

Chapter 22 Multipathway Risk Characterization

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22.1 Introduction

The last component of risk assessment, Risk Characterization, integrates the information from the exposure assessment (Chapter 20) and toxicity assessment (Chapter 21), using a combination of qualitative information, quantitative information, and a discussion of uncertainty.⁽¹⁾ Risk assessors should present the risk characterization and its components so that they are transparent, clear, and consistent with EPA guidance and policy, and thus components should support the conclusion that the analysis is reasonably conservative enough for its intended purpose. The risk summary and risk conclusions must be complete, informative, and useful for decision-makers. Major uncertainties associated with determining the nature and extent of the risk should be identified and discussed.

Risk characterization for the multipathway risk assessment is performed using the same approach as described for the inhalation pathway (Chapter 13), except that risks for both inhalation and ingestion are considered. As for inhalation-only analyses, most multipathway risk assessments for air toxics will focus on estimating individual risk and hazard. This chapter focuses on the unique features of risk characterization for multipathway analyses. ***This chapter also assumes that the inhalation risk characterization has been completed, as described in Chapter 13.***

Steps in a Multipathway Risk Characterization

1. Organize outputs of the ingestion exposure and toxicity assessments.
2. Derive cancer risk estimates and noncancer hazard quotients for each pollutant in each pathway.
3. Derive multiple pollutant cancer risk estimates and noncancer hazard indices for each pathway.
4. In consideration of target organ, develop target organ specific hazard indices, if appropriate.
5. As appropriate, combine information on cancer risk and noncancer hazard from the ingestion analysis with appropriate risk information from the inhalation analysis to derive a total estimate of cancer risk and noncancer hazard.
6. Identify key features and assumptions of exposure and toxicity assessments.
7. Assess and characterize key uncertainties associated with the assessment.
8. Consider additional relevant information (e.g., related studies).

The risk characterization should be written consistent with EPA guidance and policy, including a risk summary and risk conclusions that are complete, informative, and useful for decision-makers, and which clearly identify and discuss the major uncertainties associated with determining the nature and extent of the risk.

The general process for characterizing cancer risks and noncancer hazards for multipathway analyses can be thought of as developing information to fill in a matrix similar to that shown in Exhibit 22-1 (which presents cancer risks for a group of chemicals; a similar matrix can be developed to present noncancer hazards [see Exhibit 22-2]). A table like this would be developed for each of the types of receptors being evaluated in the study area (e.g., adult farmer – high-end exposure; adult farmer – central tendency exposures; child resident – high-end exposure). This type of presentation format shows the total risk by chemical, pathway, and across all pathways. In addition, this format allows one to quickly identify both the individual chemicals and pathways that contribute most to the total risk estimate. The following sections describe how to develop the numbers to fill in such a table for both multipathway cancer risk estimates (Section 22.2) and multipathway noncancer hazards (Section 22.3). The focus of this

chapter is on developing risks and hazards for the ingestion pathways; procedures for developing inhalation risk estimates have previously been provided in Chapter 13.

Exhibit 22-1. Example Matrix for Estimating Excess Cancer Risks for Multiple Chemical Exposure through Multiple Ingestion Pathways for a Particular Exposure Scenario					
	Pathway 1 (Vegetable Ingestion Risk Estimate) ^(a)	Pathway 2 (Fish Ingestion Risk Estimate) ^(a)	Pathway 3 (Egg Ingestion Risk Estimate) ^(a)	Pathway 4 (Beef Ingestion Risk Estimate) ^(a)	Aggregate Chemical Ingestion Risk Estimate ^(a)
Chemical 1	1×10^{-6}	3×10^{-4}	9×10^{-8}	8×10^{-5}	4×10^{-4}
Chemical 2	4×10^{-7}	4×10^{-6}	4×10^{-8}	4×10^{-7}	5×10^{-6}
Chemical 3	4×10^{-9}	7×10^{-7}	3×10^{-8}	9×10^{-9}	8×10^{-7}
Chemical 4	9×10^{-7}	1×10^{-6}	6×10^{-7}	6×10^{-7}	3×10^{-6}
Cumulative Ingestion Pathway Risk Estimate ^(a)	3×10^{-6}	3×10^{-4}	7×10^{-7}	8×10^{-5}	4×10^{-4}
^(a) Standard rules for rounding apply which will commonly lead to an answer of one significant figure in both risk and hazard estimates. For presentation purposes, hazard quotients (and hazard indices) and cancer risk estimates are usually reported as one significant figure.					

22.2 Cancer Risk Estimates

As discussed in detail in Chapter 13, estimated individual cancer risk is expressed as the probability that a person will develop cancer as a result of the estimated exposure over a lifetime. This predicted risk is the **incremental risk** of cancer from the exposure being analyzed, which are in addition to other risks due to any other factors (e.g., smoking). Due to default assumptions in their derivation, cancer slope factors (CSFs) are generally considered to be “plausible upper-bound” estimates, regardless of whether they are based on statistical upper bounds or best fits. As noted in Chapter 13, risks may be estimated for both the central tendency (average exposure) case and for the high-end (exposure that is expected to occur in the upper range of the distribution) case, or probabilistic techniques can be used to develop a distribution of estimated risks.

22.2.1 Characterizing Individual Pollutant Ingestion Risk - Scenario Approach

The first step in characterizing individual pollutant risk for an exposure scenario (e.g., a recreational fisher) is to quantify risk for each ingestion exposure pathway being evaluated. In this step, cancer risks for individual pollutants are estimated by multiplying the estimate of the lifetime average daily dose (LADD) for each ingestion exposure pathway by the appropriate CSF to estimate the potential incremental cancer risk:

$$\text{Risk} = \text{LADD} \times \text{CSF} \quad (\text{Equation 22-1})$$

where:

- Risk = Individual cancer risk (expressed as an upper-bound risk of contracting cancer over a lifetime) for each pollutant via the ingestion pathway being evaluated (unitless);
- LADD = Lifetime Average Daily Dose for the pollutant via the ingestion pathway being evaluated (mg/kg-d); and
- CSF = Cancer Slope Factor for the pollutant via the ingestion pathway being evaluated [(mg/kg-d)⁻¹]

Estimates of cancer risk are usually expressed as a probability represented in scientific notation as a negative exponent of 10. For example, an additional risk of contracting cancer of 1 chance in 10,000 (or one additional person in 10,000) is written as 1×10^{-4} . Because CSFs are typically upper-bound estimates, actual risks may be lower than predicted (see Chapter 12) – note that the true value of the risk is unknown and may be as low as zero.⁽²⁾ These statistical projections of hypothetical risk are intended as screening tools for risk managers and cannot be used to make realistic predictions of biological effects.

Risks are generally evaluated initially for **individuals** within the potentially exposed population. **Population risks** for the exposed population may also be estimated, which may be useful in estimating potential economic costs and benefits from risk reduction. Sensitive subpopulations should also be considered, when possible. Estimates of **incidence** also are possible, although there are some caveats associated with these measures (see Chapter 13).

For carcinogens being assessed based on the assumption of nonlinear dose-response, for which a reference dose (RfD) was derived that considers cancer as well as other effects, the hazard quotient approach will be appropriate for risk characterization (see Section 22.3).

22.2.2 Characterizing Risk from Exposure to Multiple Pollutants - Scenario Approach

For each exposure pathway of a scenario, exposure may be to multiple chemicals at the same time rather than a single chemical; however, CSFs are usually available only for individual compounds within a mixture. Consequently, a component-by-component approach is usually employed.⁽³⁾ The following equation estimates the predicted cumulative incremental individual cancer risk from multiple substances for a single exposure pathway, assuming additive effects from simultaneous exposures to several carcinogens:

$$\text{Risk}_T = \text{Risk}_1 + \text{Risk}_2 + \dots + \text{Risk}_i \quad (\text{Equation 22-2})$$

where:

- Risk_T = Cumulative individual ingestion cancer risk (expressed as an upper-bound risk of contracting cancer over a lifetime); and
- Risk_i = Individual ingestion risk estimate for the i^{th} substance.

In screening-level assessments of carcinogens for which there is an assumption of a linear dose-response relationship, the cancer risks predicted for individual chemicals may be added to estimate cumulative cancer risk for each pathway. This approach is based on an assumption that

the risks associated with individual chemicals in the mixture are additive. In more refined assessments, the chemicals being assessed may be evaluated to determine whether effects from multiple chemicals are synergistic (greater than additive) or antagonistic (less than additive), although sufficient data for this evaluation are usually lacking. In those cases where CSFs are available for a chemical mixture of concern, risk characterization can be conducted on the mixture using the same procedures used for a single compound.

For carcinogens being assessed based on the assumption of nonlinear dose-response, for which an RfD considering cancer as well as other effects has been derived, the hazard quotient approach will be appropriate (see Section 22.3).

22.2.3 Combining Risk Estimates across Multiple Ingestion Pathways - Scenario Approach

To evaluate risks associated with the aggregate exposure across multiple pathways of a given scenario, the individual pollutant cancer risk estimates may be summed for each chemical across the multiple ingestion pathways assessed. Additionally, a cumulative multi-pathway risk estimate may be derived by summing cumulative (multiple pollutant) cancer risk estimates across the multiple ingestion pathways.

22.2.4 Evaluating Risk Estimates from Inhalation and Ingestion Exposures

Depending on the ingestion scenario, the inhalation pathway will also have been assessed. In such cases, the inhalation exposures must be presented along with the ingestion exposures to provide an overall estimate of risk across the multiple pathways. When there is a compatibility in the exposure scenarios, inhalation and ingestion risk estimates can be combined. Essentially, an additional column for inhalation can be added to Exhibit 22-1 to achieve this result. Regardless, when both routes are assessed, risk estimates for both routes of exposure should be presented, along with descriptions regarding the populations assessed for all pathways and routes, thereby clarifying any differences in populations.

It is important to note, however, that the methods and assumptions used to derive the inhalation and ingestion risks may not always yield compatible exposure scenarios. This is particularly important when population-level (versus individual) risk estimates are being developed. For example, a scenario-based ingestion exposure assessment will not be easily amenable to producing estimates of numbers of people at different risk levels, while a population-based inhalation assessment may be more appropriate. In addition, it would generally not be appropriate to add an inhalation risk that presumes a 70-year exposure duration with an ingestion pathway that presumes a 30-year exposure duration. Any matching of exposure durations among pathways in a multipathway assessment should be carefully considered.

22.3 Noncancer Hazard

For noncancer effects (as well as carcinogens being assessed based on the assumption of nonlinear dose-response), ingestion exposure concentrations are compared to RfDs, which are estimates (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to

Aggregate vs. Cumulative Risk

Aggregate risk refers to risk attributed to a single chemical across multiple pathways/routes

Cumulative risk refers to risk attributed to simultaneous exposure to multiple chemicals via a single or multiple pathways/routes

the human population (including sensitive sub-populations) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime (see Chapter 21).

As with carcinogens, the development of hazard quotients (HQs) for ingestion typically is performed first for individual air toxics. Then, hazard indices (HIs) may be developed for multiple pollutant exposures and summed across pathways to develop multiple pathway cumulative hazard estimates. An additional step in the multipathway analysis is to evaluate combining both ingestion and inhalation hazard estimates. These steps are described in separate subsections below.

22.3.1 Characterizing Individual Pollutant Hazard - Scenario Approach

The first step in characterizing individual pollutant hazard for an exposure scenario (e.g., a recreational fisher) is to quantify hazard for each pollutant being evaluated. For ingestion exposures, noncancer hazards are estimated by dividing the estimate of the Average Daily Dose (ADD) by the chronic oral RfD to yield an HQ for individual chemicals:

$$\text{HQ} = \text{ADD} \div \text{RfD} \quad (\text{Equation 22-3})$$

where:

- HQ = Hazard Quotient for the pollutant via each ingestion pathway being evaluated (unitless);
- ADD = Estimate of the Average Daily Dose for the pollutant via the ingestion pathway being evaluated (mg/kg-d); and
- RfD = Corresponding reference dose for the pollutant via the ingestion pathway being evaluated (mg/kg-d).

In screening assessments, the chronic exposure estimate is commonly based on a simplifying assumption of continued similar conditions for a long-term period (for example, that the maximum annual average modeled concentration remains constant during the full course of the exposure duration). A more refined assessment might consider how concentration changes with time over the exposure duration. In both cases, it is important to match the type of RfD value to the specific exposure scenario. For example, for childhood scenarios (e.g., ages 0-6), risk assessors commonly use chronic RfDs (rather than subchronic). Subchronic RfDs^(a) are more commonly used to evaluate exposure scenarios that last a year or less (e.g., a construction worker who is exposed for 6 months). For exposure durations of a few years, both chronic and subchronic values may be considered, with chronic values commonly being used, particularly in screening assessments, with explicit recognition of the decision and its basis. Acute toxicity values are for exposures that are much shorter in duration (usually 24 hours or less); however, such exposures generally are not evaluated in a multipathway air toxics risk assessment.

Based on the definition of the RfD, an HQ less than or equal to one indicates that adverse noncancer effects are **not likely to occur**. With exposures increasingly greater than the RfD (i.e.,

^aAlthough subchronic RfDs are not routinely developed by EPA, ATSDR develops MRLs for “intermediate” exposures and describes them as being relevant to exposure durations on the order of weeks to months (i.e., >14 days to 364 days).

HQs increasingly greater than one), the **potential for adverse effects increases**, but we do not know by how much. An HQ of 100 does not mean that the hazard is 10 times greater than an HQ of 10. Also an HQ of 10 for one substance may not have the same meaning (in terms of hazard) as another substance resulting in the same HQ.

22.3.2 Multiple Pollutant Hazard

Noncancer health effects data are usually available only for individual compounds within a mixture. In these cases, the individual HQs can be summed together to calculate a multi-pollutant HI:

$$HI = HQ_1 + HQ_2 + \dots + HQ_i \quad (\text{Equation 22-4})$$

where

- HI = Hazard index; and
- HQ_i = Hazard quotient for the ith air toxic.

For screening-level assessments, a simple HI may first be calculated for all chemicals of potential concern (COPCs) (Exhibit 22-2). This approach is based on the assumption that even when individual pollutant levels are lower than the corresponding reference levels, some pollutants may work together such that their potential for harm is additive and the combined exposure to the group of chemicals poses greater likelihood of harm. Some groups of chemicals can also behave antagonistically, such that combined exposure poses less likelihood of harm, or synergistically, such that combined exposure poses harm in a greater than additive manner, although information needed to perform such an analysis is generally not available. Where this type of HI exceeds the criterion of interest, a more refined analysis is warranted.

The assumption of dose additivity is most appropriate to compounds that induce the same effect by similar modes of action. Thus, EPA guidance for chemical mixtures⁽³⁾ suggests subgrouping pollutant-specific HQs by toxicological similarity of the pollutants for subsequent calculations; that is, calculating a **target-organ-specific-hazard index (TOSHI)** for each subgrouping of pollutants. This calculation allows for a more appropriate estimate of overall hazard.

The HI approach encompassing all chemicals in a mixture may be appropriate for a screening-level study. However, it is important to note that applying the HI equation to compounds that may produce different effects, or that act by different mechanisms, could overestimate the potential for effects. Consequently, in a refined assessment, it is more appropriate to calculate a separate HI for each noncancer endpoint of concern when target organs or modes of action are known to be similar. Refined assessments also may employ techniques more complex than the HI derived using RfDs.⁽⁴⁾

22.3.3 Evaluating Hazard Estimates From Inhalation and Ingestion Exposures

As with carcinogenic assessments, inhalation hazards must be combined with ingestion hazards to provide total hazard across all exposure pathways for a receptor. Similar to Exhibit 22-1, inhalation and ingestion risk estimates can be combined either by chemical across pathways or across chemicals within a pathway. Essentially, an additional column for inhalation can be added to Exhibit 22-2 to achieve this result.

Exhibit 22-2. Example Matrix for Characterizing Hazard for Multiple Chemical Exposure through Multiple Ingestion Pathways for a Particular Exposure Scenario

	Pathway 1 (Vegetable Ingestion HQ Estimate) ^(a)	Pathway 2 (Fish Ingestion HQ Estimate) ^(a)	Pathway 3 (Egg Ingestion HQ Estimate) ^(a)	Pathway 4 (Beef Ingestion HQ Estimate) ^(a)	Aggregate Chemical Ingestion HQ Estimate ^(a)
Chemical 1	2×10^{-1}	2×10^{-1}	4×10^{-2}	2×10^{-1}	7×10^{-1}
Chemical 2	3×10^{-1}	7×10^{-1}	3×10^{-2}	2×10^{-1}	1
Chemical 3	1×10^{-1}	4×10^{-1}	2×10^{-1}	4×10^{-1}	1
Chemical 4	9×10^{-2}	1×10^{-2}	1×10^{-1}	2×10^{-2}	3×10^{-1}
Cumulative Ingestion Pathway HI ^(a)	7×10^{-1}	1	4×10^{-1}	9×10^{-1}	3

^(a) Standard rules for rounding apply which will commonly lead to an answer of one significant figure in both risk and hazard estimates. For presentation purposes, hazard quotients (and hazard indices) and cancer risk estimates are usually reported as one significant figure.

22.4 Interpretation and Presentation of Risks/Hazards

In the final part of the risk characterization, estimates of cancer risk and noncancer hazard should be presented in the context of uncertainties and limitations in the data and methodology. Exposure estimates and assumptions, toxicity estimates and assumptions, and the assessment of uncertainty should be discussed. Chapter 13 provides more detailed information and examples. Part VI of this reference manual discusses risk communication and other elements of the risk-based decision-making process.

Estimating Risk for Drinking Water Sources

In evaluating potential risks associated with drinking water supplies, risk assessors commonly assume that the drinking water undergoes at least a minimum level of treatment to remove solids (i.e., particles in the water which are persistent bioaccumulative hazardous air pollutants [PB-HAPs] or onto which PB-HAPs may be absorbed). Therefore, the risk assessment commonly focuses on the dissolved concentrations of PB-HAPs in drinking water sources. In addition, if the drinking water source is part of a public drinking water system, the risk assessment may also assume that the water is treated to meet applicable drinking water standards (i.e., treated to maximum contaminant levels or MCLs, unless study-specific information indicates otherwise) for chemicals regulated under the drinking water program. National Primary Drinking Water Regulations are enforceable standards that apply to public water systems. The MCLs are the highest level of a specific list of contaminants allowed in drinking water (see <http://www.epa.gov/safewater/mcl.html>).

Note that multipathway air toxics risk assessments are subject to additional sources of uncertainty as compared to inhalation risk assessments. The multimedia modeling effort is both more complex and less certain due to many factors. For example: (1) there are many more chemical-dependent and chemical-independent variables involved as input values to the models;

(2) the models involve analysis of the transfer of air toxics from the air to other media (e.g., soil, sediment, water), the subsequent movement of the air toxics between these media (e.g., soil runoff to surface water), and uptake and metabolism by biota; and (3) many variables affect the ingestion of food, water, and other media by humans and wildlife, and the exposure and risk estimates may differ considerably as a consequence of the assumptions used to derive intake estimates. Sampling of biota and abiotic media also may be more complex. Additional uncertainties are incorporated in the risk assessment when exposure estimates to multiple substances across multiple pathways are summed.

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