2. ATSDR APPROACH

ATSDR recommends a 3-tiered approach to evaluating exposure and health effects data to assess public health impacts in communities in the vicinity of sites of chemical or physical agent contamination, such as hazardous waste sites, presenting possible exposures to multiple chemicals and other stressors (Figure 1 presents an overview of the approach). Initial problem formulation activities are followed by as many as three tiers of assessment depending on the availability of exposure and health effects data, the nature of existing exposure and health effects data, and the extent and nature of community concerns for exposure and potential health effects. Parallel assessments are conducted for noncancer effects and cancer (see Figure 1).

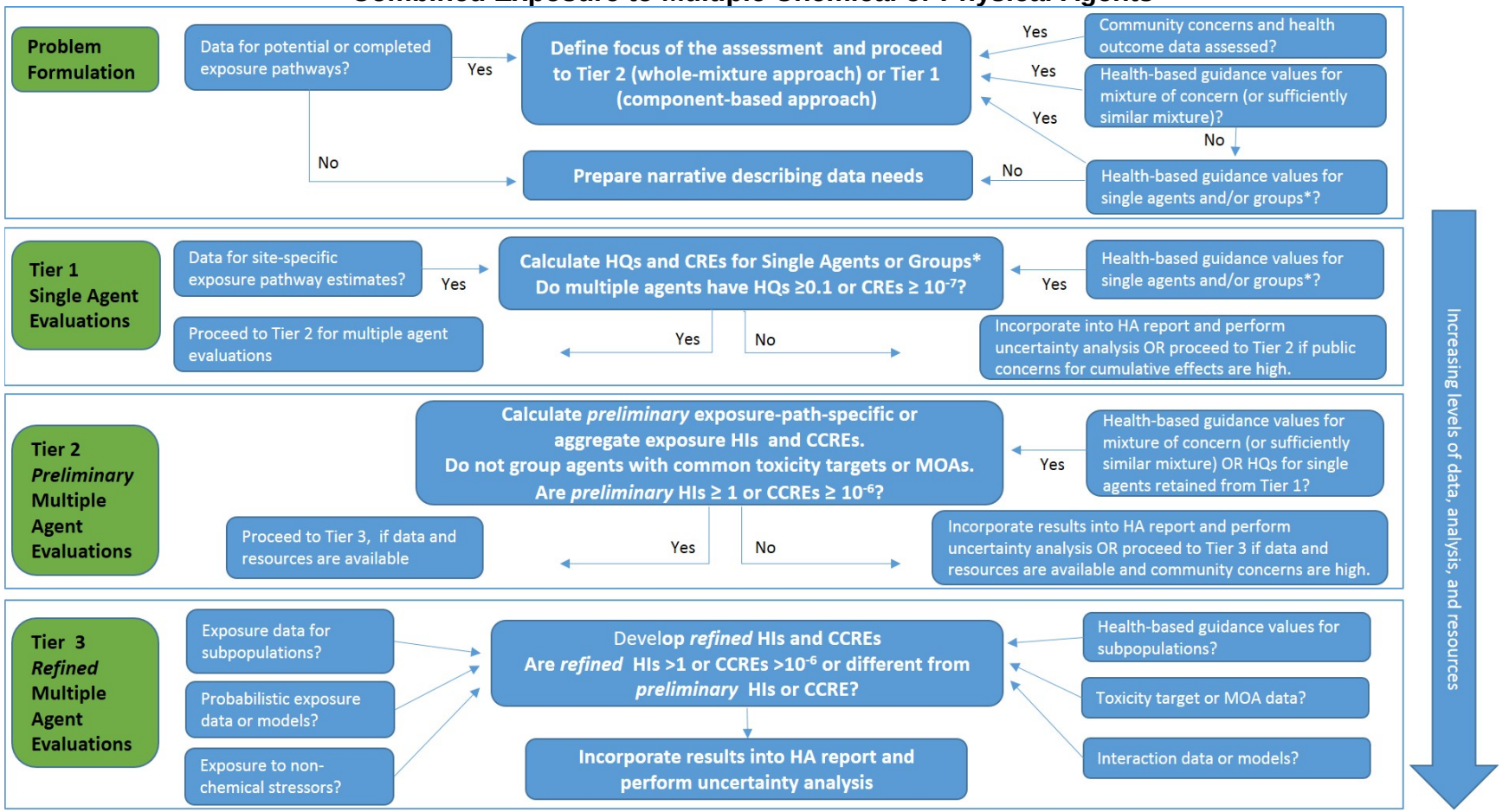
2.1. PROBLEM FORMULATION: SCOPING, PLANNING, DATA COLLECTION

Initial scoping, planning, and data collection activities are essential preliminary steps in preparing a defensible assessment of health impacts associated with contamination of a site with toxic agents (ATSDR 2005a). The initial activities are guided by legislative mandates stating ATSDR consider the following factors in its assessments.

1. *The nature and extent of contamination:* What are the contaminants of concern? What are the temporal and spatial extents of contamination? What media are contaminated (air, water, soil, sediment, food)?
2. *The demographics of exposure:* Who is expected to be exposed (population size)? What potentially susceptible subpopulations may be exposed (e.g., children, elderly, pregnant women)?
3. *The pathways of human exposure (past, present, and future):* How might people be exposed to contaminants (drinking water, eating food, breathing air, having skin contact)? What are site-specific exposure levels for specific populations based on route, frequencies, and duration of exposure and magnitude of media contamination?
4. *Possible health effects associated with site-specific exposure levels:* What toxicologic, epidemiologic, medical, or health outcome data are available to identify possible adverse effects from exposure to contaminants at a site?

The early phases of information gathering and assessment are instrumental in formulation of the problems to be addressed by the health assessment (Figure 1). Initial activities related to the exposure

Figure 1. ATSDR Tiered Approach to Evaluate Exposure and Health Effects Data to Assess Health Impacts from Combined Exposure to Multiple Chemical or Physical Agents



*"Single Agents" can include groups of chemicals with TEFs or RPFs or mixtures with health-based guidance values (e.g., MRLs or cancer slope factors). Groups of chemicals with TEFs or RPFs include dioxins, PAHs, and N-methyl carbamates. Mixtures with ATSDR health-based guidance values include jet fuels (JP-5, JP-8) and PCB mixtures (Aroclor 1254).

ATSDR = Agency for Toxic Substances and Disease Registry; CRE = cancer risk estimate; CCRE = combined cancer risk estimate; HA = health assessment; HI = hazard index; HQ = hazard quotient; MOA = mode of action; MRL = Minimal Risk Level; PAH = polycyclic aromatic hydrocarbon; PCB = polychlorinated biphenyl; RPFs = relative potency factors; TEFs = toxic equivalency factors

evaluation portion of the assessment include collecting site history data, available environmental sampling data, available fate and transport data for the contaminants detected or expected in environmental media, and available exposure and demographics data (ATSDR 2005a). Relevant routes of exposure can be identified at this stage. For example, if residential exposures to contaminated drinking water are of concern, considerations should include exposure by ingestion, inhalation when showering, and dermal exposure when showering. Activities for health effects evaluation include collecting existing health-based guidance values for acceptable levels of contaminants of concern based on toxicologic, epidemiologic, or medical data and any available health outcome data for the community of interest. ATSDR (2005a) also strongly recommends that community health concerns and health outcome data be collected, evaluated, and included in early phases of any health assessment (see Figure 1 Problem Formulation box asking, "Community concerns and health outcome data assessed?").

At this early phase, it is important to establish if the assessment will proceed using a whole-mixture or component-based approach. Ideally, the noncancer and cancer assessments would be based on existing health-based guidance values derived specifically for the site-specific mixture of concern. Only a few complex mixtures have health-based guidance values including certain jet fuels, coke oven emissions, diesel engine exhaust, and PCB mixtures (see Section 3.1). However, it is unlikely that the site-specific mixture of concern will be identical in composition to the tested mixture that is the basis for the guidance value. Alternatively, a whole-mixture approach could be used if: (1) there are high-quality epidemiological data or animal toxicological data available for the site-specific mixture of concern that could be used to derive a health-based exposure value, or (2) the mixture of concern is considered "sufficiently similar" to a tested mixture that is the basis for a guidance value. However, it is also unlikely that appropriate toxicity studies for a site-specific mixture will be available and widely-accepted methods for determining sufficient similarity have not been established (see Section 3.2 for more details regarding establishment of sufficient similarity). Therefore, site-specific health assessments often proceed using component-based approaches (see details in Section 3.3). When using a component-based approach, lumping of certain chemicals or well-defined mixtures within the complex mixture of concern may facilitate the preliminary assessment. For example, well-defined mixtures with health-based guidance values (e.g., JP-8, PCBs) and contaminants that are members of chemical groups with special approved methods for assessing health effects (e.g., relative potency factor [RPF] approach for carcinogenic polycyclic aromatic hydrocarbons [PAHs], toxic equivalency factor [TEF] approach for dioxins, and indicator chemical approach for size classes petroleum hydrocarbons) may be treated as single agents during hazard quotient (HQ) and *preliminary* hazard index calculations (see Tier 1 and 2 evaluations in Figure 1). See Sections 2.2, 2.3, and 3.3 for more details on these approaches.

It is also important to identify any non-chemical agents (e.g., biological, physical, and psychosocial stressors) that may be pertinent to human health during the problem formulation step. At the current time, however, the available scientific information is inadequate to develop specific guidelines for incorporating non-chemical agents in assessment of health impacts from multiple stressors with the exception of cancer risks associated with ionizing radiation (see Section 2.3.2). Therefore, the potential impact of the majority of non-chemical stressors will only be qualitatively examined in health assessments that progress to Tier 3 evaluation (see Section 2.4 for more information). However, it should be noted that combined exposure to noise and ototoxic substances is a recognized emerging risk (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4693596/ and https://www.cdc.gov/niosh/nioshtic-2/20042414.html)

2.2. TIER 1: PRELIMINARY EVALUATION OF EXPOSURE AND HEALTH EFFECTS DATA FOR SINGLE AGENTS AND CHEMICAL MIXTURES WITH HEALTH-BASED GUIDANCE VALUES

2.2.1. Preliminary Exposure Evaluation

To identify chemicals of concern, site history information and environmental sampling data are evaluated to determine whether or not exposure point concentrations can be determined reliably. If appropriate and reliable environmental sampling data are not available, recommendations may be made for filling this critical data gap before proceeding further (ATSDR 2005a). Often, environmental monitoring data are collected by collaborating agencies or companies, such as the EPA or principal responsible parties (PRPs) rarely by ATSDR. The availability of reliable and high quality environmental sampling data, regardless of their source, is essential to the ATSDR public health assessment process.

Information about exposure pathways for contaminants of concern is evaluated next for identifying the following five elements:

1. Source of contamination;
2. Release mechanism into water, soil, air, food, or transfer between media (i.e., fate and transport of contaminants in the environment);
3. Exposure point or area (e.g., drinking water well, soil in a residential yard, sediment in a lake or river);
4. Exposure routes (e.g., ingestion, dermal contact, inhalation);
5. Potentially exposed population (e.g., adult or children residents, clean-up workers).

If all elements are identified, a "completed" exposure pathway exists. If one or more of the elements is missing or uncertain, a "potential" exposure pathway exists. If multiple routes of exposure represent "completed" or "potential" exposure pathways, consideration can be given to aggregate exposures across routes. For completed and potential exposure pathways with appropriate exposure-point concentration data, ATSDR (2005a) conducts preliminary crude and refined screening-level health effects evaluations for each of the individual contaminants of concern (see next section). If no completed or potential exposure pathways are identified, ATSDR (2005a) usually considers that no public health hazards will exist.

2.2.2. Preliminary Health Effects Evaluation

The preliminary health effects evaluation for component-based approaches begins with a crude screening effort in which maximum values of measured (or modeled) environmental media concentrations of individual agents (in air, water, and soil or sediment) are compared to media-specific guideline concentrations for individual agents expected to be safe for the general public (i.e., environmental media comparison values). Comparison values for the crude health effects evaluation include: (1) ATSDR Environmental Media Evaluation Guides (EMEGs), calculated using ATSDR MRLs for noncancer effects from individual agents or defined mixtures of chemicals and standard exposure assumptions; (2) Reference Dose Media Evaluation Guides (RMEGs), calculated using EPA RfDs or RfCs for noncancer effects (when ATSDR chronic noncancer guidance values are not available) and standard exposure assumptions; and (3) Cancer Risk Evaluation Guides (CREGs) calculated using EPA Cancer Oral Slope Factors (OSFs) or Inhalation Unit Risks (IURs) (ATSDR 2005a). Independent and parallel evaluations for noncancer and cancer effects are conducted as illustrated in Figure 1. When appropriate ATSDR or EPA comparison values are not available, ATSDR environmental scientists may select from other health-based guidance values that may be available from other agencies (see ATSDR 2005a for more details). For noncancer effects, individual agents are retained for more refined evaluations of health impacts from individual agents, when site-specific environmental concentrations exceed the EMEGs or RMEGs. ATSDR does not derive cancer slope factors and relies on EPA for their determination. Cancer slope factors are expressed in terms of risk per exposure unit (e.g., risk per mg/kg-day for OSFs or risk per mg/m^3 for IURs), so the product of an exposure estimate and a cancer slope factor yields a cancer risk estimate (CRE). For the crude screening of individual carcinogenic agents, ATSDR multiplies the site-specific environmental concentration by the appropriate EPA cancer slope factor (OSF or IUR) and appropriate default exposure factors for adults (e.g., 2.4 L water/day for 80-kg adults) to arrive at theoretical crude oral or inhalation CREs. When a resultant crude risk estimate exceeds 10^{-6} (one in one million), the agent is retained for more refined evaluation involving site-specific exposure information and consideration of specific subpopulations, such as children or the elderly. When no environmental comparison value is available, a contaminant is retained for refined Tier 1 evaluation with site-specific exposure information, if it has a health-based guidance value, such as an MRL or a cancer OSF or IUR, the assessment proceeds according to the flow chart (Figure 1) (ATSDR 2005a).

The preliminary screening-level health evaluation of single agents ends with a refined evaluation that incorporates site-specific exposure information into the exposure assessment to arrive at administered doses (in units of mg/kg/day for ingestion of water or soil) or concentrations (mg/m^3 in air), which are

compared with health-based guidance values, such as ATSDR MRLs or EPA RfDs/RfCs directly (not EMEGs or RMEGs) in the assessment for noncancer effects or used to calculate CREs from EPA OSFs or IURs (ATSDR 2005a). For noncancer effects, the HQ is the comparative method used. The HQ is the ratio of the exposure estimate to the health-based guidance value. If the exposure estimate is 1 mg Chemical X/kg/day and the MRL is 0.1 mg Chemical X/kg/day, the HQ = (1 mg/kg/day) / (0.1 mg/kg/day) = 10. In Figure 1, the central box for Tier 1 analysis calls for calculation of HQs and CREs for single agents. As described in the Problem Formulation section, the term, "single agents" in Figure 1 is meant to include groups of chemicals with special approved methods for assessing health or mixtures with health-based guidance values (e.g., MRLs). Recommended refined modifications of the hazard index approach can be used to derive HQs for certain groups of chemicals, such as the TEF approach for dioxins and dioxin-like compounds and RPF approaches developed by the EPA Office of Pesticide Programs (OPP) for certain classes of pesticides (organophosphate, carbamate, and pyrethroid insecticides and triazine and chloroacetanillide herbicides). Sections 3.3.5 and Appendix C (Section C.8) of this manual discuss these approaches in more detail.

For sites contaminated with gasoline and other complex petroleum products enriched in hydrocarbons, specific component-based approaches could be used to assess noncancer health impacts (e.g., ASTM 2015; MassDEP 2002; Ohio EPA 2010; Oklahoma DEQ 2012; Total Petroleum Hydrocarbon Criteria Working Group 1997, 1998a, 1998b; Weisman 1998). These approaches involve: (1) lumping the complex mixture into groups of hydrocarbons with similar chemical structures (e.g., aromatic hydrocarbons with 5–9 carbons, aliphatic hydrocarbons with 5–8 carbons); (2) collecting data for concentrations of these groups of hydrocarbons in environmental media; (3) selecting a representative chemical with adequate dose-response data to indicate hazard potential and dose-response relationship for each group (i.e., an indicator chemical); and (4) using the guidance value of the indicator chemical coupled with exposure estimates for all members of the group in the subject mixture to estimate health risk from the group (i.e., calculate class-specific HQs for site-specific exposure pathways). The approach is based on an assumption that toxicity of all detected members of the class can be estimated by the indicator chemical. ATSDR did not derive MRLs for automotive gasoline because of the wide compositional range of formulations for gasoline and the likelihood that components have widely differing environmental fate and transport properties (ATSDR 1995a, 1999; Pohl et al. 1997). Consequently, exposed populations are likely to be exposed to fractions that are not sufficiently similar to the original mixture. The total petroleum hydrocarbon (TPH) approach represents a way to incorporate site-specific environmental data in assessments of potential health impacts for fractions of hydrocarbons in complex petroleum-based products.

Site-specific exposure information to include in the Tier 1 refined exposure assessment can include variability in values for media-specific concentrations, exposure frequencies (days/year), exposure durations (years), intake rates (e.g., liters of water consumed/day or volume of air inhaled/day), or body weights that are different from the crude exposure assumptions. For example, in a crude assessment, the maximum concentration in media samples may have been used, but a refined assessment would consider the variability of concentrations in environmental samples, the frequency of "detects" and non-detects" among the samples, the degree to which concentration variability may be due to spatial variability or "hot spots", and spatial differences in accessibility to the public (ATSDR 2005a).

Chemicals (or defined groups/mixtures treated as single agents) are retained for further in-depth analysis, when the site-specific exposure estimate exceeds the MRL or RfD/RfC (the HQ is $\geq$1) or the CRE is $\geq 10^{-6}$ (see Section 2.2.1). While agents with HQs <1 or CREs $<10^{-6}$ (e.g., 10^{-7} or 10^{-8}) are expected to individually pose no health impacts, they may have an impact when combined exposure to multiple agents is considered. Therefore, all agents with HQs $\geq$0.1 or CREs $\geq 10^{-6}$, are retained for further Tier 2 analysis of noncancer or cancer health impacts from combined exposure to multiple agents (see Figure 1 box asking, "Do multiple agents have HQs $\geq$0.1 or CREs $>10^{-6}$?"). If aggregate exposure is identified as a concern during problem formulation, HQs should be summed across routes of exposure.

2.3. TIER 2: PRELIMINARY ANALYSIS OF EXPOSURE AND HEALTH EFFECTS DATA FOR MULTIPLE AGENTS

Exposure pathways and agents retained in the Tier 1 evaluation can be subjected to further analysis outlined in this (Tier 2) and the following (Tier 3) sections (see Figure 1). The health assessment outcome of these activities is a qualitative narrative description of whether site exposure conditions are of sufficient nature, frequency, and magnitude to adversely impact public health (ATSDR 2005a). The narrative should clearly state what is known and unknown about any of the agents of concern from a site-specific exposure pathway, indicate how the potential for toxic effects from combined exposures to multiple agents at the site was evaluated, and concisely describe the uncertainties in the assessment.

2.3.1. Noncancer Health Impacts from Multiple Agents

Consideration of the potential for toxic effects from combined exposure to multiple agents at a contaminated site is especially important when: 1) Tier 1 evaluations of single agents and chemicals with health guidance values identify multiple agents that approach or exceed MRLs (i.e., the HQ approaches or

exceeds 1); and 2) scoping activities indicate the potential contamination of environmental media (water, soil, or air) with multiple toxic agents from specific processes or products. A hazard index approach is recommended to *preliminarily* evaluate the potential for noncancer toxic effects from combined exposure to multiple agents at a site. As discussed in Section 2.1, the problem formulation phase of a health assessment should determine whether a whole mixture or component-based method should be applied.

For whole mixture approaches, the *preliminary* hazard index would be based on the health-based guidance value for the mixture of concern or a sufficiently similar mixture, rather than on the sum of the HQs for the individual components. It is important to note that the "sufficiently similar" approach would only be a part of the *preliminary* hazard index, if a specific approach has been developed and received widespread review and acceptance. Currently, only qualitative approaches to sufficient similarity determinations have been applied, but statistical approaches are being evaluated and developed (see Section 3.2 for more discussion). One example that could be applied is the ATSDR (2000b) intermediate-duration oral MRL for PCB mixtures that was based on the assumptions that: (1) PCB mixtures are sufficiently similar for dose-response assessment purposes and (2) an MRL based on the lowest LOAELs from studies of specific PCB mixtures (i.e., a simulated environmental mixture and a commercial PCB mixture, Aroclor 1254) would be protective for PCB mixtures in general (see Section 3.2 for more details).

For component-based approaches, the hazard index is based on the assumption of dose addition, and a *preliminary* hazard index is a sum of HQs $\geq$0.1 of all known and measured chemicals for site-specific exposure pathways. The *preliminary* hazard index does not group chemicals based on shared toxicity targets (i.e., common adverse outcomes) or modes of action (MOAs); Tier 3 calls for this type of refinement if data are available and concerns are high for health effects from combined exposure to multiple agents (Figure 1). Chapter 3 of this manual provides more in-depth discussion of the hazard index, the underlying rationale for using the approach, and examples of its applications and modifications.

When a *preliminary* hazard index value exceeds 1, further evaluation is recommended, following guidance for Tier 3 analyses (Figure 1). If aggregate exposure is identified as a concern during problem formulation, *preliminary* hazard indices can be summed across routes of exposure.

2.3.2. Cancer Impacts from Multiple Agents

Public health impacts from combined exposure to multiple carcinogenic agents are assessed with an approach that is separate from, and parallel to, the approach for noncarcinogenic agents (see Section 3.3.6). As discussed in Section 2.1, the problem formulation phase of a health assessment should determine whether a whole mixture or component-based method should be applied.

For whole mixture-based approaches, the *preliminary* combined cancer risk estimate (CCRE) would be based on the cancer slope factor for the mixture of concern or a sufficiently similar mixture, rather than on the sum of the CREs for the individual components. Limitations of the sufficiently similar approach described for noncancer impacts in Section 2.3.1 are applicable to cancer impacts as well.

The component-based approach for cancer, initially recommended by EPA (1986), assumes independent action of carcinogenic agents and adopts the most conservative form of response addition (completely negative correlation of tolerances; i.e., individuals most sensitive to chemical A are least sensitive to chemical B and vice versa; see Appendix A). Individual CREs are calculated by multiplying the site-specific exposure estimate by the EPA cancer slope factor (oral exposure) or IUR for the agent of concern. It is recommended that the combined cancer risk estimates (CCREs) be calculated for all carcinogenic agents identified in site-specific exposure pathways as presenting individual CREs $\geq 10^{-6}$ (see Section 3.3.6). Because EPA Integrated Risk Information System (IRIS) values for slope factors or unit risks are typically upper 95% confidence limit estimates on the lifetime excess cancer risk of individual agents, concern has been raised that summing upper bound risks may lead to unreasonably high estimates of the mixture risk. However, an analysis by Kodell and Chen (1994) suggested that the error in the simple sum of the upper bound risks is small relative to other uncertainties. Furthermore, Cogliano (1997) concluded that the sum of the upper bound risks provides useful information regarding the overall risk from mixtures of carcinogens.

There are embedded variables and assumptions involved in deriving cancer risk estimates for individual carcinogenic agents, as well as the basis for assigning agents to weight-of-evidence (WOE) cancer classification groups. Effective description of these variables and assumptions is important when communicating cancer hazard potential to a community faced with contamination from chemical carcinogens. In the final health assessment, individual and combined cancer risk estimates should be discussed to: (1) qualitatively describe the cancer-causing potentials of identified individual carcinogens and (2) compare site-specific exposure estimates with exposure levels resulting in increased risk for

cancer in toxicology studies or epidemiology studies forming the basis of the slope factors for oral exposure or unit risk estimates for inhalation exposures (ATSDR 2005a). Combined cancer risk estimates from multiple agents in a site-specific exposure pathway in the range of 10^{-6}–10^{-4} or greater are taken to present evidence of a potential health hazard from cancer, but the health assessment narratives should do more than just present estimated risk numbers for individual agents or multiple agents (ATSDR 2005a). CCREs $\geq 10^{-6}$ warrant additional Tier 3 evaluation by including considerations of: (1) the potential for interactions among the identified carcinogenic agents; (2) the relative contributions of specific types of cancer to the combined risk; (3) the relative contributions of individual agents to the overall combined risk; and (4) and the relationship of the CCRE to any community health outcome data and/or concerns.

For the assessment of cancer from ionizing radiation or radionuclides, experts can be consulted to assist in the application of exposure models that estimate radiation dose to specific organs and tissues (ATSDR 2005a). These models and health guidance values for different types of ionizing radiation and radionuclides can be used to calculate CREs for radiation in an analogous approach to the approach for chemical carcinogens. It is recommended that site-specific cancer risk estimates from ionizing radiation and radionuclides be added to those from non-radioactive chemical carcinogens to initially screen for CCREs in site-specific exposure pathways. Estimates of combined cancer risk estimates $\geq 10^{-6}$ warrant additional Tier 3 evaluation. Specific approaches for estimating cancer risks from two classes of chemicals, dioxins and dioxin-like compounds and PAHs, are discussed in more detail in Section 3.3.5. If aggregate exposure is identified as a concern during problem formulation, *preliminary* CCREs should be summed across routes of exposure.

2.4. TIER 3: REFINED ANALYSIS OF EXPOSURE AND HEALTH EFFECTS DATA FOR MULTIPLE AGENTS

Further analysis of exposure and health effects data and other types of data for multiple agents should be conducted when: (1) results of Tier 2 analyses indicate that site-specific exposure pathways have *preliminary* hazard indices ≥ 1 or *preliminary* CCREs $\geq 10^{-6}$; (2) community concerns are high for health effects from multiple site-specific agents of concern; and/or (3) additional community health outcome data provide evidence of health effects from multiple agents (see Figure 1).

Because the dose-additive hazard index approach for noncancer effects and the response-additive approach for adding cancer risks do not account for possible interactions among agents of concern, it is important to determine what is known and unknown about possible greater-than additive or less-than-additive interactions among agents of concern. A first step is to access the information presented in the

Interactions with Other Chemicals sections of the ATSDR Toxicological Profiles for the agents of concern, if available. Section 3.3.1.2 of this framework (*Evidence to Support or Refute the Use of Default Dose-Additivity Approaches*) can also be reviewed. The *in vivo* and *in vitro* research studies reviewed in Section 3.3.1.2 provide support that: (1) dose additivity often provided adequate descriptions of responses to defined mixtures of various classes of chemicals; (2) positive and negative deviations from dose additivity were small from a risk assessment perspective (generally <5-fold); and (3) observed responses to mixtures of chemicals were often below values predicted by dose addition, but higher than values predicted by response addition. Further research may help to confirm or refute the validity of this assumption, in particular for chronic exposure scenarios and for early life exposures with possible later life health outcomes. It is important to understand and communicate that recommended approaches using default assumptions of dose additivity or response additivity are practical tools, which could overestimate or underestimate actual health impacts.

If sufficient data on interaction between mixture components are available, a qualitative WOE approach can be used to evaluate scientific evidence that binary combinations of agents of concern may act in an additive, greater-than-additive or less-than-additive manner (see Section 3.3.4 and Appendix B for more details about this binary weight of evidence [BINWOE] approach). Based on such analysis, qualitative statements can be prepared regarding evidence of interactions that may cause the site-specific exposure pathway hazard index or combined cancer risk estimate to overestimate or underestimate health impacts. The BINWOE approach was used in ATSDR Interaction Profiles for a number of priority chemical mixtures (Pohl and Abadin 2008; Pohl et al. 2003, 2004, 2009; see www.atdr.cdc.gov/interaction profiles). The Interaction Profiles can provide useful recommendations, if the subject mixture components overlap with agents of concern for site-specific exposure pathways.

It is also useful to determine if mixture/interaction physiologically based pharmacokinetic/ pharmacodynamic (PBPK/PD) models exist for combinations of site-specific agents of concern. These types of models have been used to determine external exposure levels at which interactions and deviations from dose additivity may exist (see Section 3.3.7 for more discussion of developed mixture/interaction PBPK and PBPK/PD models and their application).

Because the *preliminary* screening approach for assessing health impacts from exposure to multiple agents is based on simplifying assumptions (e.g., adding HQs or CREs for all agents of concern, regardless of toxicity target or MOA), it can be useful to compare the outcome of the *preliminary* hazard index approach with more refined and stringent applications of the hazard index approach. The most

stringent application requires that all components produce a common effect via a common MOA (this approach is applied by the EPA OPP to produce cumulative risk assessments for various classes of pesticides; see Appendix C, Section C.8), whereas a less stringent application requires that all components produce toxic effects in a common target tissue or organ (see Section 3.3.3 for more details of the Target-organ Toxicity Dose [TTD] modification to the hazard index approach). Comparing the relative magnitudes of exposure-pathway-specific hazard indices calculated for all agents of concern, all agents affecting common toxicity targets, and all agents producing common adverse outcomes via a common MOA can convey a qualitative indicator of the magnitude of uncertainty and the effect of simplifying assumptions on the estimates of potential health impact of multiple agents associated with site-specific exposure pathways. A separate analogous comparison of the *preliminary* CCRE for multiple carcinogenic agents of concern with refined combined estimates based on agents producing common types of cancer and agents producing common types of cancer via common MOAs can also be conducted.

The Tier 3 analysis can also consider probabilistic refinements of exposure models, if appropriate site-specific information is available, and the development of exposure estimates and hazard indices for specific subpopulations of the community that may be more susceptible to the site-specific agents of concern, especially children. Exposure estimates for children and other potentially susceptible populations can be developed as a part of the Tier 1 analysis, using general information on the exposures and potential susceptibility of children and other susceptible populations found in ATSDR toxicological profiles on the agents of concern.

If exposures to physical agents are experienced by communities with contaminated sites and if health guidance values are developed, Tier 3 analyses can: (1) include exposure estimates in site-specific exposure pathways, and (2) calculate individual HQs or individual cancer risks for the physical agent, and 3) add them to the *preliminary* hazard indices or CCREs for site-specific exposure pathways. Currently, the only class of physical agents pertaining to this recommendation is ionizing radiation.

As discussed in Section 3.3.8 of this framework manual, there have been calls for developing guidelines for including nonchemical stressors including biological, physical, and psychosocial stressors in cumulative assessments of health impacts or risks of multiple agents. At the current time, however, the available scientific information is inadequate to develop more specific guidelines for incorporating biological, physical, or psychosocial stressors in assessing health impacts from multiple stressors.

2.5. PRESENTING FINDINGS IN THE HEALTH ASSESSMENT DOCUMENT

Upon completion of the ATSDR 3-tiered approach, assessors should consult Section 8.7 of the ATSDR (2005a) *Public Health Assessment Guidance Manual* for guidance on preparing clear and concise narratives that communicate to the public the findings of the analysis of potential health impacts from single and multiple agents of concern. The health assessment document should contain a narrative of the uncertainties associated with the hazard assessment, regardless of what tier the assessment reached (e.g., uncertainties in exposure modeling, unidentified fractions of the mixture, components with no health effects information, multiple chemicals with HQs near 0.1).