfund (RAGS) Part A (baseline risk assessment) provides overarching guidance on the evaluation of potential adverse health effects due to chemical exposure (EPA 1989). Adverse health effects are categorized as either carcinogenic or non-carcinogenic; for the purposes of this supplement, only the non-cancer endpoints are considered. To assess the non-cancer effects for a multichemical or mixture exposure, the HQs for each pertinent substance in the mixture are summed into a single HI. Several assumptions are made with this approach:

(1) Supporting toxicity data (reference dose (RfD)) must be available for all of the chemicals in the mixture.
(2) The levels and period of exposure for each chemical are known.
(3) The toxicity is dose additive.
(4) Simultaneous subthreshold exposures could result in an adverse effect.

There are limitations to this approach, as not all RfDs have equivalent certainty/confidence nor do the critical effects have equivalent biological significance. Additionally, not all chemicals act, in combination, as dose additive. In some cases, the toxicity increases in a nonlinear manner as a result of synergism or potentiation. Conversely, the toxicity may be blunted through antagonism of the chemicals. Finally, the assumption of dose additivity suggests that the mechanism of action (MOA) is the same for all of the compounds in the mixture. In many if not most cases, the MOA for a chemical has not been defined and chemicals with different MOA can impact toxicity via synergism, potentiation or antagonism. In recognition of these limitations, RAGS does allow for more sophisticated approaches for refining risk estimates as referred to in the EPA documents described in the following section.

The RAGS guidance allows for the "segregation of HIs by effect and mechanism of action" (EPA 1989). Though RAGS does not provide explicit guidance on how to assign substance-specific toxicity values to different effects and/or mechanisms of action, it does provide some guidance. For example:

- "The RfD[1] is developed from a NOAEL[2] [or benchmark dose] for the most sensitive, or critical, effect based in part on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented. It should be remembered during the risk characterization step of the risk assessment that if exposure levels exceed the RfD, then adverse effects in addition to the critical toxic effect may begin to appear" (EPA 1989).

- "If one of the effect-specific hazard indices exceeds unity, consideration of the mechanism of action might be warranted. A strong case is required, however, to indicate that two compounds which produce adverse effects on the same target organ system (e.g., liver), although by different mechanisms, should not be treated as dose additive" (EPA 1989).

[1] Reference dose (RfD).
[2] No-observable-adverse-effect-level (NOAEL)

- "Segregation of hazard indices requires identification of the major effects of each chemical; including those seen at higher doses than the critical effect…Major effect categories include neurotoxicity, developmental toxicity, reproductive toxicity, immunotoxicity, and adverse effects by target organ (i.e., hepatic, renal, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, and dermal/ocular effects). Although higher exposure levels may be required to produce adverse health effects other than the critical effect, the RfD can be used as the toxicity value for each effect category as a conservative and simplifying step" (EPA 1989).

Under the RAGS framework, only general guidance for approaching a mixtures risk assessment is provided. The guidance is limited because risk assessments are performed on a site-by-site basis, and each site represents a unique situation and mixture exposure scenario. These circumstances have resulted in the development of inconsistent or incomplete approaches across the various organizations that perform risk assessments under the RAGS framework. For the purposes of this supplement, only chemicals that have defined RfDs or Reference Concentrations (RfCs) are considered. It is beyond the scope of this document to address chemicals that do not have an established toxicity value. Additionally, because the critical effect is considered to be protective, noncritical effects are not incorporated into this method.

2.2 EPA Mixtures Guidance (1986), Supplementary Mixtures Guidance (2000), and Cumulative Effects Resource Document (2007)

The 1986 mixtures guidance (EPA 1986) recommended three approaches for use in chemical risk assessments; the supplementary guidance (EPA 2000) incorporates and expands on them. The first approach, used when toxicity data are available on the mixture of concern, entails a qualitative risk assessment performed directly from the preferred data. The second approach is used when no toxicological data are available for the mixture, but data from a similar mixture are available. In this case, the guidance recommends using the surrogate toxicity data to derive a qualitative risk assessment for the mixture of concern (EPA 2000). The third recommended approach is to evaluate the mixture of concern by analyzing its components; this approach is used when no direct or similar mixture data are available.

The EPA supplementary guidance (2000) provides more specific details on the nature of the desired information and on the procedures to use in data analysis. These methods include using whole-mixture data from a toxicologically similar mixture, incorporating information on toxicological interactions to modify a HI, and generalized procedures for mixtures involving classes of similar chemicals (EPA 2000). The method for a whole mixture approach varies, depending on the type of available data. These methods include—

(1) Evaluating the mixture as a whole if there are health effects and exposure data,
(2) Evaluating a sufficiently similar mixture if data exists, or
(3) Evaluating a group of similar mixtures if data exists (EPA 2000).

The component-based approach mainly focuses on dose- or response-additive models when there is insufficient evidence of toxicological interactions. However, if there is any quantitative information on toxicological interaction, it should be incorporated into the component-based approach. Thus, there are three main areas of focus: chemicals that are toxicologically similar (dose addition), those that are toxicologically independent (response addition), and those that have evidence of toxicological interactions (EPA 2000). The primary method for component-based chemical risk assessments is the HI method, which is based on dose addition. Two additional methods based on dose addition are an interaction-based HI method and the Relative Potency Factor (RPF) method. The last component-based approach method included in the guidance is the Response Addition Method, which tends to be applied when the components of a mixture are understood to be toxicologically independent (EPA 2000).

The cumulative effects resource document (EPA 2007) presents numerous methods of chemical grouping to simplify cumulative risk assessment into manageable categories. These groups are based on potential for co-occurrence, either through common release mechanisms, sources, fate and transport; co-existence in media at a given time; or a common physiological endpoint. The method presented here expands upon the latter, termed Target Organ Toxicity Doses (TTDs), by providing a standardized methodology for TTD grouping and, subsequently, HI segregation into these groups.

The methods described in these three EPA documents present several approaches to estimating the toxicity of chemical mixtures, but they are elaborate and not necessarily based on the critical effect. While the components-based HI method approach is the most similar to both the RAGS approach and the method described herein, its implementation is more elaborate compared to the simple, target organ approach presented here. Therefore, using the components-based HI method as a screening-level approach is not as attractive, even though it introduces several approaches that scale down the level of conservatism.

2.3 ATSDR Interaction Profiles and Joint Toxic Action of Chemical Mixtures Guidance

The ATSDR Interaction Profiles recommend exposure-based approaches for evaluating data on the toxicology of a priority mixture and the joint toxic action of the chemicals in the mixture (ATSDR 2001). Interaction profiles focus on identifying the health effects of concern, determining if the data can be used as a basis for a minimum risk level (MRL) for the mixture and if physiologically-based pharmacokinetic/pharmacodynamic models (PBPK/PD) would be relevant to use for the mixture. Interaction profiles tend to provide more guidance on health effects and toxicological data and also include information about any relevant studies on the mixture. Based on the provided information, a recommended approach is suggested, as is the reasoning behind it. The interaction profiles also provide a breakdown of critical effects and target organs, or endpoints, of the chemical mixtures. Note that interaction profiles are intended for use with simple mixtures, which are defined as mixtures containing no more than ten chemicals (EPA 2000). While interaction profiles can be very useful, they are available in limited number. As of October 2020, only 15 interaction profiles appeared on the ATSDR website (ATSDR 2014); 12 had been finalized, and 3 were considered draft versions.

Another notable guidance document is the ATSDR's *Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors* (ATSDR 2018), which is consistent with the EPA's mixture guidance documents. The manual explains the two main concepts of examining the mixture as a whole, or, if the relevant data are not available, addressing the components of the chemical.

While the ATSDR approach builds from the basic HI approach in RAGS and is similar to the approach in this supplement, it focuses more on the interactions between certain select chemicals than on addressing the critical effect of each individual chemical. While the ATSDR methods may be useful at a site with simple mixtures, the ATSDR approach has limited utility for the purposes of a simple, standard screening-level approach. The APHC method described herein uses a basic version of the toxicity-based HI approach, which does not include chemical interactions (e.g., synergistic or antagonistic effects). By limiting the emphasis of chemical-specific effects and focusing on the critical effects, this HI approach is more conservative than those suggested in the other guidance documents discussed herein.

3. ASSIGNING TOXICITY TARGET ORGANS AND SYSTEMS

3.1 Intent and Application

The framework and method presented here are intended to provide a screening tool for use when the summed total HI of a mixture of chemicals is greater than 1.0. The method relies upon placing each toxicity value applicable to the particular site under assessment into a target organ and system category (Adams et al. 2017). Thus, the method can be utilized across routes or durations of exposure if a toxicity value is available that is intended for use with the exposure pattern chosen. If it is determined that unity is exceeded in a single organ or system, the risk assessor will need to conduct a more extensive review in order to proceed with an assessment. This document is not intended to provide a standalone method but rather to standardize a step within the larger risk assessment process.

3.2 Conceptual Framework

The method presented here is based on a simple hierarchical framework for segregating HIs according to anatomical organization. The human body is composed of several systems consisting of organs, tissues, structures, and cells. Each system contributes to the functionality of the entire organism. For the purposes of this TG supplement, the mode and/or mechanism of action (collectively designated as "MOA") are not used for the development of the HI. The main reason for this exclusion is that for most chemicals, the MOAs, which occur at the subcellular level, have not been characterized, and the critical effect is descriptive of an organ or tissue level response. When multiple chemicals are considered, the available toxicity information between chemicals in a mixture are only comparable at a similar descriptive level, so unless the MOAs are available for all the chemicals in the mixture of concern, the MOAs would revert to the appropriate organ- or tissue-level responses. Although the EPA recommends using MOAs in cumulative risk assessments, the EPA provides no standardized guidance for incorporating MOA information (Public Law 1996, EPA 1998). This TG methodology is designed to

standardize the simplest approach and at this juncture, the MOA database is incomplete and not universally applicable. As more mechanistic toxicity data are developed, the utility of incorporating the data into the HI method can be reassessed.

3.3 Framework Terminology

The following definitions are adopted for the purpose of describing this framework.

- Target System: An assembly of tissue structures (or organs) that together perform a specific function. These target systems may be impacted in specific ways from exposure to a specific substance.

- Target Organ: A specific organ or a collection of tissues having organ status (i.e., a group of cells defined by similar function) from which an adverse effect has been reported in the literature.

- Mode/Mechanism of Action: MOAs are considered collectively for this TG. MOAs describe key subcellular (e.g., molecular and biochemical) events and processes (e.g., absorption, metabolism and distribution) leading to functional changes that explain the nature of an observed adverse effect (Borgert et al. 2004; Faustman and Omenn 2008).

3.4 Standardized Target Systems and Target Organs

Twelve target systems have been defined, integrating information from three reference texts:

- *Anatomy & Physiology* (Thibodeau and Patton 1993).
- *Gray's Anatomy* (Williams et al. 1995).
- *Van Nostrand's Scientific Encyclopedia* (Considine 2002).

A list of possible target organs associated with these target systems is also presented. Since target organs may be added or edited over time as needed, this method document will be revised accordingly. Specific toxicity values for a given substance can be linked to one or more of these target organs and, thus, to the target systems. For this method, 12 target systems and a "whole organism" category were chosen. The whole organism category is designed to address situations where toxicity data describe only general organism-level effects such as weight loss or gain. The major effect and target organ categories listed by the EPA in RAGS (EPA 1989) served as a starting point, and the reproductive system was categorized as two systems, specific to males or females. **Table 1** presents the standard target organs and systems (Adams et al. 2017).

Table 1. Standardized Toxicity Target Organs and Systems

Target Systems[a,b]	Target Organs[b,c]		
Alimentary accessory organs	Teeth Tongue	Salivary Glands Pancreas	Liver Gall bladder
Alimentary system	Alimentary system – unspecified Gastrointestinal tract – unspecified Mouth/palate Pharynx	Esophagus Stomach Large intestine	Small intestine Rectum Anal canal
Endocrine system	Endocrine system – unspecified Adrenal glands Thyroid glands Parathyroid glands Pituitary gland	Pineal gland Hypothalamus Pancreas Other ducted glands	Neurosecretory systems/cells Chromaffin systems/cells Gonads
Haemolymphoid system	Central Venous System – unspecified Lymph system – unspecified Circulatory system – unspecified Immune system – unspecified Heart Arterial system Venous system	Capillaries Blood (excludes white blood cells/ immune system) Bone marrow White Blood Cells	Blood vessels Lymph Lymph nodes/tissues Thymus Spleen Thoracic duct
Integumental system	Skin Eyes	Hair	Nails
Muscular system	Muscles (non-heart)		
Nervous system	Nervous system – unspecified Central Nervous System – unspecified Peripheral Nervous System – unspecified Visual perception (ocular effects)	Auditory perception (hearing effects) Olfactory perception (smelling effects) Taste perception Touch perception (tactition)	Balance (vestibular sense) Brain Spinal cord Nerves Optic nerve
Reproductive System (Male)	Male reproduction – unspecified Testes Sperm	Prostate Urethra Mammary glands	Male supporting structures
Reproductive System (Female/Fetus)	Female reproduction – unspecified Developmental – unspecified Ovaries	Oocytes Uterus Vagina	Conceptuses/Fetuses/Neonates Mammary glands
Respiratory System	Respiration – unspecified Nasal-pharynx-nose-paranasal sinuses	Larynx Lungs Trachea	Upper respiratory system Lower Respratory system
Skeletal System	Bone Connective tissue	Cartilage Ligaments	
Urinary System	Bladder	Kidneys	Ureters/urethra
Whole Organism	Whole Organism – unspecified		

Notes:
[a] This table has been designed using three reference texts: *Gray's Anatomy* (Williams et al 1995), *Van Nostrand's Scientific Encyclopedia, 9th Edition* (Considine 2002), and *Anatomy and Physiology* (Thibodeau and Patton 1993).
[b] See definitions in **Section 3.3**.
[c] Unspecified target organs are applicable when a substance has been reliably stated as either targeting or affecting that system, whether or not the reported effects are associated with a specific target organ or tissue within that system.

The target systems are historically delineated by anatomy (alimentary, skeletal, respiratory, etc.) and to a lesser extent by physiology (endocrine and haemolymphoid). The anatomically based systems have both structural and functional components. For example, the “alimentary accessory organs” (AAO) system consists of teeth, tongue, salivary glands, pancreas, liver, and gall bladder. The groupings of these tissues and organs are based on their individual contributions to the functional performance of the alimentary system. Note that organs that are structural components may be affected by a toxicant differently than organs that have a functional role in a given system. For example, toxicological findings on the tongue may be related to portal of entry effects, e.g., oral cavity contact with the chemical resulting in burns or blisters on the tongue. In this circumstance, it may be useful to evaluate the chemical-specific relevant toxicity reports for other indicators of portal of entry effects. Understanding whether portal of entry effects are present will facilitate the risk assessment process if the route of exposure changes or if multiple routes of exposure are present.

An alternative approach based solely on key organ functional physiology (pathway approach) was evaluated but not chosen at this time. The pathway approach would merge the target organs and systems into basic processes: hepatotoxicity, nephrotoxicity, neurotoxicity, cardiovascular toxicity, respiratory toxicity, immunotoxicity, and reproductive toxicity. Although this approach would simplify the assignment process, it was deemed inadequate for assigning critical effects derived from specific histological or biomarker findings. Conversely, in many cases, there is insufficient published data beyond gross morphological or blood chemistry findings to make an assumption regarding the affected physiological process. As with the MOA approach, the pathway approach is limited by the disparity of available toxicity data for each chemical. As more mechanistic data become available, it may be worthwhile to revisit implementation of the pathway approach to determine if functional process categorization based on mode(s) of action reduces the uncertainty and aids the risk assessor in identifying the critically affected organ, e.g., the liver or kidney.

4. ASSIGNMENT OF TOXICITY VALUES TO TARGET ORGANS AND SYSTEMS

4.1 Target System/Organ Assignment Protocol

In order to systematically perform HI segregations by target organs and systems, every noncancer toxicity value must be assigned to one or more of the standardized target organs. Under this framework (illustrated in Table 1), each target organ assignment is automatically linked to a target system. The following steps are involved in the TTOS assignments for each toxicity value.

It is first necessary to select the appropriate toxicity reference value to be used. Once a value is chosen for each chemical of interest, the critical effect used to calculate the value must be investigated. While the source documents may not always provide both the target organ and the corresponding target system for the critical effect, most will provide at least one. If a critical effect identifies a particular target organ, then that organ determines the target system (refer to **Table 1**).

If the benchmark value's critical effect does not identify the target system or organ, then knowledge about the critical effect must be used to determine which of the target organs and its associated system best fits the benchmark value's critical effect. This determination may lead to a number of complications including, but not limited to, the following:

- The RfD is derived solely from whole organism observations (e.g., weight loss), and no additional data regarding target organs/systems are available. When this occurs, the whole organism category is selected. Examples of other observations that are grouped into the whole organism category include (1) instances where the only critical effect provided is the change in multiple unspecified organ weights without specific details regarding absolute or relative weight changes; (2) reduced survival, or (3) increased mortality. Because these toxic signs are so general, the target organ equivalent for the whole organism target system is defined as "unspecified."

- Clinical chemistry changes or biomarkers are used as the critical effect. In such instances, the relevant organ or tissue that pertains to the test is selected as the target organ. Some common examples include alanine aminotransferase (ALT) — a marker for hepatocyte injury — and serum/plasma/blood cholinesterase (ChE) — a surrogate marker for central nervous system ChE activity.

- An inhalation benchmark value has been derived by means of route-to-route extrapolation from an oral benchmark value. When this occurs, the target organ/system associated with the oral benchmark will also be used for the inhalation benchmark. Route-to-route extrapolation is accepted when the chemical in question is believed to have the same toxic effect regardless of route of exposure. There are additional factors to consider when using route-to-route exposure extrapolation. First, the duration of exposure may be different for occupational versus environmental scenarios. Secondly, inhalation exposures can be either particulate or vapor, either of which can influence the toxic effect and response.

Three particular organs are listed in more than one target system: the pancreas, the ovaries, and the testes. The pancreas, as shown in **Table 1,** is listed under both the AAO system and the endocrine system. When this endpoint is assigned, the value would be assigned to both target systems, and it would be included in the HI calculations for both target systems. The ovaries and testes are listed not only for the reproductive systems of females and males, respectively, but also for the endocrine system as gonads, to include both sexes. Generally, the reproductive endpoint should be used when histological or physical changes are seen in the organ, as well as changes to the respective gametes they produce. When changes in sex hormones such as estrogen, androgen, testosterone, and progesterone are noted, the endocrine system assignment is appropriate. Critical effects that may appear to fit into two different target systems should be categorized to match the effect as specifically as possible. For example, if the critical effect is for the eyes, it should be determined whether the target system is under the integumental system, if unspecified effects are provided, or under the nervous system, if vision is affected.

The examples below show how to determine the target system and organ for a chemical, using several different benchmark values as the starting point.

4.2 Toxicity Target Organs and Systems Assignment Examples

4.2.1 Integrated Risk Information System Reference Dose for 1,1,2-Trichoropropane

As of 26 September 1988, the Integrated Risk Information System (IRIS) RfD for 1,1,2-Trichloropropane is 0.005 mg/kg d. The stated critical effect is “mild lesions in the liver, kidney and thyroid” from an oral subchronic rat study (EPA 2016). The following assignments were made using the standardized TTOS table.

Chemical:	1, 1, 2-Trichloropropane
Toxicity Value:	IRIS RfD of 0.005 mg/kg·d
Critical Effect:	Mild lesions in the liver, kidney and thyroid
Assigned Targets:	(1) AAO – Liver
	(2) Urinary System – Kidneys
	(3) Endocrine System – Thyroid glands

4.2.2 IRIS Reference Dose for Dacthal

As of 1 August 1994, the IRIS RfD for Dacthal is 0.01 mg/kg·d. The stated critical effect is “effects on the lungs, liver, kidney, thyroid and thyroid hormones in both males and females and the eyes of females” from a 2-year rat feeding study (EPA 2016). The following assignments were made using the standardized TTOS table. In the effects noted, the eyes of females only were affected. This outcome will be incorporated into the HI equation to protect the females despite resulting in a more conservative approach for the males.

Chemical:	Dacthal
Toxicity Value:	IRIS RfD of 0.01 mg/kg·d
Critical Effect:	Effects on the lungs, liver, kidney, thyroid, and thyroid hormones in both males and females and also the eyes in females alone
Assigned Targets:	(1) Respiratory System – Lungs
	(2) AAO – Liver
	(3) Urinary System – Kidneys
	(4) Endocrine System – Thyroid glands
	(5) Integumental System – Eyes

4.2.3 IRIS Reference Concentration for 1,3-Dichloropropene

As of 25 May 2000, the IRIS RfC for 1, 3-Dichloropropene is 0.02 mg/m^3. The critical effect is listed as hypertrophy/hypertension of the nasal respiratory epithelium from a chronic inhalation study in mice (EPA 2016). The following assignments were made using the standardized TTOS table. There are three possible choices for the target organ due to the nasal respiratory epithelium being the specified critical effect area. Since nasal respiratory epithelium is not a listed organ in the respiratory system, it is necessary to see if, based on its definition and location, it could be associated with a target organ listed under the respiratory system in the standardized TTOS table. The respiratory epithelium lines the respiratory tract, which is divided

into three segments: the upper respiratory tract, respiratory airways, and the lungs (Spence and Mason 1999). The upper respiratory tract comprises the nose and nasal passages, paranasal sinuses, and the pharynx. Because the critical effect specifies nasal respiratory epithelium, and "nasal" pertainsg to the nose, the three target organs that are closely related to nasal respiratory epithelium are the nose, nasal-pharynx, and paranasal sinuses.

Chemical:	1,3-Dichloropropene
Toxicity Value:	IRIS RfC of 0.02 mg/m^3
Critical Effect:	Hypertrophy/hyperplasia of the nasal respiratory epithelium
Assigned Targets:	Respiratory System – Nose, Nasal-pharynx, paranasal sinuses

4.2.4 IRIS Reference Concentration for 1,2,4-Trimethylbenzene

As of 09 September 2016, the IRIS RfC for 1, 2, 4-Trimethylbenzene is 0.06 mg/m^3. The stated critical effect is "decreased pain sensitivity" from a subchronic inhalation study in rats (EPA 2016). The listed target system is the nervous system, with the assigned target organ being the peripheral nervous system–unspecified, because pain sensation occurs in the peripheral nervous system (Friel 1985). (See Table 1.)

Chemical:	1,2,4-Trimethylbenzene
Toxicity Value:	IRIS RfC of 0.06 mg/m^3
Critical Effect:	Decreased pain sensitivity
Assigned Targets:	Nervous System – Peripheral nervous system - unspecified

4.2.5 California EPA Acute Reference Exposure Level for Methylene Chloride

As of 1 June 2008, the California EPA (CalEPA) acute reference exposure level (REL) for Methylene chloride is 14 mg/m^3. The critical effect is listed as "subtle impairment of the central nervous system" from an acute inhalation study on healthy adults (CalEPA 2008). The listed target system is the nervous system, with the assigned target organ being the central nervous system-unspecified, because of the lack of specific detail as to where the impairment occurs within the nervous system (see Table 1).

Chemical:	Methylene chloride
Toxicity Value:	CalEPA acute REL of 14 mg/m^3
Critical Effect:	Subtle impairment of the central nervous system
Assigned Targets:	Nervous System – Central nervous system – unspecified

4.2.6 IRIS Reference Dose for Norflurazon

As of 31 January 1987, the IRIS oral RfD for Norfluazon is 0.04 mg/kg d. The critical effect is listed as “Liver and thyroid effects” from a 6-month dog feeding study (EPA 2016). The liver effects were increased weights, congestion, and swelling of the hepatocytes; and the thyroid changes involved a slight increase in colloidal vacuoles (EPA 2016). The listed target organs are the liver and the thyroid, with the assigned target systems being the AAO system and the endocrine system, respectively (see Table 1).

Chemical:	Norfluazon
Toxicity Value:	IRIS oral RfD is 0.04 mg/kg d
Critical Effect:	Liver and thyroid effects
Assigned Targets:	(1) AAO System – Liver
	(2) Endocrine System – Thyroid

4.2.7 IRIS Reference Dose for Hexachloroethane

As of 23 September 2011, the IRIS oral RfD for Hexachloroethane is 0.0007 mg/kg d. The critical effect is listed as “degeneration of renal tubules” from a rat subchronic study (EPA 2016). The assigned target system is the urinary system. The assigned target organs are the kidneys (see Table 1).

Chemical:	Hexachloroethane
Toxicity Value:	IRIS oral RfD is 0.0007 mg/kg d
Critical Effect:	Degeneration of renal tubules
Assigned Targets:	(1) Urinary System – Kidneys

4.2.8 IRIS Reference Dose for Ethylbenzene

As of 31 January 1987, the IRIS oral RfD for Ethylbenzene is 0.1 mg/kg d. The critical effect is listed as “Liver and thyroid toxicity” from a rat subchronic-to-chronic oral bioassay (EPA 2016). The assigned target systems are AAO and endocrine. The assigned target organs are the liver and the thyroid gland (see Table 1).

Chemical:	Ethylbenzene
Toxicity Value:	IRIS oral RfD is 0.1 mg/kg d
Critical Effect:	Liver and thyroid toxicity
Assigned Targets:	(1) AAO System – Liver
	(2) Endocrine System – Thyroid

5. CHARACTERIZING NON-CANCER HAZARDS BY TARGET SYSTEMS AND ORGANS

5.1 Segregation of the Hazard Index

Once the target organs and/or systems are identified for each chemical, the next step is to develop the HIs based on target organ/system toxicity. Note that segregation is not necessary if the total HI is less than 1.0, as there is no discernible excess risk with the hazards in combination. Once all the chemicals have been placed into corresponding groups, the HIs are then summed within each group to obtain a HI for each target system and target organ, depending on the type information available for each exposure pathway. Using this strategy, the risk assessor will better understand the extent of the hazard the chemicals could pose for each endpoint. For completeness, the effects categorized as "whole organism" are carried through the assessment process. In the event that the whole organism HI is larger than the HI for the other target systems/organs, a nonsegregated HI should be calculated and used instead.

5.2 Hazard Index Equations

The standard HI equation (EPA 1989) states that the HI is equal to the sum of the individual chemical HQs, where the HQ is the exposure level or intake divided by the RfD for a particular toxicant. For the purposes of this document, the same equation will be applied; however, RfD will be changed to reference value (RfV). RfV is a general exposure dose that can represent RfDs, RfCs, or RELs (EPA, 2002). See Equation 1.

$$HI = \frac{E_1}{RfV_1} + \frac{E_2}{RfV_2} + \ldots + \frac{E_i}{RfV_i} \qquad \text{(Equation 1)}$$

Where:
HI = Hazard Index (nonsegregated)
E_i = Exposure estimate for the i^{th} chemical
RfV_i = Reference value for the i^{th} chemical

Note: E_i and RfV_i are expressed in the same units and represent the same exposure time.

To obtain the segregated HI for target organs or systems, a slightly modified applicationof this general equation is necessary. Instead of summing all of the chemicals together, only those chemicals that have been grouped together within the same target organ and/or target system will be summed together. This method is repeated for each target organ and system, resulting in a separate HI for each. Following the guidance stated in the RAGS, "If one of the effect-specific hazard indices exceeds unity, consideration of the mechanism of action might be warranted. A strong case is required, however, to indicate that two compounds which produce adverse effects on the same target organ (e.g., liver), although by different mechanisms, should not be treated as dose additive" (EPA 1989).

Equation 2 illustrates how the target organ HI is calculated, and Equation 3 shows how the target system HI is calculated (Adams et al. 2017).

$$HI_j = \sum_{i=1}^{N_j} \left(\frac{E_{ij}}{RfV_i}\right) \quad \text{(Equation 2)}$$

Where:
HI_j = Hazard index for the j^{th} target organ
E_{ij} = Exposure estimate for the i^{th} chemical assigned to the j^{th} target organ
RfV_i = Reference value for the i^{th} chemical
N_j = Number of chemicals assigned to the j^{th} target organ

Note: E_{ij} and RfV_i are expressed in the same units and represent the same exposure time.

$$HI_k = \sum_{i=1}^{N_k} \left(\frac{E_{ik}}{RfV_i}\right) \quad \text{(Equation 3)}$$

Where:
HI_k = Hazard index for the k^{th} target system
E_{ik} = Exposure estimate for the i^{th} chemical assigned to the k^{th} target system
RfV_i = Reference value for the i^{th} chemical
N_k = Number of chemicals assigned to the k^{th} target organ

Note: E_{ik} and RfV_i are expressed in the same units and represent the same exposure time.

5.3 Example of Hazard Index Segregation

This section provides an example of implementing the HI segregation method.

This example demonstrates how to perform HI segregation for an oral exposure to soil at a specific residential site using the TTOS assignments for a selection of the example chemicals in shown Section 4. Note that the risk assessor first calculated an unsegregated HI that was greater than 1.0. Based on this exposure scenario, only those chemicals with oral RfDs will be used; however, the method may be used across exposure pathways as long as the reference values chosen pertain to the pathway of the exposure to which they are being compared. The five example chemicals with TTOS assignments for oral RfDs are 1, 1, 2-Trichloropropane, Dacthal, Norflurazon, Hexachloroethane, and Ethylbenzene. **Table 2** presents the TTOS assignments for these chemicals.

Table 2. TTOS Assignments for IRIS Oral Reference Doses of Example Chemicals

Target Systems	Chemicals	Target Organs	Chemicals
Alimentary Accessory Organs	1,1,2-Trichloropropane, Dacthal, Norflurazon, Ethylbenzene	Liver	1,1,2-Trichloropropane Dacthal, Norflurazon, Ethylbenzene
Urinary System	1,1,2-Trichloropropane, Dacthal, Hexachloroethane	Kidney	1,1,2-Trichloropropane Dacthal, Hexachloroethane
Endocrine System	1,1,2-Trichloropropane, Dacthal, Norflurazon, Ethylbenzene	Thyroid	1,1,2-Trichloropropane Dacthal, Norflurazon, Ethylbenzene
Respiratory System	Dacthal	Lungs	Dacthal
Integumental System	Dacthal	Eyes	Dacthal

Table 2 shows five different target systems and five target organs for which a HI will need to be calculated. To calculate the segregated HIs, the intakes for the chemicals must first be calculated from hypothetical soil concentrations. For the purposes of this example, the intake values were generated using the EPA's Human Health Risk Assessment Guidelines equation and default values for the ingestion of chemicals in soil at a residential site (EPA 1989). Soil concentration values and corresponding intake rates, RfDs, and individual HI calculations are shown in **Table 3**. Tese generated individual HIs can now be used to calculate the HIs for each of the target organs and systems. Since there are only five chemicals in this example, the equations are the same for both the target organs and systems, but all are shown to provide a better understanding of the process. The example equations follow **Table 3**.

Table 3. Concentrations, Intake Rates, RfDs, and Individual HIs for Example Chemicals

Chemical	Soil Concentration (mg/kg)	Intake Rate (mg/kg d)	RfD (mg/kg d)	HI
1,1,2-Trichloropropane	2000	2.9E-03	0.005	5.7E-01
Dacthal	1000	1.4E-03	0.01	1.4E-01
Norflurazon	2000	2.9E-03	0.04	7.1E-02
Ethylbenzene	2000	2.9E-03	0.1	2.9E-02
Hexachloroethane	450	6.4E-04	0.0007	9.2E-01

5.3.1 Target System: Alimentary Accessory Organs

$$HI_k = \sum_{i=1}^{N_k} \left(\frac{E_{ik}}{RfV_i}\right) = \frac{E_1}{RfV_1} + \frac{E_2}{RfV_2} + \frac{E_3}{RfV_3} + \frac{E_4}{RfV_4} = 0.81 \quad \text{(Equation 4)}$$

Where:
HI_k = Hazard index for the alimentary accessory organs
E_1 = Intake value for 1, 1, 2-Trichloropropane (2.9E-3 mg/kg d)
E_2 = Intake value for Dacthal (1.4E-3 mg/kg d)
E_3 = Intake value for Norflurazon (2.9E-3 mg/kg d)
E_4 = Intake value for Ethylbenzene (2.9E-3 mg/kg d)
RfV_1 = Reference dose for 1, 1, 2-Trichloropropane (0.005 mg/kg d)
RfV_2 = Reference dose for Dacthal (0.01 mg/kg d)
RfV_3 = Reference dose for Norflurazon (0.04 mg/kg d)
RfV_4 = Reference dose for Ethylbenzene (0.1 mg/kg d)

5.3.2 Target System: Urinary System

$$HI_k = \sum_{i=1}^{N_k} \left(\frac{E_{ik}}{RfV_i}\right) = \frac{E_1}{RfV_1} + \frac{E_2}{RfV_2} + \frac{E_3}{RfV_3} = 1.63 \quad \text{(Equation 5)}$$

Where:
HI_k = Hazard index for the urinary system
E_1 = Intake value for 1, 1, 2-Trichloropropane (2.9E-3 mg/kg d)
E_2 = Intake value for Dacthal (1.4E-3 mg/kg d)
E_3 = Intake value for Hexachloroethane (6.4E-4 mg/kg d)
RfV_1 = Reference dose for 1, 1, 2-Trichloropropane (0.005 mg/kg d)
RfV_2 = Reference dose for Dacthal (0.01 mg/kg d)
RfV_3 = Reference dose for Hexachloroethane (0.0007 mg/kg d)

5.3.3 Target System: Endocrine System

$$HI_k = \sum_{i=1}^{N_k} \left(\frac{E_{ik}}{RfV_i}\right) = \frac{E_1}{RfV_1} + \frac{E_2}{RfV_2} + \frac{E_3}{RfV_3} + \frac{E_4}{RfV_4} = 0.81 \quad \text{(Equation 6)}$$

Where:
HI_k = Hazard index for the endocrine system
E_1 = Intake value for 1, 1, 2-Trichloropropane (2.9E-3 mg/kg d)
E_2 = Intake value for Dacthal (1.4E-3 mg/kg d)
E_3 = Intake value for Norflurazon (2.9E-3 mg/kg d)
E_4 = Intake value for Ethylbenzene (2.9E-3 mg/kg d)
RfV_1 = Reference dose for 1, 1, 2-Trichloropropane (0.005 mg/kg d)
RfV_2 = Reference dose for Dacthal (0.01 mg/kg d)
RfV_3 = Reference dose for Norflurazon (0.04 mg/kg d)
RfV_4 = Reference dose for Ethylbenzene (0.1 mg/kg d)

5.3.4 Target System: Respiratory System

$$HI_k = \sum_{i=1}^{N_k} \left(\frac{E_{ik}}{RfV_i}\right) = \frac{E_1}{RfV_1} = 0.14 \quad \text{(Equation 7)}$$

Where:
HI_k = Hazard index for the respiratory system
E_1 = Intake value for Dacthal (1.4E-3 mg/kg d)
RfV_1 = Reference dose for Dacthal (0.01 mg/kg d)

5.3.5 Target System: Integumental System

$$HI_k = \sum_{i=1}^{N_k} \left(\frac{E_{ik}}{RfV_i}\right) = \frac{E_1}{RfV_1} = 0.14 \quad \text{(Equation 8)}$$

Where:
HI_k = Hazard index for the integumental system
E_1 = Intake value for Dacthal (1.4E-3 mg/kg d)
RfV_1 = reference dose for Dacthal (0.01 mg/kg d)

5.3.6 Target Organ: Liver

$$HI_j = \sum_{i=1}^{N_j} \left(\frac{E_{ij}}{RfV_i}\right) = \frac{E_1}{RfV_1} + \frac{E_2}{RfV_2} + \frac{E_3}{RfV_3} + \frac{E_4}{RfV_4} = 0.81 \quad \text{(Equation 9)}$$

Where:
HI_j = Hazard index for the liver
E_1 = Intake value for 1, 1, 2-Trichloropropane (2.9E-3 mg/kg d)
E_2 = Intake value for Dacthal (1.4E-3 mg/kg d)
E_3 = Intake value for Norflurazon (2.9E-3 mg/kg d)
E_4 = Intake value for Ethylbenzene (2.9E-3 mg/kg d)
RfV_1 = Reference dose for 1, 1, 2-Trichloropropane (0.005 mg/kg d)
RfV_2 = Reference dose for Dacthal (0.01 mg/kg d)
RfV_3 = Reference dose for Norflurazon (0.04 mg/kg d)
RfV_4 = Reference dose for Ethylbenzene (0.1 mg/kg d)

5.3.7 Target Organ: Kidney

$$HI_j = \sum_{i=1}^{N_j} \left(\frac{E_{ij}}{RfV_i}\right) = \frac{E_1}{RfV_1} + \frac{E_2}{RfV_2} = 1.63 \quad \text{(Equation 10)}$$

Where:
HI_j = Hazard index for the kidney
E_1 = Intake value for 1, 1, 2-Trichloropropane (2.9E-3 mg/kg d)
E_2 = Intake value for Dacthal (1.4E-3 mg/kg d)
E_3 = Intake value for Hexachloroethane (6.4E-4 mg/kg d)
RfV_1 = Reference dose for 1, 1, 2-Trichloropropane (0.005 mg/kg d)
RfV_2 = Reference dose for Dacthal (0.01 mg/kg d)
RfV_3 = Reference dose for Hexachloroethane (0.0007 mg/kg d)

5.3.8 Target Organ: Thyroid

$$HI_j = \sum_{i=1}^{N_j} \left(\frac{E_{ij}}{RfV_i}\right) = \frac{E_1}{RfV_1} + \frac{E_2}{RfV_2} + \frac{E_3}{RfV_3} + \frac{E_4}{RfV_4} = 0.81 \quad \text{(Equation 11)}$$

Where:
HI_j = Hazard index for the thyroid
E_1 = Intake value for 1, 1, 2-Trichloropropane (2.9E-3 mg/kg d)
E_2 = Intake value for Dacthal (1.4E-3 mg/kg d)
E_3 = Intake value for Norflurazon (2.9E-3 mg/kg d)
E_4 = Intake value for Ethylbenzene (2.9E-3 mg/kg d)
RfV_1 = Reference dose for 1, 1, 2-Trichloropropane (0.005 mg/kg d)
RfV_2 = Reference dose for Dacthal (0.01 mg/kg d)
RfV_3 = Reference dose for Norflurazon (0.04 mg/kg d)
RfV_4 = Reference dose for Ethylbenzene (0.1 mg/kg d)

5.3.9 Target Organ: Lungs

$$HI_j = \sum_{i=1}^{N_j} \left(\frac{E_{ij}}{RfV_i}\right) = \frac{E_1}{RfV_1} = 0.14 \quad \text{(Equation 12)}$$

Where:
HI_j = Hazard index for the lungs
E_1 = Intake value for Dacthal (1.4E-3 mg/kg d)
RfV_1 = Reference dose for Dacthal (0.01 mg/kg d)

5.3.10 Target Organ: Eyes

$$HI_j = \sum_{i=1}^{N_j} \left(\frac{E_{ij}}{RfV_i}\right) = \frac{E_1}{RfV_1} = 0.14 \quad \text{(Equation 13)}$$

Where:
HI_j = Hazard index for the eyes
E_1 = Intake value for Dacthal (1.4E-3 mg/kg d)
RfV_1 = Reference dose for Dacthal (0.01 mg/kg d)

5.3.11 Summary of Example Results

Table 4 presents the results for the above example calculations. In this example data set, the urinary system and kidney (HI= 1.63) would be considered the sensitive endpoints that may require further assessment.

Table 4. Segregated Hazard Index Results for the IRIS Oral Reference Dose Examples

Target System	HI	Target Organ	HI
Alimentary Accessory Organs	0.81	Liver	0.81
Urinary System	1.63	Kidney	1.63
Endocrine System	0.81	Thyroid	0.81
Respiratory System	0.14	Lungs	0.14
Integumental System	0.14	Eyes	0.14

6. FUNDAMENTAL LIMITATIONS AND UNCERTAINTIES

Although uncertainty exists as to whether segregated HIs developed by this methodology will represent an adequate measure of environmental human health hazard, risk management decisions remain necessary. This method offers a tool to better inform risk managers when unity is exceeded and a hazard may exist due to a mixture of chemicals.

The most important limitations and sources of uncertainty within this methodology should be understood, and attempts should be made to reduce them where possible. They are presented below in no particular order.

- This approach is meant as a simple screening approach; it does not account for quantitative interaction. For example, if it is known that there are two compounds present at the same site whose combined toxicity is five times greater than the sum of the toxicities for the two compounds, then a more detailed approach may be appropriate (see Section 2.2 of this document).

- There is uncertainty associated with adding HQs with RfVs whose confidence levels vary among the studies used and whose uncertainty and modifying factors also vary, such as extrapolation from animals to humans, or from the lowest observed adverse effect levels (LOAELs) to the applicable NOAELs.

- Some critical effects for RfVs can have effects that target only one sex. The equations in this document describe only "average adult" and "child" and do not account for sex. Thus, any overestimates in the hazards for certain target organs might require further analysis.

- Some toxicity values are listed with multiple critical effects, resulting in multiple target organ and system assignments. Thus, the HI will be counted multiple times, once towards each assignment. As this method is intended as a conservative screening approach, this uncertainty is acceptable because it will alert the risk assessor to potential excess risk at each of the possible endpoints.

- It is possible that in a risk assessment context, sufficient exposure could occur whereby other target organs/systems could be affected in addition to those identified as the critical effect from the chosen RfD.

7. SUMMARY OF CHANGES

This is the first publication of this TG 373 Supplement. Over time, if it is determined to be inconsistent with evolving methodologies and/or regulations, it should be revised. Key changes made during revisions should be highlighted in this section.

APPENDIX A

REFERENCES

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GLOSSARY

AAO
Alimentary accessory organs

ALT
Alanine aminotransferase

APHC
U.S. Army Public Health Center

ATSDR
Agency for Toxic Substances and Disease Registry

CalEPA
California Environmental Protection Agency

ChE
Cholinesterase

EPA
U.S. Environmental Protection Agency

HI
Hazard Index

HQ
Hazard Quotient

IRIS
Integrated Risk Information System

LOAEL
Lowest observed adverse effect level

MOA
Mode and/or mechanism of action

MRL
Minimum risk level

NOAEL
No observable adverse effect level

PBPK/PD
Physiologically-based pharmacokinetic/pharmacodynamic models

RAGS
Risk Assessment Guidance for Superfund

REL
Reference Exposure Level

RfC
Reference Concentration

RfD
Reference Dose

RfV
Reference value

RPF
Relative Potency Factor

TTDS
Target organ toxicity doses

TTOS
Toxicity target organs and systems