4. ATSDR APPROACH

4.1. OVERVIEW

The ATSDR DT approach to the assessment of the joint toxic action of chemical mixtures reflects the unique nature of ATSDR's mandate to assess the public health implications associated with uncontrolled release of hazardous substances into the environment. The health effects of low-level exposures are of particular concern. As described in ATSDR's *Public Health Assessment Guidance Manual*, the determination of public health implications involves not only an assessment of potential hazard to public health based on estimated exposure levels and health guideline values, but also evaluation of uncertainties, health implications of other medical and toxicological factors and sensitive subpopulations, community-specific health outcome data, and the consideration of community health concerns (ATSDR 1992). The outcome of this process is a health assessment document that classifies the public health hazard posed by a site into one of five categories, ranging from urgent to no hazard. Follow-up activities, consistent with the degree of hazard, are recommended, and may include actions to protect public health, obtain additional health information, or obtain additional site-characterization information (ATSDR 1992; De Rosa et al. 1996; Hansen et al. 1998; Johnson and De Rosa 1995). The assessment of potential hazard to public health based on estimated exposure levels and health guideline values is called "exposure-based assessment of joint toxic action" in this Mixtures Guidance Manual, and is only one part of the overall process of evaluating the potential impact of exposure to mixtures on public health.

Any public health assessment should clearly state that the approaches used rely on data for which interactions of the of the components of concern are known or can be inferred. If toxicological information on some of the components is insufficient to include them in the mixture assessment, the contribution of those components to possible interactions is unknown.

The strategy for exposure-based assessment of the potential impact of joint toxic action of chemicals, including radioactivity, in mixtures on public health is presented in detail in the text of Chapter 4, and the decision process is illustrated in flow charts. The strategy integrates the use of other ATSDR documentation, including toxicological profiles, interaction profiles, and ATSDR-sponsored research on chemical mixtures, into a screening approach for the assessment of health hazard. The conclusions from this mixtures assessment can then be taken into account along with the community-specific health outcome data, community health concerns, and biomedical judgment, to determine the public health implications and follow-up activities.

The general approach is consistent with the approach articulated by EPA (Figure 1) and used to some extent, formally or informally, by a number of agencies. This approach involves the use of exposure and toxicological information on the mixture of concern or a similar mixture as the preferred method. Exposure data are site-related. If available, toxicological information on a mixture of concern (or similar mixture) for hazardous waste sites are likely to be reviewed and evaluated in ATSDR documents, including interactions profiles on specific chemicals of concern and radionuclides, and toxicological profiles. These documents may provide MRLs or other health guideline values for the whole mixture, or guidance for other approaches. When such data are not available from ATSDR documents (or comparable documents from other agencies), an approach based on the components of the mixture is advisable, if the exposures are high enough so that the joint toxic action of the components may pose a hazard due to additivity or interactions or both. The approach will provide additional clarification of hazard, for example:

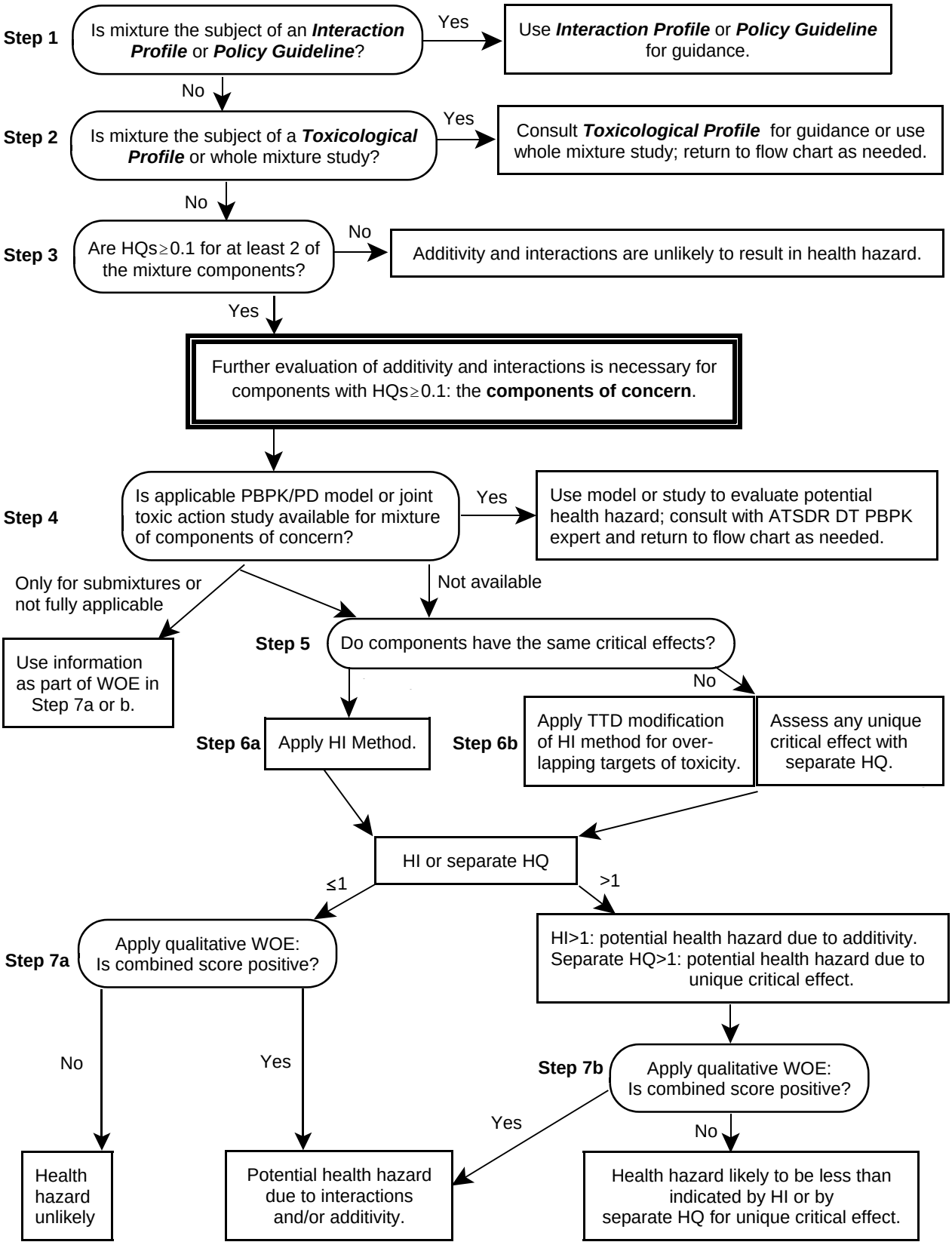
- when exposures to the components are not clearly hazardous when considered singly, but potentially hazardous due to additivity or interactions when considered together;
- when the community-specific health outcome data indicated that the site might have an adverse impact on human health, but the exposure-based assessment of each separate component did not; or
- when the health outcome data were ambiguous or did not indicate an adverse impact on human health, but the exposure-based assessment identified a potential hazard from one or more of the components.

4.2. STEPS IN EXPOSURE-BASED ASSESSMENT OF JOINT TOXIC ACTION OF CHEMICAL MIXTURES

4.2.1. Procedures for Assessment of Noncarcinogenic Effects (Figure 2)

The flow chart in Figure 2 gives an overview of the steps for exposure-based assessment of the potential impact of joint toxic action on public health. The analysis of exposure pathways and intakes or concentrations should be performed using ATSDR (1992) methods for public health assessment. The process described in the flow chart and accompanying text is designed to answer the question: do the estimated levels of exposure of human populations to the mixture or to the mixture components constitute a potential health hazard? Thus, the flow chart focuses on a decision process. If a potential hazard is identified, this result does not mean that an actual public health hazard has been identified. Rather, it indicates that further evaluation using ATSDR (1992) methods for public health assessment will be needed (see Section 4.1, paragraph 1 of this mixtures guidance).

Figure 2. Strategy for Exposure-Based Assessment of Joint Toxic Action of Chemical Mixtures: Noncarcinogenic Effects *(See text for detailed explanation)*



Step 1: Use Interaction Profile or Policy Guideline if available for mixture of concern.

ATSDR provides guidance on some mixtures in *Interaction Profiles* (on simple mixtures of concern for hazardous waste sites) and in *Policy Guidelines* (to date, available only for dioxins and dioxin-like compounds in soil [Appendix B of ATSDR 1998b]). These documents may be identified by searching the ATSDR website, and should be used for guidance. These documents recommend specific approaches to be used with waste-site-specific exposure data in order to assess potential health hazard from joint toxic action of certain mixtures. The recommended approaches may include the use of whole mixture data, assessment of components singly, PBPK/PD, TEF, hazard index, TTD, WOE, indicator chemical or other approach. The policy guideline and interaction profiles provide the needed TEF, BINWOE, and TTD values. If the document offers only partial coverage of the mixture, use as appropriate and return to flow chart for additional guidance. For example, an interaction profile may cover some of the chemicals in the mixture but not others. The flow chart can be used to further define the components of concern before deciding whether the mixture "matches" the mixture in the interaction profile, and to account for components of concern not covered by the profile. If no ATSDR documentation is available and relevant information is available from another agency, evaluate the information for suitability and use if appropriate. Otherwise, return to the flow chart at Step 2.

Step 2: Consult Toxicological Profile or use whole mixture study if available for mixture of concern.

A number of *Toxicological Profiles* deal with intentional and generated mixtures, and can be identified by searching the ATSDR website. These mixtures include fuels (e.g., ATSDR 1998a), PCBs (ATSDR 2000), CDDs (ATSDR 1998b), PAHs (ATSDR 1995b, 1999), pesticides such as toxaphene (ATSDR 1996b), and total petroleum hydrocarbons (ATSDR 1999). Some of these mixtures are assessed as whole mixtures (certain fuels and pesticides, PCBs), others are assessed with MRLs for individual components or using a fraction approach (PAHs), or on the basis of dose-additivity of the components (CDDs and CDFs; see also *Policy Guideline* in Step 1). For complex mixtures of petroleum hydrocarbons, similar components are lumped into fractions for exposure and health effects assessment, and MRLs for the fractions are recommended based on a single representative (surrogate) component or a similar mixture. For some fractions, an indicator chemical approach is used (ATSDR 1999). ATSDR has considered some mixtures, such as gasoline and Stoddard Solvent, too variable in composition for MRL derivation (ATSDR 1995a, 1995c). It was suggested, in a separate publication, that when appropriate, the most toxic (known) chemical from the mixture could be selected as a marker (indicator) chemical for the mixture, assuming that the indicator chemical would drive the risk assessment. An example is using benzene as a marker or indicator chemical for environmental exposure to automotive gasoline (Pohl et al.

1997). Alternatively, a fraction approach, as discussed previously for complex mixtures of petroleum hydrocarbons (ATSDR 1999), in conjunction with a components approach for the nonhydrocarbon components (such as methyl-*t*-butyl ether), may be useful for gasoline. If the toxicological profile does not provide MRLs or recommendations for health assessment approaches, and relevant documentation from other agencies is not available or is not suitable, the literature can be searched for studies on the mixture of concern (whole mixture), and any available studies can be evaluated for possible use as the basis for a MRL, or to identify potential health effects of concern from exposure to the mixture. Studies of wildlife or companion animals exposed to site-related chemicals may be useful in identifying that a hazard exists at environmental levels of exposure, if evaluated for relevance to potential effects on human health. MRLs are derived in accordance with ATSDR (1996a) guidance. Additional guidance regarding implementation of a "whole mixture" approach is provided in ATSDR (2001). If information sufficient to conduct a mixtures assessment is not identified, return to the flow chart.

Step 3: If no ATSDR document is available for the mixture of concern, select components of concern.

If Steps 1 and 2 do not reveal suitable approaches or information for a mixtures assessment, or if the information is incomplete, a components approach is employed. The components approach focuses on components that are likely contributors to health hazard either because their individual exposure levels exceed health guidelines, or because joint toxic action with other components, including additivity or interactions, may pose a health hazard.

Components for which exposures are less than a ratio of 0.1 relative to noncancer health guidelines (i.e., have hazard quotients less than 0.1, HQs<0.1) are considered unlikely to pose a health hazard due to interactions, and unless there are a relatively large number of components that act similarly, are not likely to pose an increased hazard due to additivity. These components are eliminated from further consideration in Step 3. The value 0.1 is chosen as a reasonable point of departure for simple mixtures consisting of approximately 10 components or fewer. If *all* of the components have HQs<0.1, additivity and interactions among the components are unlikely to result in a hazard to public health, and further assessment of the mixture is not necessary. (If only one component is present at a HQ≥0.1, and if the HQ for that component exceeds unity, this situation is not considered a mixtures problem. The single component should be evaluated further using ATSDR [1992] public health assessment guidance.)

If two or more components have HQs≥0.1, these chemicals are components of concern for joint toxic action. Proceed with the evaluation of additivity and interactions in Steps 4–7 for these components of concern. Judgment should be used, however, in applying this value. With a mixture of more than

10 components that act similarly, or with several components with HQs just slightly below 0.1 and other HQs above 0.1, a slightly lower point of departure may be appropriate (see Section 4.2.2.7 for an example).

When used in the assessment of hazardous waste sites, the hazard quotient is commonly reported to one significant figure (EPA 1989a). For example, a hazard quotient of 0.13 is rounded to 0.1, and a hazard quotient of 1.6 is rounded to 2.

Step 4: Evaluate and use PBPK/PD model or joint toxic action studies, if available and appropriate.

If a PBPK, or PBPK/PD model and/or joint toxic action study is available for the complete mixture of components of concern, evaluate its relevance to human exposure by the anticipated route(s) and duration, and to the noncancer health effects of concern for the components. Studies of joint toxicokinetics or joint toxic action are commonly performed to validate the models. The effects of concern will include the critical effects and any relatively sensitive effects in common among two or more of the mixture components. The critical effect is the effect that is the basis for the MRL (or RfD or RfC). Examples of existing PBPK and PBPK/PD models and their potential usefulness were presented in Section 2.3.7 of this guidance.

Evaluation of the model also should include whether the models for the individual components have been linked in a reasonable manner, based on the components' toxicokinetics and mechanisms of action, and the extent of validation of the model. If a model appears directly useful for predicting the potential health hazard of defined levels of exposure to the components of concern, consult with an ATSDR DT PBPK/PD expert regarding the possibility of obtaining and using the model. The literature reports of some models or studies of joint action may be directly useful, for example, if they report apparent threshold exposures for interactions relevant to human exposure or that the components will not interact. This information can be used in Step 7 during the WOE evaluation and as part of the rationale for the components approach. The availability of linked PBPK and PBPK/PD models for mixtures is limited as of this writing, but research in this area is highly active. Therefore, update searching of an appropriate database such as TOXLINE should be conducted to identify pertinent PBPK or PBPK/PD models. For some mixtures, models may be available only for submixtures, including pairs of components, within the mixture. In this case, the hazard index method (Step 6a) or the TTD modification of the hazard index or separate HQ (Step 6b) can be chosen as appropriate, and reported results of the modeling for pairs of components can be used as part of a WOE approach. If no suitable models are available or if the models are to be used as part of the WOE evaluation, proceed to Step 5.

Step 5: Evaluate whether components have the same or different critical effects.

Assess whether the components that contribute to a particular exposure pathway of concern appear to affect primarily the same endpoints, particularly in terms of critical effects or critical target organs. If so, apply the hazard index method (Step 6a). If the components appear to have a variety of critical effects, apply the TTD modification to the hazard index (Step 6b). If most, but not all, of the mixture's components have the same critical effect, the hazard index method can be chosen on the grounds of practicality.

Step 6a: Apply hazard index method to components with similar critical effects.

The hazard index method was discussed in Section 2.3.1. A hazard index is estimated for a specific receptor population, for the duration and pathway of concern. The exposure units should be the same as the units for the health guideline (e.g., mg/kg/day for oral exposure pathways, when using oral MRLs [or RfDs] as health guideline values, and units of air concentration for inhalation exposure pathways, when using inhalation MRLs [or RfCs] as health guideline values). For example, adapting equations 2 and 1(b) for use with MRLs (and RfDs for components lacking oral MRLs) results in the following equation for the oral hazard index (HI_{oral}) for pathways involving oral exposure:

$$HI_{oral} = \sum_{i=1}^{n} HQ_{i\ oral} = \sum_{i=1}^{n} \frac{E_{i\ oral}}{MRL_{i\ oral}\ or\ RfD_i} \qquad \textbf{(7)}$$

where $HQ_{i\ oral}$ is the oral hazard quotient, $E_{i\ \mathrm{oral}}$ is the oral exposure in mg/kg/day, and $MRL_{i\ oral}\ or\ RfD_i$ is the oral MRL or RfD in units of mg/kg/day, for the i^{th} component.

If the resulting hazard index exceeds one, the mixture constitutes a *potential* health hazard due to additivity. Further evaluation of interactions is needed to gauge the extent of the hazard (Step 7). If the resulting hazard index is less than or equal to one, further evaluation of interactions is required to assess the potential for interactions to increase the apparent hazard (Step 7). As was the case for the hazard quotient (Step 3), the hazard index is rounded to one significant figure (EPA 1989a).

Step 6b: Apply TTD modification of hazard index method for components with different critical effects.

The TTD modification to the hazard index method was discussed in Section 2.3.2, and example equations were presented there. Separate hazard indexes are estimated for each major endpoint or target organ affected by two or more components of the mixture (i.e., the overlapping targets of toxicity). The MRL (or RfD or RfC) for a component is used when the hazard index is for the endpoint on which that health

guideline is based. TTDs are used for the other major effects of the component. The equations are similar to equation 7 above. For example, a hazard index for hepatic effects from a pathway involving oral exposure is calculated as follows:

$$HI_{oral\ hepatic} = \sum_{i=1}^{n} HQ_{i\ oral\ hepatic} = \sum_{i=1}^{n} \frac{E_{i\ oral}}{MRL_{i\ oral}\ or\ RfD_i\ or\ TTD_{i\ oral\ hepatic}} \quad \textbf{(8)}$$

where $HI_{oral\ hepatic}$ is the oral hazard index for hepatic effects, HQ_i is the hazard quotient, $E_{i\ \mathrm{oral}}$ is the oral exposure in mg/kg/day, and $MRL_{i\ oral}\ or\ RfD_i\ or\ TTD_{i\ oral\ hepatic}$ is the oral MRL or RfD or TTD for hepatic effects in units of mg/kg/day, for the i^{th} component.

If any of the endpoint-specific hazard indexes exceed one, the mixture constitutes a *potential* health hazard due to additivity. Further evaluation of interactions is needed to gauge the extent of the hazard (Step 7). If all the endpoint-specific hazard indexes are one or less than one, further evaluation is required to assess the potential for interactions to increase the hazard (Step 7). In addition, if any component of the mixture has a unique critical effect (effect not produced by any of the other components), this effect should be addressed by assessing whether the hazard quotient exceeds unity, in which case it would be considered a *potential* health hazard. The qualitative WOE method also should be applied (Step 7) to gauge whether any of the other mixture components may influence the toxicity of this component with regard to this critical effect.

Step 7(a and b): Apply Qualitative WOE.

The qualitative WOE methodology, summarized previously in Section 2.3.3, provides a means of predicting joint toxic action when the data are not sufficient (as is usually the case) to use more quantitative means. The BINWOE determinations are used to make judgments regarding whether the health hazard may be greater or lesser than would be predicted on the basis of the hazard index alone. BINWOEs need to be route-, duration-, and endpoint- or target-organ-specific. This specificity may be accommodated within a single BINWOE determination, or through separate BINWOE determinations. Before using a BINWOE, make sure it is applicable to the route(s), duration(s), and effect(s) of concern for the particular assessment.

The qualitative BINWOE scores for the components, if similar in direction, are the basis for a conclusion. For example, consider a mixture of four components, all present at toxicologically significant levels. The number of possible chemical pairs in a mixture of N components is $(N^2\text{-}N)/2$. Thus, this mixture of 4 components has 6 pairs of components and potentially 11 BINWOEs for a given route, duration, and effect. Suppose nine of the BINWOEs are greater-than-additive (positive) with alphanumeric

classifications indicating a relatively high degree of confidence, and the remaining three BINWOEs are additive (0), also with relatively high degrees of confidence. In this case, the weight of evidence suggests that the mixture is likely to pose a greater hazard than that indicated by the hazard index.

A likely pattern of qualitative BINWOEs for a mixture is a mixed pattern (some greater than additive, some less than additive, and some additive BINWOEs). In this case, still using the qualitative WOE approach, the qualitative BINWOE scores are converted to numerical scores, and the scores are summed to give a combined score. If the combined BINWOE score is positive and significantly different from zero, the weight of evidence suggests that the mixture is likely to pose a greater hazard than indicated by the hazard index. Conversely, if the combined BINWOE score is negative and significantly different from zero, then the weight of evidence suggests that the health hazard is likely to be less than indicated by the hazard index. If the combined BINWOE score is zero or close to zero, the weight of evidence does not suggest that interactions will alter the potential health hazard as represented by the hazard index. Professional judgment by a qualified environmental health scientist or toxicology in ATSDR should be sought to interpre the impact of the WOE on the hazard index.

Step 7a: This part of Step 7 describes the application of the qualitative WOE to hazard indexes that are less than or equal to unity ($HI \leq 1$). If the BINWOE alphanumeric scores indicate greater than additivity, or if the combined BINWOE numerical score is positive and significantly greater than zero, and particularly if the hazard index is near unity, these levels of exposure to the mixture constitute a *potential* health hazard. Further evaluation using the methods in ATSDR (1992) is necessary. Conversely, if the BINWOE alphanumeric scores indicate less than additivity or additivity, or the combined numerical score is negative or very close to zero, the mixture is unlikely to be a health hazard at the hazardous-waste-site related exposure levels.

Step 7b: This part of Step 7 describes the application of the qualitative WOE to hazard indexes that are greater than unity ($HI > 1$). If the BINWOE alphanumeric scores indicate greater than additivity or additivity, or if the combined BINWOE numerical score is positive, these levels of exposure to the mixture constitute a *potential* health hazard due to interactions and/or additivity. Further evaluation using the methods in ATSDR (1992) is necessary. Conversely, if the BINWOE alphanumeric scores indicate less than additivity, or the combined numerical score is negative and significantly different from zero, the mixture health hazard is likely to be less than indicated by the hazard index. Further evaluation using the methods in ATSDR (1992) is needed.

4.2.2. Example Applications of Exposure-Based Assessment of Joint Toxic Action for Noncarcinogenic Effects of Chemical Mixtures

The following examples are hypothetical examples chosen to illustrate how the procedures outlined in Figure 2 can be applied to a variety of exposure situations. Each example is for a single pathway and duration (assume intermediate or chronic) of exposure.

4.2.2.1. Residential Soil Contamination with CDDs and CDFs

Under Step 1, the ATSDR website is searched for relevant information, and the draft policy guideline for dioxin and dioxin-like compounds in soil (De Rosa et al. 1997a) is identified and downloaded. Further investigation locates the final policy guideline published as an appendix to the CDDs profile (ATSDR 1998b). This policy guideline provides the necessary guidance for health effects assessment of these mixture components; the guideline applies to noncarcinogenic effects (and to carcinogenic effects). Additional background can be obtained from the supporting documentation (De Rosa et al. 1997b, 1997c) and the toxicological profiles on CDDs and CDFs (ATSDR 1994, 1998b).

4.2.2.2. Groundwater Contamination with Chemicals A, B, and C

An interaction profile is available on this particular common mixture and can be identified by searching the ATSDR website. The interaction profile provides specific guidance on an approach for the assessment of joint toxic action for noncarcinogenic (and carcinogenic) effects of this mixture. Use the recommended approach to conduct exposure-based assessment of joint toxic action to screen for potential health hazard of the mixture, and use the ATSDR (1992) guidance for public health assessment for the other aspects of public health assessment.

4.2.2.3. Residential Soil Contamination with Toxaphene

Although no policy guideline or interaction profile (Step 1) is available for this mixture, a toxicological profile is available (Step 2), and provides MRLs for noncarcinogenic effects (and risk-specific doses, slope factor, and unit risk for carcinogenic effects) of toxaphene assessed as a whole mixture. These health guideline values and other information in the profile are used in accordance with ATSDR guidance for public health assessment (ATSDR 1992).

4.2.2.4. Groundwater Contamination with Chemicals D, E, F, and G

No policy guideline, interaction profile, or toxicological profile is identified for this mixture (Steps 1 and 2, Figure 2), but toxicological profiles are available for the individual chemicals. A components approach is therefore initiated. The following four "cases" are hypothetical and are presented to illustrate the use of the approach in Figure 2 for mixtures with a relatively small number of components.

Case 1: The hazard quotient (ratio of the exposure dose [oral intake in mg/kg/day] to the oral MRL [or RfD if MRL not available]) for each chemical is estimated as follows.

chemical D:	(exposure dose)/MRL	= (0.05 mg/kg/day)/(0.5 mg/kg/day)	= 0.1
chemical E:		= (0.03 mg/kg/day)/(0.09 mg/kg/day)	= 0.3
chemical F:		= (2 mg/kg/day)/(0.5 mg/kg/day)	= 4
chemical G:		= (12 mg/kg/day)/(2 mg/kg/day)	= 6

Thus, the hazard quotients for chemicals D, E, F, and G are 0.1, 0.3, 4, and 6, respectively. Because the hazard quotients for chemicals F and G are above unity, these individual components can be considered potential health hazards. For all four chemicals, the hazard quotients are at least 0.1 (HQs$\geq$1), and all four are selected as components of concern (Step 3). Further evaluation is necessary to assess the potential impact of additivity and interactions on the degree of hazard. No PBPK/PD or PBPK model is available for the mixture (Step 4). The critical effects for all four components are the same, hepatic (Step 5). Therefore, a hazard index is calculated as the sum of the hazard quotients (HI = 0.1 + 0.3 + 4 + 6 = 10.4, rounded to 10) (Step 6a). The magnitude of the hazard index indicates a potential health hazard due to additivity. Evaluation of interactions (Step 7b for HI>1) is needed. BINWOE scores that are relevant to the route, duration, and endpoint for the six chemical pairs are provided by ATSDR. The BINWOEs are additive for the effect of chemical D on the toxicity of chemical E, less than additive for E on D, and indeterminate for F on D. The remaining nine BINWOEs are greater than additive. The additive and indeterminate BINWOEs are for effects on the toxicities of components with relatively low HQs (D and E), whereas the greater-than-additive BINWOEs include effects of the components with relatively high HQs (F and G) on each other's toxicity, and also reflect relatively high confidence (high numerical BINWOE scores). Summing the BINWOE scores results in a combined score of +4.99. These results indicate that the hazard is likely to be greater than would be predicted on the basis of the default assumption of additivity (the hazard index of 10). Thus, the mixture is a *potential* health hazard at the

estimated levels of exposure, and will be subjected to further evaluation according to procedures in ATSDR's guidance for public health assessment (ATSDR 1992).

Case 2a: The hazard quotients for chemicals D, E, F, and G are estimated at 0.02, 0.2, 0.5, and 0.4 in a manner similar to that shown for Case 1. Three of the chemicals (E, F, and G) have HQs$\geq$0.1; these chemicals are components of concern as indicated by Step 3. The hazard quotient of 0.01 for chemical D, however, is an order of magnitude lower than the other three, and much lower than 0.1. Chemical D is considered unlikely to have an impact due to additivity or interactions, so it is dropped from further consideration. No PBPK/PD or PBPK model is available for the three-component mixture, but a PBPK model is available for a binary mixture of chemicals E and F, and is applicable to oral exposure (Step 4). The model will be considered subsequently during the evaluation of interactions for this pair. The critical effects (Step 5) for the three components are hepatic effects. The hazard index (Step 6a) is 1 (HI = 0.2 + 0.5 + 0.4 = 1.1, rounded to 1). To further assess the potential hazard, a qualitative WOE evaluation is undertaken (Step 7a for HI$\leq$1), using relevant BINWOEs available from ATSDR. The BINWOEs for the mixture of chemicals E and F were based in part on the PBPK model predictions. Four of the six BINWOEs for the three possible pairs are greater than additive (positive) and two are additive (0); thus, the weight of evidence suggests the hazard will be greater than indicated by the hazard index. The combined BINWOE score will be positive. Consistent with Step 7, it is concluded that the mixture constitutes a *potential* health hazard at the estimated exposure levels. It should be evaluated further using ATSDR guidance for public health assessment (ATSDR 1992).

Case 2b: Identical to Case 2a, except that, in step 7, the six BINWOEs for the three possible pairs are less than additive (negative) and additive. Because the hazard index is 1, and the BINWOEs suggest that the hazard will be less than predicted by the hazard index, it is unlikely that the mixture would be a health hazard at the estimated exposure levels.

Case 3: The hazard quotients for chemicals D, E, F, and G are 0.8, 1, 2, and 0.8. As indicated by Step 3, further evaluation is necessary. No PBPK/PD or PBPK model is available for the mixture (Step 4). The components all have the same critical effects (hepatic) (Step 5). The hazard index (Step 6a) is 5 (HI = 0.8 + 1 + 2 + 0.8 = 4.6, rounded to 5). The mixture is considered to constitute a potential health hazard on the basis of additivity. Five of the BINWOEs are less than additive, including some scores for the effects on the toxicity of chemical F, which has the highest hazard quotient. The remaining seven BINWOEs are additive. Thus, the qualitative WOE approach (Step 7b) would indicate that the hazard may be less than indicated by the hazard index. Although this result indicates that the health hazard is likely to be less than indicated by the hazard index of 5, the result should be interpreted with care.

Exposure to a mixture of hazardous substances that may act antagonistically may be considered to be less hazardous than if the joint toxic action of those substances were additive or synergistic, but it does not rule out all concern, particularly when the hazard index is not close to 1. Further evaluation using ATSDR (1992) guidance for public health assessment is needed.

4.2.2.5. Groundwater Contamination with Chemicals H, I, J, K, and L

No suitable documents for the mixture are available (Steps 1 and 2). The hazard quotients for chemicals H, I, J, K, and L are 0.1, 0.2, 0.5, 0.4, and 0.3; all four chemicals are components of concern (Step 3). PBPK/PD or PBPK models are not available (Step 4). The components have different critical effects (hepatic for chemicals H and I, renal for chemical J, and hematological for chemical K, and dermal for chemical L) (Step 5). Estimation of endpoint-specific hazard indexes using the TTD modification of the hazard index (Step 6b), and TTDs available from ATSDR, results in an hazard index of 0.6 for hepatic effects, 0.7 for renal effects, 0.5 for hematological effects, and 0.4 for developmental effects (included because three of the components have developmental effects). Dermal effects are a "unique critical effect" in that they are the critical effect of one chemical (L), but are not caused by any of the other chemicals; the hazard quotient for this effect is 0.3 as noted above. Thus, the endpoint-specific hazard indexes all are less than one and the hazard quotient for the unique critical effect is also less than one. A qualitative WOE evaluation is undertaken (Step 7a). BINWOE evaluations are available for hepatic (less than additive and additive), renal (less than additive), and hematological effects (less than additive or additive). BINWOEs for the effects of the other mixture components on the dermal toxicity of chemical L are less than additive or indeterminate. Little information on interactions or mechanisms specifically relevant to developmental effects is available, so all evaluations for developmental are indeterminate or additive with low scores. Concern for greater-than-additive interactions for developmental toxicity is low, however, because greater-than-additive interactions are not seen for the four other endpoints. Because the endpoint-specific hazard indexes are less than one, the hazard quotient for the unique critical effect is less than one, and the WOE evaluations are mainly additive to less than additive (with none greater than additive), it is concluded that the mixture is not likely to be a health hazard at the estimated levels of exposure.

4.2.2.6. Air Contamination with Chemicals M, N, and O

No interaction profile or guidance policy is available for this mixture (Step 1), and toxicological profiles and MRLs are not available for the mixture (Step 2), but are available for the individual components. The

hazard quotients (ratios of exposure concentrations to inhalation MRLs, or RfCs if MRLs not available) for the components are 0.3, 0.4, and 0.3:

chemical M:	(Exposure concentration)/MRL	= (0.2 ppm)/(0.6 ppm)	= 0.3
chemical N:		= (0.08 ppm)/0.2 ppm)	= 0.4
chemical O:		= (0.6 ppm)/(2 ppm)	= 0.3

Thus, all three components are components of concern (Step 3). PBPK/PD models are available for all three possible pairs (M and N, M and O, N and O) but not for the entire three-component mixture (Step 4). The components have the same critical effect, renal (Step 5). The hazard index (Step 6a) is 1 (HI = 0.3 + 0.4 + 0.3). Based on the PBPK/PD models, which extrapolate from animal data to humans by the inhalation route and have been further calibrated with human inhalation data, the site-specific exposure levels for each pair of chemicals are within the exposure range where dose-additivity is predicted by the model. Less-than-additive results are predicted at higher exposure levels. The models were published recently and therefore were not cited in the BINWOEs available from ATSDR, but conclusions are reasonably consistent with the BINWOEs. Therefore, the mixture is considered unlikely to constitute a health hazard at the estimated exposure levels.

4.2.2.7. Groundwater Contamination with 12 Chemicals

No interaction profile or guidance policy is available for this mixture, but toxicological profiles and MRLs or other comparison values are available for the components. Hazard quotients range from 0.0009 to 0.3, with only one component having a hazard quotient of 0.1 or more. Although the usual conclusion, according to Step 3, would be that the mixture is unlikely to pose a health hazard due to additivity or interactions of the components, in this case, because of the larger number of components, components slightly below the point of departure (0.1) for the hazard quotient are evaluated further.

Five of the components have hazard quotients that are 0.01 or less, well below the point of departure, and therefore are dropped from the assessment. Six components have hazard quotients approaching 0.1 (i.e., 0.07, 0.08, 0.07, 0.09, 0.09, and 0.08), and are retained, along with the component with the hazard quotient of 0.3, for further assessment. PBPK or PBPK/PD models are not available for the full mixture or for any of the pairs of chemicals within the mixture (Step 4). Six of the seven components of concern are organic compounds that affect the liver and nervous system. The critical effects are hepatic for four of the organics and neurological for two, but chemical-specific LOAELs for these two endpoints vary by less than a factor of two, as do the NOAELs. The seventh component is an inorganic chemical, for which

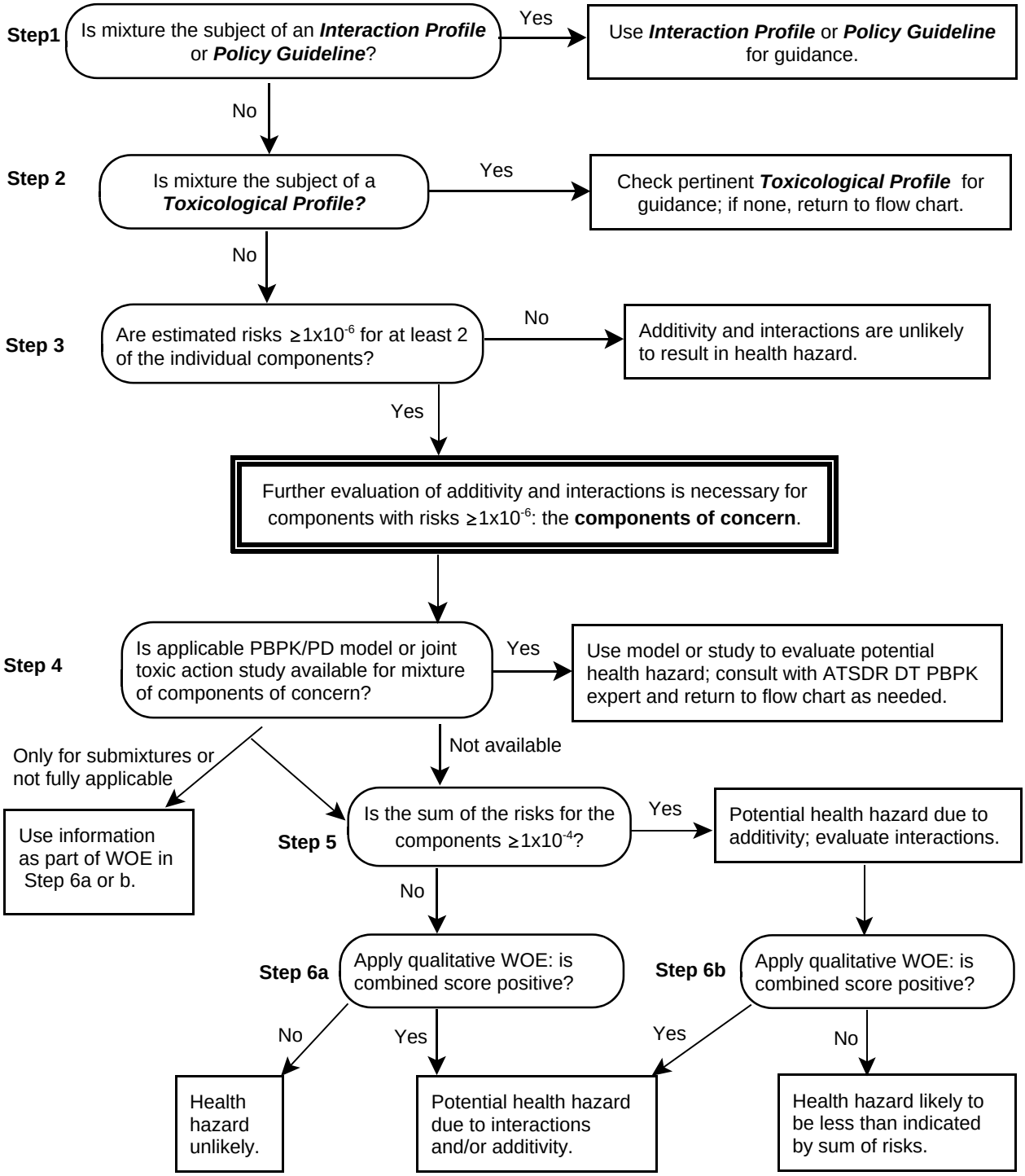
the critical effect is renal; this component also affects the liver at higher exposures. The TTD approach would be preferable for this mixture of concern, but because of the number of components and the similarity of effects for six of the seven, the hazard index approach (Step 6a) could be chosen as a more practical interim approach. The hazard index for the six organic components with similar effects is 0.7 (rounded from 0.69). Inclusion of the hazard quotient of 0.09 for the component with renal effects would result in a hazard index of 0.8 (rounded from 0.78).

The potential impact of interactions should be evaluated. For this mixture, if the 6 components with similar endpoints are evaluated with WOE method, there would be 15 pairs of chemicals, requiring 30 BINWOEs. If BINWOEs are available from ATSDR for these pairs, then further evaluation as described in Step 7 can be readily undertaken. If the TTD approach is chosen, TTDs will be needed for the endpoints mentioned above, and possibly for others, and may be available from ATSDR. BINWOEs will also be needed for these endpoints. If BINWOEs or TTDs are not readily available, biomedical judgment and careful consideration of the community-specific health outcome data and community health concerns could be used to decide whether further analysis is needed, using ATSDR guidance for public health assessment (ATSDR 1992). If the decision is to pursue further analysis, ATSDR DT mixtures toxicologists should be consulted, and methods outlined in Section 2.3.2 (TTDs) and Section 2.3.3 (WOE) can be used. Additional detail regarding the derivation of BINWOEs is provided in ATSDR (2001).

4.2.3. Procedures for Assessment of Carcinogenic Effects (Figure 3)

The flow chart in Figure 3 gives an overview of the steps for exposure-based assessment of the potential impact of joint toxic action on public health. The analysis of exposure pathways and intakes or concentrations should be performed using ATSDR (1992) methods for public health assessment. The process described in the flow chart and accompanying text is designed to answer the question: do the estimated levels of exposure of human populations to the mixture or to the mixture components constitute a potential health hazard? Thus, the flow chart focuses on a decision process. If a potential hazard is identified, this result does not mean that an actual public health hazard has been identified. Rather, it indicates that further evaluation using ATSDR (1992) methods for public health assessment will be needed (see Section 4.1, paragraph 1 of this mixtures guidance).

Figure 3. Strategy for Exposure-Based Assessment of Joint Toxic Action of Chemical Mixtures: Carcinogenic Effects *(See text for detailed explanation)*



Step 1: Use Interaction Profile or Policy Guideline if available for mixture of concern.

ATSDR provides guidance on some mixtures in *Interaction Profiles* (on simple mixtures of concern for hazardous waste sites) and in *Policy Guidelines* (to date, available only for dioxins and dioxin-like compounds in soil [ATSDR 1998b, Appendix B]). These documents may be identified by searching the ATSDR website, and should be used for guidance. These documents recommend specific approaches to be used with waste-site-specific exposure data in order to assess potential health hazard from joint toxic action of certain mixtures. The recommended approaches may include the use of whole mixture data, assessment of components singly, PBPK/PD, TEF, WOE, indicator chemical or other approach, and provide the needed TEFs and BINWOEs. If the document offers only partial coverage of the mixture, use as appropriate and return to flow chart for additional guidance. For example, an interaction profile may cover some of the chemicals in the mixture but not others. The flow chart can be used to further define the components of concern before deciding whether the mixture "matches" the mixture in the interaction profile, and to account for components of concern not covered by the profile. If no ATSDR documentation is available and relevant information is available from another agency, evaluate the information for suitability and use if appropriate. Otherwise, return to the flow chart.

Step 2: Consult Toxicological Profile if available for mixture of concern.

In addition, a number of *Toxicological Profiles* deal with intentional and generated mixtures, and can be identified by searching the ATSDR website. These mixtures include fuels (e.g., ATSDR 1998a), PCBs (ATSDR 2000), CDDs (ATSDR 1998b), PAHs (ATSDR 1995b, 1999), pesticides such as toxaphene (ATSDR 1996b), and total petroleum hydrocarbons (ATSDR 1999). Some of these mixtures are assessed as whole mixtures (certain pesticides, PCBs), others can be assessed using a relative potency approach for carcinogenicity (PAHs), or on the basis of dose-additivity of the components (CDDs and CDFs; see also *Policy Guideline* in Step 1). ATSDR provides perspective on the relevance to public health of the carcinogenicity data, reports the conclusions of other agencies that assess carcinogenicity, and reports EPA dose-response assessment values (e.g., slope factors, unit risks). IRIS may also be consulted for these values. If the toxicological profile (or IRIS or other suitable documentation from other agencies) does not provide recommendations for health assessment approaches, return to the procedures in the flow chart.

Step 3: If no ATSDR document is available for the mixture of concern, select components of concern.

As was the case for noncarcinogenic effects, the following approach for carcinogenic effects focuses on components that are likely contributors to health hazard either because their individual exposure levels exceed health guidelines, or because joint toxic action with other components, including additivity or interactions, may pose a health hazard. Thus, components for which exposures do not exceed guideline values (based on an increased lifetime cancer risk of $1x10^{-6}$, a conservative level) are considered unlikely to pose increased risk due to interactions or additivity, and are dropped from further consideration in Step 3. If all the components have risks less than $1x10^{-6}$, additivity and interactions among the components are unlikely to result in a hazard to public health, and further assessment of the mixture is not necessary. (If only one component is present at a risk$\geq 1x10^{-6}$, and if the risk for that component is $\geq 1x10^{-4}$, this situation is not considered a mixtures problem. The single component should be evaluated further using ATSDR [1992] public health assessment guidance.)

If estimated risks equal or exceed $1x10^{-6}$ for two or more of the components, these chemicals are components of concern for joint toxic action. Proceed with the evaluation of additivity and interactions in Steps 4–6 for these components of concern.

Increased lifetime cancer risks are estimated by multiplying the slope factor (for oral exposure) or unit risk (for inhalation exposure) by the estimated exposure in the same units (mg/kg/day for oral, air concentration for inhalation). When used in the assessment of hazardous waste sites, risks are commonly reported to one significant figure (e.g., an estimated risk of $1.4x10^{-5}$ is rounded to $1x10^{-5}$, and $9.8x10^{-7}$ is rounded to $1x10^{-6}$).

Step 4: Evaluate and use PBPK/PD model or joint toxic action studies, if available and appropriate.

If a PBPK or PBPK/PD model is available for the mixture of components of concern, evaluate its relevance to human exposure by the anticipated route(s) and duration, and to the cancer health effects of the components. Studies of joint toxicokinetics or joint toxic action are commonly performed to validate the models. Examples of existing PBPK models and their potential usefulness were presented in Section 2.3.7 of this guidance.

Evaluation of the model also should include whether the models for the individual components have been linked in a reasonable manner, based on the components' toxicokinetics and mechanisms of action, and the extent of validation of the model. If a model appears directly useful for predicting the potential health

hazard of defined levels of exposure to the components of concern, consult with an ATSDR DT PBPK/PD expert regarding the possibility of obtaining and using the model. The literature reports of some models or studies of joint toxic action may be directly useful, for example, if they report apparent threshold exposures for interactions relevant to human exposure or that the components will not interact. This information can be used in Step 6 during the WOE evaluation. The availability of linked PBPK and PBPK/PD models for mixtures is limited as of this writing, but research in this area is highly active. Therefore, update searching of an appropriate database such as TOXLINE should be conducted to identify pertinent PBPK or PBPK/PD models. For some mixtures, models may be available only for submixtures, including pairs of components, within the mixture. In this case, the reported results of the modeling for pairs of components can be used as part of a WOE approach. If no suitable models are available or if the models are to be used as part of the WOE evaluation, proceed to Step 5.

Step 5: Sum the cancer risks.

If the sum of the cancer risks for a pathway exceeds the point of departure for significant impact on lifetime cancer risk, the mixture constitutes a *potential* health hazard due to additivity. A risk of $1x10^{-4}$ (1 in 10,000) is selected as the point of departure for significant risk (ATSDR 1992; De Rosa et al. 1993). Further evaluation of interactions, using the methods described in Step 6, is needed to gauge the extent of the hazard. If the sum of the cancer risks is less than the point of departure, further evaluation of interactions is required to assess the potential for interactions to increase the apparent hazard (Step 6).

Step 6: Apply qualitative WOE.

The qualitative WOE methodology, summarized previously in Section 2.3.3, provides a means of predicting joint toxic action when the data are not sufficient (as is usually the case) to use more quantitative means. The BINWOE determinations are used to make judgments regarding whether the health hazard may be greater or lesser than would be predicted on the basis of the sum of the cancer risks alone. BINWOES need to be route-, duration-, and endpoint-specific. This specificity may be accommodated within a single BINWOE determination, or through separate BINWOE determinations. Before using a BINWOE, make sure it is applicable to the route(s), duration(s), and effect(s) of concern for the particular assessment.

The qualitative BINWOE scores for the components, if similar in direction, are the basis for a conclusion. For example, consider a mixture of four components, all present at toxicologically significant levels. The number of possible chemical pairs in a mixture of N components is $(N^2-N)/2$. Thus, this mixture of

4 components has 6 pairs of components and potentially 11 BINWOEs for carcinogenicity by a given route and duration. Suppose nine of the BINWOEs are greater-than-additive (positive) with alphanumeric classifications indicating a relatively high degree of confidence, and the remaining three BINWOEs are additive (0), also with relatively high degrees of confidence. In this case, the weight of evidence suggests that the mixture is likely to pose a greater hazard than that indicated by the sum of the risks.

A likely pattern of qualitative BINWOEs for a mixture is a mixed pattern (some greater than additive, some less than additive, and some additive BINWOEs). In this case, still using the qualitative WOE approach, the qualitative BINWOE scores are converted to numerical scores, and the scores are summed to give a combined score. If the combined BINWOE score is positive and significantly different from zero, the weight of evidence suggests that the mixture is likely to pose a greater hazard than indicated by the sum of the risks. Conversely, if the combined BINWOE score is negative and significantly different from zero, then the weight of evidence suggests that the health hazard is likely to be less than indicated by the sum of the risks. Professional judgment is used in the interpretation of the impact of the WOE on the sum of the estimated cancer risks.

Step 6a: This portion of Step 6 describes the application of the qualitative WOE when the sum of the risks for the components is less than $1x10^{-4}$. If the BINWOE alphanumeric scores indicate greater than additivity, or if the combined BINWOE numerical score is positive and significantly greater than zero, and particularly if the sum of the risks is near $1x10^{-4}$, these levels of exposure to the mixture constitute a *potential* health hazard. Further evaluation using the methods in ATSDR (1992) is necessary. Conversely, if the BINWOE alphanumeric scores indicate less than additivity or additivity, or the combined numerical score is negative or very close to zero, the mixture is unlikely to be a health hazard at the hazardous-waste-site related exposure levels.

Step 6b: This portion of Step 6 describes the application of the qualitative WOE when the sum of the risks is greater than or equal to $1x10^{-4}$. If the BINWOE alphanumeric scores indicate greater than additivity or additivity, or if the combined BINWOE numerical score is positive, these levels of exposure to the mixture constitute a *potential* health hazard due to interactions and/or additivity. Further evaluation using the methods in ATSDR (1992) is necessary. Conversely, if the BINWOE alphanumeric scores indicate less than additivity, or the combined numerical score is negative and significantly less than zero, the mixture health hazard is likely to be less than indicated by the sum of the risks. Further evaluation using the methods in ATSDR (1992) is needed.

4.2.4. Example Applications of Exposure-based Assessment of Joint Toxic Action for Carcinogenic Effects of Chemical Mixtures

The following examples are hypothetical examples chosen to illustrate how the procedures outlined in Figure 3 can be applied to a variety of exposure situations. Each example is for a single pathway and duration (assume intermediate or chronic) of exposure. The first three examples also were presented under Section 4.2.2 because they apply to the assessment of both noncarcinogenic and carcinogenic effects.

4.2.4.1. Residential Soil Contamination with CDDs and CDFs

Under Step 1, the ATSDR website is searched for relevant information, and the draft policy guideline for dioxin and dioxin-like compounds in soil (De Rosa et al. 1997a) is identified and downloaded. Further investigation locates the final policy guideline published as an appendix to the CDDs profile (ATSDR 1998b). This policy guideline provides the necessary guidance for health effects assessment of these mixture components; the guideline applies to carcinogenic effects (and to noncarcinogenic effects). Additional background can be obtained from the supporting documentation (De Rosa et al. 1997b, 1997c) and the toxicological profiles on CDDs and CDFs (ATSDR 1994, 1998b).

4.2.4.2. Groundwater Contamination with Chemicals A, B, and C

An interaction profile is available on this particular common mixture and can be identified by searching the ATSDR website. The interaction profile provides specific guidance on a health assessment approach for carcinogenic (and noncarcinogenic) effects of this mixture. Use the recommended approach to conduct exposure-based assessment of joint toxic action to screen for potential health hazard of the mixture, and use the ATSDR guidance for public health assessment (1992) for the other aspects of public health assessment.

4.2.4.3. Residential Soil Contamination with Toxaphene

Although no policy guideline or interaction profile (Step 1) is available for this mixture, a toxicological profile is available (Step 2), and provides risk-specific doses, a slope factor, and a unit risk for carcinogenic effects of toxaphene (from EPA), as well as MRLs for noncarcinogenic effects of toxaphene assessed as a whole mixture. These values and other information in the profile are used in accordance with ATSDR guidance for public health assessment (ATSDR 1992).

4.2.4.4. Groundwater Contamination with Chemicals D, E, F, and G

No policy guideline, interaction profile, or toxicological profile is identified for this mixture (Steps 1 and 2, Figure 3), but toxicological profiles are available for the individual chemicals, all of which have carcinogenic effects. A components approach is therefore initiated. The following four "cases" are hypothetical and are presented to illustrate the use of the approach in Figure 3 for mixtures with a relatively small number of components. It is assumed for the purposes of illustration that the point of departure for risk levels considered to have a significant impact on lifetime cancer risk is $1x10^{-4}$.

Case 1: The increased lifetime cancer risks for the individual components are estimated by multiplying the exposure dose by the slope factor.

chemical D:	exposure dose x slope factor	= 0.0001 mg/kg/day x $(1.0x10^{-3})$ $(mg/kg/day)^{-1}$	= $1x10^{-7}$
chemical E:		= 0.000043 mg/kg/day x $(4.7x10^{-4})$ $(mg/kg/day)^{-1}$	= $2x10^{-8}$
chemical F:		= 0.016 mg/kg/day x $(3.1x10^{-2})$ $(mg/kg/day)^{-1}$	= $5x10^{-4}$
chemical G:		= 0.003 mg/kg/day x 1.1 $(mg/kg/day)^{-1}$	= $3x10^{-3}$

Thus, the increased lifetime cancer risks for the components are $1x10^{-7}$, $2x10^{-8}$, $5x10^{-4}$, and $3x10^{-3}$. The first two component risks are below $1x10^{-6}$, and therefore are not expected to have a significant impact due to additivity or interactions. These two components are dropped from further consideration (Step 3). An applicable PBPK/PD model is not available for the components of concern (F and G) (Step 4). The sum of the risks for chemicals F and G results in a total risk of $3.5x10^{-3}$, which is rounded to $4x10^{-3}$, indicating that the mixture poses a *potential* health hazard due to additivity (Step 5). The qualitative WOE is applied to assess the potential impact of interactions (Step 6b). The BINWOE determinations are negative with a sum of -1.21. Thus, the potential health hazard is likely to be less than indicated by the sum of the cancer risks. Nevertheless, considering that the sum of the risks is significantly higher than the $1x10^{-4}$ point of departure, further evaluation using the methods in ATSDR (1992) is needed.

Case 2a: The estimated increased lifetime cancer risks (calculated in a manner similar to that in Case 1) are $1x10^{-7}$, $9x10^{-6}$, $3x10^{-5}$, and $5x10^{-5}$ for chemicals D, E, F, and G. The risk for chemical D is below $1x10^{-6}$, so this chemical is dropped from further consideration (Step 3). The estimated risks for chemicals E, F, and G are above $1x10^{-6}$, so these components are retained for further evaluation. No PBPK/PD or PBPK model is available for this three-component mixture, but a PBPK model is available for a binary mixture of chemicals E and F, and is applicable to oral exposure (Step 4). The model will be considered

subsequently during the evaluation of interactions for this pair. The sum of the risks for components E, F, and G is $9x10^{-5}$ (rounded from $8.9x10^{-5}$) (Step 5). The qualitative WOE method is used to assess the potential impact of interactions (Step 6a). BINWOEs for carcinogenic effects for the three possible pairs are available and are pertinent to carcinogenic effects. The BINWOEs for chemicals E and F have taken into account the PBPK model. The majority of the BINWOEs for the pairs in this mixture are greater than additive (positive) and a few are additive (0). Consistent with Step 6a, and considering that the total risk for the mixture is close to $1x10^{-4}$, it is concluded that the mixture constitutes a *potential* health hazard. Further evaluation using the methods in ATSDR (1992) is necessary.

Case 2b: Identical to Case 2a, except that, in Step 6a, the six BINWOEs for the three possible pairs are mainly less than additive (negative) and a few are additive (0). Because the BINWOEs indicate that the hazard is likely to be less than the sum of the risks, which in turn is less than $1x10^{-4}$, it is concluded that the mixture is unlikely to be a health hazard at the waste-site specific exposure levels (Step 6a).

Case 2c: Identical to Case 2a, except that the six BINWOEs for the three possible pairs are fairly evenly divided among greater than additive (positive), additive (0) and less than additive (negative). The sum of the BINWOE numerical scores is negative due to the greater strength of the evidence for the less-than-additive interactions. Consistent with Step 6a for a mixture with total risk less than $1x10^{-4}$, this result indicates that the mixture is unlikely to be a health hazard the health hazard at the estimated levels of exposure.

4.2.4.5. Air Contamination with Chemicals H, I, and J

No interaction profile or guidance policy is available for this mixture, but toxicological profiles and cancer inhalation unit risks are available for the individual components. Increased lifetime cancer risks for these chemicals are estimated by multiplying the exposure concentrations (converted to $\mu g/m^3$ if necessary) by the inhalation unit risks as follows:

chemical H:	exposure concentration x unit risk	= 0.2 $\mu g/m^3$ x ($3.2x10^{-4}$) $(\mu g/m^3)^{-1}$	= $6x10^{-6}$
chemical I:		= 0.006 $\mu g/m^3$ x ($1.8x10^{-3}$) $(\mu g/m^3)^{-1}$	= $1x10^{-5}$
chemical J:		= 0.05 $\mu g/m^3$ x ($8.4x10^{-5}$) $(\mu g/m^3)^{-1}$	= $4x10^{-6}$

Risks for all three chemicals are greater than $1x10^{-6}$ (Step 3). PBPK or PBPK/PD models are not available for the whole mixture or for the pairs of components (Step 4). The sum of the risks is $2x10^{-5}$ (Step 5). Following the procedures in Step 6, a qualitative WOE evaluation is undertaken. BINWOEs for

all three pairs, obtained from ATSDR, are additive (0) or less than additive (negative). BINWOEs for the effects of another component of concern, identified during the assessment of noncarcinogenic effects, on the carcinogenicity of these three chemicals are less than additive or indeterminate. Therefore, it is considered unlikely that exposure to these components in combination at the site-specific exposure levels will constitute a health hazard, although there is some uncertainty due to the indeterminate BINWOEs.

4.2.4.6. Groundwater Contamination with 12 Chemicals

No interaction profile or guidance policy is available for this mixture, but toxicological profiles and cancer slope factors or other cancer-based comparison values are available for three of the components (the others are not considered carcinogenic, but six of these other chemicals are considered components of concern for noncarcinogenic effects). One component, with an estimated cancer risk of $1x10^{-8}$, is dropped from further consideration (Step 3). Risks for the other two components are $1x10^{-6}$ and $3x10^{-6}$; these components are retained as components of concern (Step 3). PBPK or PBPK/PD models are not available for this mixture or for any of the pairs of chemicals within the mixture (Step 4). BINWOEs for the pair of carcinogenic components of concern are greater than additive, and for the effects of the other six components on the two carcinogenic components are a mixed pattern. The sum of the BINWOE numerical scores (combined score) is +0.14. This value is so close to zero that it does not significantly raise concern for greater-than-additive interactions, and the mixture is considered unlikely to be a health hazard at these levels of exposure.

4.3. MULTIPATHWAY EXPOSURE

If the same receptor subpopulation or individual can reasonably be expected to be exposed to site-related chemicals through more than one pathway, the hazard quotients, hazard indexes, and risks for a given duration can be summed across pathways to give the total hazard quotient, hazard index, and risk. Alternatively, the procedure outlined by Mumtaz et al. (1995) for estimating total integrated exposure and total tolerable levels could be explored.

4.4. NON-SITE-RELATED EXPOSURES AND MULTIPLE STRESSORS

The strategy for exposure-based assessment of joint toxic action of chemical mixtures described in Section 4.2 focuses on chemical mixtures associated with hazardous waste sites. As mentioned in the overview to this manual, additional non-site-related exposures also may be occurring to a variety of chemicals such as those in alcohol, tobacco, medicines, foods, vehicle exhaust fumes, drinking water, and

in the workplace. Information regarding these additional exposures can be taken into account during interpretation of the community-specific health outcome data and biomedical evaluation (ATSDR 1992). This information also may be helpful identifying populations that may be unusually sensitive to site-related chemicals, due to other chemical exposures. Similarly, populations exposed to physical, psychological, or biological stressors may be more susceptible to chemical insult to the body, as is suspected for some veterans of the Persian Gulf War (Yang 2000).