

## The development and application of the chemical mixture methodology in analysis of potential health impacts from airborne release in emergencies

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### Short Abstract for Table of Contents

*“The chemical mixture methodology (CMM) is recommended for emergency response planning and safety analysis by the U.S. Department of Energy. The CMM estimates the potential impacts of exposure to airborne chemical mixtures on human health and the resulting ability of individuals to take protective actions. The CMM uses health code numbers to identify the target organ groupings that may be impacted by exposure to each chemical in a mixture. This paper reviews improvements made to the CMM since its introduction.”*

### ABSTRACT

The Chemical Mixture Methodology (CMM) is used for emergency response and safety planning by the U.S. Department of Energy, its contractors, and other private and public sector organizations. The CMM estimates potential health impacts on individuals and their ability to take protective actions as a result of exposure to airborne chemical mixtures. They are based on the concentration of each chemical in the mixture at a designated receptor location, the protective action criteria (PAC) providing chemical-specific exposure limit values, and the health code numbers (HCNs) that identify the target organ groupings that may be impacted by exposure to each chemical in a mixture. The CMM has been significantly improved since its introduction more than 10 years ago. Major enhancements involve the expansion of the number of HCNs from 44 to 60 and inclusion of updated PAC values based on an improved development methodology and updates in the data used to derive the PAC values. Comparisons between the 1999 and 2009 versions of the CMM show potentially substantial changes in the assessment results for selected sets of chemical mixtures. In particular, the toxic mode hazard indices (HIs) and target organ HIs are based on more refined acute HCNs, thereby improving the quality of chemical consequence assessment, emergency planning, and emergency response decision making. Seven hypothetical chemical storage and processing scenarios are used to demonstrate how the CMM is applied in emergency planning and hazard assessment.

**Keywords:** chemical mixture methodology; health code numbers; acute health effects; chronic health effects; exposures; emergency

## INTRODUCTION

The U.S. Department of Energy (DOE) utilizes the Chemical Mixture Methodology (CMM) to assess the potential health impacts on individuals that would result from simultaneous exposure to an airborne mixture of hazardous chemicals. Developed and maintained under the sponsorship of the DOE Office of Emergency Management (NA-41), the CMM is recommended for use in emergency preparedness and response and safety analysis decision making in the DOE complex in accordance with DOE Order 151.1C (DOE, 2005).

The CMM assesses mixtures of chemicals that are separable into their component elements or compounds by pure physical processes. The mixtures are defined at the receptor location; the individual chemicals may have been stored as a mixture prior to the event that initiated their atmospheric release or may have been stored separately and only mixed after their release to the atmosphere. Chemical reactions in the atmosphere between source and receptor are not accounted for by the CMM. One of the main assumptions of the CMM is that “most interactions should be considered additive until proven otherwise.” Detailed discussions of the robustness of this assumption are seen in Craig *et al.* (1999).

The CMM quantifies the effects of exposure to the individual chemicals in a mixture based on target organ impacts and mode of action. Both short-term (i.e., acute) and long-term (i.e., chronic) toxic health effects are included. The CMM assumes that impacts on different target organ groups are independent of each other unless there is evidence to the contrary. This approach allows the CMM to separately consider the impact on organ systems from each chemical in a mixture and then add the effects of all chemicals to yield a cumulative impact for each target organ group. This approach yields more realistic results for cumulative health impact than two other commonly applied alternatives:

1. treating all chemicals in a mixture independently and assuming that there is no cumulative impact on the exposed individual (i.e., the human health impact is estimated by the exposure to the chemical that would do the most harm). This non-conservative approach tends to underestimate human health impacts.
2. adding the exposures to all the chemicals, regardless of the different target organs impacted by these chemicals. This conservative approach tends to overestimate cumulative health effects.

The CMM is currently incorporated into a Microsoft Excel<sup>®</sup> workbook that can accommodate a mixture consisting of up to 30 chemicals. To use the CMM workbook, identification information for each chemical in a mixture, usually the chemical abstract service registry number (CASRN), the type of protective action criteria (PAC) to be used to establish exposure limits, and atmospheric dispersion results are entered into an input worksheet. This worksheet is linked to a chemical information worksheet which contains data on over 3,300 chemicals. Calculations are performed within the workbook using embedded macros that automatically estimate the potential health impacts from exposure to the specified chemical mixture. Two types of health impacts are of most concern in the emergency management applications for which the CMM is typically applied: (1) irreversible or other serious health effects and (2) impaired ability to take protective

actions. Although the CMM workbook is set up to use PAC as exposure limits, other exposure limits can be employed if a user chooses to do so.

Information about and access to the CMM is provided on the DOE Subcommittee on Consequence Assessment and Protective Actions (SCAPA) (<http://orise.orau.gov/emi/scapa/chem-mixture-methodology/default.htm>). The CMM is part of the SCAPA mission to provide the DOE and its contractors with technical information, tools, and recommendations to support emergency preparedness and assist in safeguarding the health and safety of workers, collocated workers and the public.

This paper focuses on how the CMM works and describes the major changes in the CMM since its first publication (Craig *et al.*, 1999). To illustrate the impact of these changes, a comparison of health impact calculations using the 1999 CMM data set version (Rev 15) and the 2009 version of the CMM data set (Rev 25) is provided. Applications of CMM in several hypothetical emergency scenarios are also presented.

## THE CHEMICAL MIXTURE METHODOLOGY

The CMM is used to analyze exposures to chemical mixtures based on the principles of the U.S. Environmental Protection Agency (EPA) Guidelines for the Health Risk Assessment of Chemical Mixtures (EPA, 1986). Although a Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures became available in 2000 (Choudhury *et al.*, 2000), the principles and concepts put forth in the original guidelines remain in effect.

The CMM uses the following information to evaluate health impacts:

- The estimated concentration of each chemical in the mixture at a given receptor location (as typically determined through the use of an atmospheric dispersion model). This information is input by the user.
- A health-based concentration limit for exposure to each chemical. The default CMM uses PAC to define a concentration limit for each chemical in a mixture. Four different PAC benchmark values (PACs, i.e., PAC-0, -1, -2, and -3) are defined for each of the chemicals listed in the CMM workbook. Each successive PAC benchmark value is associated with a higher level of exposure and an increasingly severe health effect. PAC-2 is most often used in CMM analyses because it represents a chemical exposure level that could impair an individual's ability to take protective actions (DOE, 2005; Appendix F of DOE, 2007). The CMM can be modified to use different concentration limit values in place of PACs.
- The Health Code Number (HCN) values assigned to each chemical indicate which target organ groups are impacted by exposure to that chemical. HCNs offer a convenient way of categorizing identical or similar target organ effects. HCNs are similar to medical diagnostic codes in that they are code numbers and identify specific acute or chronic toxic effects on individual target organs. Like PAC values, HCN values are provided for each chemical in the CMM workbook

The first two pieces of information are used to compute the hazard index (HI) for each chemical at the designated receptor location. The HI is a ratio of the airborne concentration of a chemical to an appropriate guideline concentration for that chemical. The summation of the HIs for all chemicals in a mixture having the same or similar HCNs is typically used to determine whether the given exposure to a chemical mixture at a receptor location might exceed exposure criteria and potentially prevent an individual from taking effective protective actions<sup>1</sup>.

### **Estimating Chemical Airborne Concentrations**

The estimated concentration of each chemical in the mixture at a given receptor point is generally obtained using a Gaussian atmospheric dispersion model such as EPIcode (DOE, 2004a, b) or Areal Locations Of Hazardous Atmospheres (ALOHA) (EPA and NOAA, 2007; Thoman *et al.*, 2006). These type of dispersion models compute exposure for the individual components in a chemical mixture based on the amount of each chemical available for release to the atmosphere, the method of release (e.g., spill, explosion), the properties of each chemical, time within the plume, release event parameters, and meteorological conditions.

### **Obtaining PAC Values**

The CMM allows its users to select which PAC values or concentration limit to use in their individual analyses. PAC values are determined from Acute Exposure Guideline Level (AEGL) values (Rusch *et al.*, 2000; Rusch *et al.*, 2002), Emergency Response Planning Guideline (ERPG) values (Rusch, 1993), and Temporary Emergency Exposure Limit (TEEL) values (Craig *et al.*, 1995, Craig *et al.*, 2000) using the following priority (DOE, 2005, 2008):

1. Use AEGLs including final or interim values, if available.
2. If not available, use ERPGs.
3. If there are no AEGL or ERPG values available, use TEELs.

The four different PAC values defined for each chemical are:

- PAC-0 (or TEEL-0<sup>2</sup>) is the threshold level below which no adverse health effects are expected.
- PAC-1 provides the threshold of mild or transient health effects.
- PAC-2 provides the threshold of irreversible or other serious health effects or symptoms that could impair a person's ability to take protective actions.
- PAC-3 provides the threshold of life-threatening health effects.

Information on how PACs are derived and links to additional information on AEGLs, ERPGs, and TEELs is provided on the PAC/TEEL web pages that are accessible at <http://orise.orau.gov/emi/scapa/teels.htm>. DOE/NA-41 supports an ongoing program to derive

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<sup>1</sup> Other evaluation criteria such as lethality could be used in an alternative application of the CMM.

<sup>2</sup> Only TEELs have a 0 level value; therefore the PAC-0 value is always the TEEL-0 value.

PACs for new chemicals and to review and update existing PACs on a periodic basis (based on changes to AEGL, ERPG, and TEEL values).

### Obtaining HCNs

Currently, 60 different health code numbers (HCNs) are available for characterizing the potential target organ or health effects caused by exposure to a chemical. **Table 1** lists the HCNs, their associated target organ effect, and their rank for emergency planning and response applications. Since the publication of Craig *et al.* (1999), 16 new HCNs were added to improve the representation of toxicological effects. Most notably, 13 acute HCNs (these are presented in bold font in **Table 1**) were added to mirror the chronic target organ HCNs described in the original CMM publication. Acute effects are the most life-limiting factors in an emergency event. A threshold of seven days was chosen to align with the nature of chemical emergency events, since some could go for a few days but seldom beyond a week. In addition, the shorter duration for acute exposures indicated in Sax's Dangerous Properties of Industrial Materials (Lewis, 2004), lack of sub-acute HCNs, and the indication time (sometimes months) for chronic exposures led to this definition (Lewis, RA, 1998; Lewis, RJ, 2004; NIOSH, 2008). Before the new acute HCNs were added, the CMM used chronic HCNs as "surrogates" in the analysis of target organ effects to represent potential acute effects. The addition of the new acute HCNs allows more representative characterization of potential acute effects from an unplanned release. HCNs that represent severe and moderate irritation or effects that can significantly inhibit protective action and an individual's ability to self-rescue are assigned a higher priority than their corresponding chronic effects to reflect their relative importance in an emergency event.

In addition to the 13 new acute HCNs, 3 new chronic HCNs were added (as presented in italicized font in **Table 1**). The previous CMM contains only the acute HCNs for these organ systems.

A detailed procedure was developed to describe how the HCN development team identified applicable HCNs for each chemical. This procedure involves reviewing appropriate publications (see **Table 2**) to obtain relevant information on potentially impacted target organs and health effects caused by exposure to a given chemical. Compared with the HCN development procedure used in 1999, more references are used currently to develop HCNs. The priority order assigned to the literature has also changed. **Table 2** presents the literature used to identify HCN values and the relative priority of each reference. Most recent literatures are used whenever available.

The general HCN development guidelines include the following protocol:

1. Human data should be preferred to animal data, regardless of the reference priority. In cases where there is an abundance of human data, only human data will be used.
2. When using animal data, only whole-animal (i.e., mammalian) toxicity data should be used. Due to the difficulty in extrapolating in vitro data to a human exposure, in vitro data should not be used.
3. Use specific HCNs rather than general HCNs when the data in the references state that specific effects occur to a specific target organ. When the effects in the references are

non-specific, use general HCNs. For example, use 7.00 (general nervous system—acute effects) for unspecified acute nervous system effects. If the data show that there is a more specific result, like an acute effect that affects the central nervous system (CNS), then use 7.01 (CNS—acute effects).

Many of the chemicals chosen for HCN development using the references cited in **Table 2** have more than 10 HCNs. For these chemicals, the 10 HCNs with the most significant health effects (i.e., determined using the ranking priority shown in **Table 1**) are reported in the CMM workbook<sup>3</sup>. The ranking of health effects was developed in part by using national vital statistics data for the year 2000 for death from various causes published by the National Center for Health Statistics (NCHS, 2001; <https://www.cdc.gov/nchs/>). HCN health effects are initially ranked in the order of their seriousness, from serious bodily injury or death in a fraction of a second to generally low-risk health effects. The rankings are then adjusted to incorporate the impact of the health effect on a person's ability to take protective action in an emergency situation. As a result some health effects (e.g., a moderate skin irritation) that have negligible long term consequences but may hinder protective actions can have a higher ranking than those HCNs that involve more significant long-term consequences (e.g., chronic central nervous system effects) but may not immediately hinder an individual's capability to evacuate or take other protective actions.

If the toxicity references do not list a target organ for a chemical but only mention chronic or acute effects in general, toxicity is assumed to be systemic (i.e., HCN 3.00 for chronic or 4.00 for acute). Routinely assigning the broad categories HCN 4.00 (acute short-term high hazard effects) and/or HCN 3.00 (chronic effects) to chemicals for any acute or chronic effect will essentially result in most chemicals with these kinds of effects being placed in nearly all acute and chronic target organ categories. When used in the CMM, the broad category assignment forces the exposures for all HCN 4.00 and HCN 3.00 chemicals in the mixture to be added, thereby defeating the CMM purpose of separating exposures by target organ effects. Following the guidelines will minimize this overly conservative effect while at the same time ensuring that HCN 4.00 and HCN 3.00 are assigned when appropriate where hazardous acute effects or general chronic effects exist in the absence of any more specific acute or chronic effects.

Once the HCNs are developed for a chemical, the chemical category is determined. The chemical category provides the concentration-limit classification used to determine whether the toxicological consequences of exposure to a chemical are concentration-dependent, dose-dependent, or both (Craig *et al.*, 1999). The chemical category is not used directly in the CMM calculations, but it does have an indirect impact because it is used to set the exposure period for atmospheric dispersion modeling.

The definition of the chemical category is adapted from Patty's Industrial Hygiene and Toxicology (Cralley and Cralley, 1985) as introduced by Craig *et al.* (1999). Six categories—1A, 1B, 1C, 2, 3, and 4 are defined. Chemicals in category 1A have ceiling standards. Chemicals in category 1B are primarily irritants. Chemicals in category 1C are Permissible

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<sup>3</sup> The order in which the HCNs are listed for a given chemical in the CMM workbook does not affect the CMM calculations.

Exposure Limits (PELs) set by OSHA by either technological feasibility or good industrial hygiene practices. Category 2 encompasses acute toxicants. Category 3 encompasses cumulative toxicants. Chemicals in Category 4 may present both acute and cumulative toxic effects. Chemicals in 1A, 1B, or 1C categories are concentration-dependent. The concentration at the receptor point of interest is calculated as the peak 15-minute time-weighted average (TWA) for concentration-dependent chemicals. Chemicals in 2, 3, or 4 categories are dose-dependent. The concentration at the receptor point of interest may be calculated as the peak 60-minute TWA concentration for dose-dependent chemicals (Cralley and Cralley, 1985).

### Applying the CMM

The first step performed by the CMM is to calculate the HI for each chemical species (i) at a receptor location, as shown in eqn. 1:

$$HI_i = C_i / L_i \quad \text{eqn. 1}$$

where  $C_i$  is the concentration of chemical “i” at the receptor, and  $L_i$  is the selected concentration limit. The DOE default CMM recommends using PAC values as concentration limits, either PAC-0, -1, -2, or -3 for chemical “i” (i.e.,  $L_i = PAC_i$ ).

The  $HI_i$  for each chemical in the mixture at the receptor point of interest is then summed, as in eqn 2.

$$\sum_{i=1}^n HI_i = HI_1 + HI_2 + \dots + HI_n \quad \text{eqn. 2}$$

The summation of  $HI_i$  is used as an initial screening to determine if additional analysis is needed.

If  $\sum_{i=1}^n HI_i$  is less than or equal to unity (1.0), then no further assessment is needed, as it is assumed that the exposed individual will not experience concentrations that would approach the level of concern that would impair his/her ability to take appropriate protective actions. If the sum of the  $HI_i$  values is greater than unity, then the HCNs need to be employed to provide a more realistic, although still somewhat conservative, assessment of the hazards to target organs.

If warranted by initial screening results, the next step in the method involves a toxicity classification using the HCNs. The CMM assumes that different target organ groups do not interact with each other to any significant degree. Therefore, exposures can be separated, and same or similar toxicity can be added within these target organ bins. In addition, chemicals targeting the same or similar organs can exhibit acute or chronic effects. These are considered additive to the target organ by the same mode of toxicity as (eqn. 3).

$$\sum_{i=1}^n HI_{i(p)} = HI_{1(p)} + HI_{2(p)} + \dots + HI_{n(p)} \quad \text{eqn. 3}$$

where  $p$  represents a specific target organ and/or mode of action. The CMM analysis provides a toxic effect matrix of chemicals with target organ effects, and/or mode of action. The term “target organ effect” is used throughout this paper to mean either the combined toxic effect on a specific organ or tissue (e.g., the kidney) or their combined effect in producing a particular mode of effect that may involve multiple organs or tissues (e.g., respiratory irritation).

## RESULTS

### Assessment of Exposures to Chemical Mixtures, Now and Then

The same chemical mixture containing 14 components used by Craig *et al.* (1999) is chosen to illustrate the differences between the 1999 and 2009 versions of the CMM. This test mixture represents a hypothetical accident scenario at a DOE facility. The comparisons between the original 1999 HCNs and concentration-limit classifications (i.e., categories) and the new 2009 HCNs and concentration-limit classifications are presented in **Table 3**. Most of the original HCNs from 1999 came directly from Patty’s Industrial Hygiene and Toxicology (Cralley and Cralley, 1985).

**Table 4a and 4b** present airborne chemical concentrations and HIs computed using two different concentration limits (i.e., PAC-2 and PAC-3) at two receptor points. **Table 4a** provides results for all of the chemicals in the mixture using the 1999 version of the CMM. Similarly, **Table 4b** provides the results for the 2009 version of the CMM. The individual HI and summation of HIs at or above 0.5 are highlighted in bold in both tables. The PAC values (then simply called TEEL values) from the 1999 version of the PAC/TEEL data set were used to calculate HIs in **Table 4a**. The PAC values from the 2009 version of PAC/TEELs data set are used to calculate the HIs in **Table 4b**.

**Table 5a and 5b** presents HCNs, HI values, and a summation of the HIs. **Table 5a** presents data for chemicals in the mixture that have chronic health impacts (i.e., HCNs in the 3.xy series, where the letters x and y represent the two digits used to describe a target organ or mode of action toxic effect, as shown in **Table 1**) using HCN values from the 1999 version of the CMM workbook. **Table 5b** presents data for chemicals in the mixture that have acute health impacts (i.e., HCNs in the 4.xy series) using HCN values from the 2009 version of the CMM workbook. The PAC values from the 2009 version of PAC/TEELs are used to calculate the HIs in **Table 5a** and **5b**.

**Table 6** shows the comparison between 1999 and 2009 versions of the CMM for the summation of HIs,  $\sum_{i=1}^n HI_{i(p)}$ , for chemicals in the mixture having the same toxic effect. Similarly to **Table 5a** and **5b**, the PAC values from the 2009 version of PAC/TEELs are used to derive the HIs. Results are provided for four different target organs or organ systems:

- narcosis (HCN = 8)
- irritant (HCN = 14.xy, 15.xy, and 16.xy)
- nervous system acute effects (HCNs = 6.00, 8.00, 7.00, or 7.01)

- respiratory effects (HCNs = 11.00 or 11.01).

The numerical values (14, 15, or 16) and x and y in the HCN are used to denote the level of severity, such as severe, moderate, and mild, and target organs of an irritant (see **Table 1** for details).

**Table 7** illustrates a hypothetical case involving leakage of chemical waste during transfer at a DOE facility. The CMM evaluates which target organ effect or mode is the “limiting” factor (i.e., the factor that contributes to the summation of hazard indices most significantly by mode or by target organ). **Table 7** lists the chemical in the mixture, aerosol volume, mass of chemical released, duration, peak 15-min TWA concentration at 100 meters, and individual HI. Mass of the chemical released is calculated by multiplying the concentration of each chemical and its source-term aerosol volume. The 15-minute peak TWA is calculated using EPIcode (Homann, 2003). Individual HIs are obtained from the CMM analysis.

**Table 8** gives the summary of seven hypothetical accident cases, including the one illustrated in **Table 7**, all of which are obtained using the current CMM workbook.

## DISCUSSION

The following section discusses the impact that updated PAC values and new HCNs have on CMM results, including their affect on emergency analyses. In addition, several examples are provided of how CMM has been used in chemical mixture analysis in “real-world” applications.

### Difference of HIs, Then and Now

#### *Changes in HCNs from 1999 to 2009*

For a sample mixture of 14 chemicals, **Table 3** illustrates the difference in HCNs and concentration limit classifications between 1999 and 2009 versions of the CMM. There are two readily noticeable differences. First, there are substantially more HCNs for each chemical in the 2009 version of the CMM than in the 1999 version. The maximum number of HCNs among all chemicals is 5 in 1999 for this particular mixture. In the 2009 version, each chemical has at least 10 HCNs, with any additional lower-ranking HCNs dropped from consideration. As described earlier, the top 10 HCNs are selected based on the ranking priorities shown in **Table 1**. Because each chemical has different HCNs, the top 10 HCNs sorted using the ranking priority are not the same. Acute toxic effects are given higher priority in the current ranking order considering emergency preparedness and response requirements. The increased number of HCNs per chemical is a direct result of the newly added HCNs to better represent acute and chronic effects in an emergency scenario. Second, the chemical category definition, including concentration limit classification and exposure duration treatment, has changed for 10 of the 14 chemicals. For example, in 1999 acetone was defined as 1B (irritant); while in 2009 it is more appropriately defined as 1A (a ceiling/short-term exposure limit (STEL) standard). This illustrates that a more accurate definition for each chemical has become possible as more information has become available.

### ***Evolving PAC/TEELs***

**Table 4a** and **4b** provide the comparison of PACs and HIs in the same mixture using the 1999 and 2009 versions of the CMM workbooks. For comparison, the modeled concentrations of each chemical at the receptor are kept the same. The two receptor points remain 30 meters and 100 meters downwind from the release site. There are some major changes between 1999 and 2009. All the listed PAC values have changed since 1999 except for the PAC-3 value for biphenyl. This value is italicized in **Table 4b**. Some changes in the PAC values are significant (i.e., more than 10%, numerically). A number of changes are in the range of a factor of 2 to 4. These changes directly result in the different HI values because  $HI_i = C_i/Limit_i$  or  $HI_i = C_i/PAC_i$ .

Examining individual chemicals in **Table 4a** and **4b**, it is clear that the 2009 PAC-2 values are significantly lower for some chemicals, such as biphenyl, resulting in lower chemical-specific HIs. For example, for the 30-meter distance the HIs for biphenyl decreases from 7.16 to 0.828 when going from the 1999 to 2009 PAC-2 values. However, not all HI values are lower than before. For example, acetone and methylene chloride have higher HIs using the 2009 PAC values. The changes in the numerical values of the HIs for each chemical are direct results of the changes made to the PAC values since 1999.

Because of the PAC changes noted above, the summed HIs for mixtures are generally expected to be different between the 1999 and 2009 CMM analysis. In this example, three of the 2009 cases result in a lower HI for the mixture under consideration, whereas the PAC-3 at 100-meter receptor point is the only case that remains unchanged. In addition, for the PAC-2 at 100-meter case, the summed HIs go from 1.2 (**Table 4a**) to 0.4 (**Table 4b**), which would result in a change of the assessment result, i.e., from beyond acceptable limit to acceptable (recall that a summed HI threshold value greater than 1.0 is used to determine whether protective actions need to be taken to reduce toxic effects in a DOE complex. This indicates that the toxic mode hazard indices and target organ HIs are not as conservative when compared to past results.

### **The Effect of New HCNs**

The effect of the new HCNs on the CMM analysis will be illustrated in this section. The main use of HCNs lies in the analysis of target organ or mode of action toxic health effects. These are illustrated in **Table 5a** and **5b**, **Table 6**, and **Table 7**. To better illustrate the change brought by the new HCNs, and remove the influence of updated PAC values, all of these tables use the PAC values from the 2009 version of the PAC/TEEL data set.

### ***Improved Representation of Acute Effects***

**Table 5a** presents HIs for the chemicals in the sample mixture that have chronic toxic effects and is based on the 1999 version of the CMM. The chronic toxicity-based HCNs were used in 1999 to represent acute toxic effects when acute HCNs were lacking. **Table 5b** shows the new HCNs and HIs based on the 2009 version of the CMM. The new acute system HCNs (or  $HCN = 4.xy$ ) are highlighted in bold in **Table 5b**. For ease of viewing, other acute HCNs (i.e., 9.00, 7.00,

7.01, 8.00, 11.00, 11.01, 13.00, 14.01, 14.02, 15.01, 15.02, and 16.01) have not been highlighted in **Table 5b**.

One main difference between the 1999 and 2009 tables is that all the chemicals in the sample mixture have specific 4.xy acute system HCNs in 2009 compared to none of the chemicals having acute HCNs in 1999. Due to the increase in the number of chemicals that have acute HCNs, the sums of HIs for chemicals with acute systemic toxic effects have increased. For instance, the sums of HIs for all chemicals at the 30-meter receptor point using PAC-2 and PAC-3 values as the concentration limits are 4.5 and 2.1 in 2009 compared to 2.5 and 1.0 in 1999, respectively. The comparison between **Table 5a** and **Table 5b** indicates that the new HCNs are driving analysis results to be more specific toward acute toxic effects. In addition, the lack of acute HCNs in the past has been alleviated to a large extent by the introduction of new acute HCNs that mirror the chronic HCN effects.

### ***Improved Binning of Target Organ Effects***

**Table 6** shows the comparison of the summation of HIs for chemicals in the sample mixture having the same toxic consequences by mode of action and target organ. Two modes are compared here: narcosis (HCN = 8.00) and irritation (HCNs = 14.xy, 15.xy, and 16.xy). Compared to the 1999 version, the summations of HIs for narcosis are higher using the 2009 version of the CMM for all four cases. This is because all but one of the 14 chemicals in the mixture now has a HCN 8.00. Only eight of the chemicals had a HCN 8.00 in 1999. Similarly, the summations of HIs for irritants are higher in 2009 than in 1999. As seen in **Table 6**, all but one of the chemicals now have HCNs 14.xy, 15.xy, or 16.xy compared to 9 of the 14 chemicals in the 1999 version of the CMM. Because the same PAC values are being used for this comparison, the summations of HIs are higher in 2009 than in 1999 due to the increased number of chemicals that now have either narcotic or irritant HCNs.

In addition to the comparison of summations of HIs by mode, the new HCNs provide more analytical results of toxic consequences to target organs. Two examples of target organs are shown in **Table 6**. The first is the nervous system acute effects including HCNs 8.00, 6.00, 7.00, and 7.01; and the second is the respiratory system, including HCNs 11.00 and 11.01. These results indicate that acute toxic effects on nervous system and respiratory system are quite important for this chemical mixture, especially when the receptor points are within 30 meters of the release location. The description of specific target organs is not as detailed in the 1999 version of the CMM. This further illustrates that the new HCNs have improved the performance of the CMM for emergency management and response applications.

### ***Applications***

**Table 7** and **Table 8** present results of CMM applications in the assessment of toxicity of seven hypothetical waste mixtures. A variety of emergency response scenario cases are postulated: waste transfer leak, fire causing release from a contaminated facility, mixing of incompatible materials, flammable gas deflagration, tank failure due to excessive loads, above ground structure failure, release during excavation or drilling, and nuclear criticality. **Table 7** provides

an example of how the toxicological assessment is conducted in one of these scenarios, the waste transfer leak. To use the CMM workbook, the users need to prepare entry data that include the concentration of each chemical at the receptor point. For emergency management hazard analyses, the highest 15-min TWA concentration at the receptor over the duration of the scenario is used (DOE, 2007). EPIcode version 7.0 is used to calculate the concentration at the receptor point (Homann, 2003). PAC-2 values are used to calculate the HIs for each chemical. The limiting mode or target organ sum of HIs refers to the greatest summation of hazard indices from the CMM output where these parameters are provided for different toxic mode HIs and target organ HIs.

**Table 8** lists the summary of the CMM analysis results for all seven emergency response scenarios. Multiple endpoint (toxic mode)-specific or target organ-specific sums of HIs can be the limiting factor. The limiting factor refers to the endpoint or target organ that has the greatest sums of HIs concerning specific toxic effects. Respiratory system toxins and acute reproductive system toxins seem to exert a higher impact on human health than others from the aspect of target organ toxic effects. Acute system toxins, acute respiratory toxins, and chronic system toxins exert the highest impact from the aspect of endpoint toxic consequence among the seven scenarios. Appropriate precautions and actions need to be taken to ensure adequate protections are in place in the event of one of the hypothetical cases.

## Conclusions

The CMM is used for emergency response planning and safety analysis by the DOE, its contractors, and other private and public sector organizations. The CMM estimates potential health impacts on individuals as a result of exposure to airborne chemical mixtures after accidental releases. These estimates, in the form of HIs, are based on the concentration of each chemical in the mixture at a designated receptor location, the concentration limit that provide chemical-specific exposure limit values, and the HCNs that identify the target organ groupings that may be impacted by human exposure to each chemical. The DOE default method recommends that the PAC be used as the concentration limit when using the CMM method.

The screening HI for a given chemical is  $HI_i = C_i/L_i$ , where  $C_i$  is the concentration of chemical “i” at the receptor, and  $L_i$  ( $L_i = PAC_i$ ) is the selected concentration limit for taking protective action. For screening a chemical mixture, the HIs are summed over all chemicals. If the sum is greater than unity, further CMM analysis is required. In this additional analysis, HIs are summed based upon the HCNs of each chemical in the mixture. The individual HCNs are developed to represent specific target organ effects or modes of toxicity for a chemical in the CMM. This analysis provides a more realistic estimate of the potential impacts of the chemical mixture and may provide an estimate on the exposed individual’s ability to take effective protective actions.

The CMM has been significantly improved since its introduction over 10 years ago (Craig *et al.*, 1999). Major enhancements involve the inclusion of 13 new HCNs describing acute effects, 3 new HCNs describing chronic effects, updated chemical categories for concentration-limit classification, and updated PAC values based on an improved development methodology, and updates in the data used to derive the PAC values.

Comparisons between the 1999 and 2009 versions of the CMM assessments show potentially substantial changes in results for test sets of chemical mixtures. In particular, the endpoint-specific HIs and target organ-specific HIs are more accurate concerning acute toxic effects when computed using the 2009 version of the CMM. More emphasis is now placed on HCNs that estimate acute health impacts and less emphasis is provided to chronic impacts. These enhancements should allow users to avoid having to employ unneeded emergency management controls and focus resources on more pressing health and safety concerns.

Development and maintenance work on the CMM is continuing. HCNs are currently being reviewed and updated for all of the more than 3,300 chemicals in the CMM. New chemicals are being added to the CMM to coincide with their addition to the PAC data set. A number of enhancements are also being evaluated for future application to the CMM. One effort would explore options for more readily integrating atmospheric dispersion data into the CMM. This would allow HIs to be generated for a grid of receptor locations rather than just a single point. This advancement may involve breaking the CMM away from its Excel workbook framework and incorporating it into a user-friendly, standalone model that would read output from one or more dispersion models. Alternatively, the CMM may be directly incorporated into one or more existing chemical atmospheric dispersion models.

Another area to be investigated involves the utilization of HCN data. Currently, both acute and chronic HCNs are available to compute HIs, with a maximum of the 10 highest ranked of the applicable HCNs being used for every chemical. Because acute HCNs tend to be assigned higher priority rankings (e.g., the top 27 of the 60 ranked HCNs are associated with acute impacts), chronic HCNs play a relatively minor role in computing the HIs for many chemicals. A potential change to the CMM would be to expand the number of HCNs used to compute the HIs but only use acute HCNs for emergency preparedness applications while using both acute and chronic HCNs for other types of safety analyses.

The CMM development team plans to continue to actively solicit comments and recommendations from its user community as it works to enhance the technical quality and usability of the CMM.

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## References

- Choudhury H, Hertzberg R, Rice G, Gogliano J, Mukerjee D, Teuschler L, Doyle E, Woo Y, Schoeny R, Margosches E, and others. 2000. Supplementary guidelines for the health risk assessment of chemical mixtures. In: Agency EP, editor. Washington, DC: Federal Register.
- Cralley LJ and Cralley LV. 1985. Theory and rationale of industrial hygiene practice. Patty's industrial hygiene and toxicology. 2nd ed. New York, Chichester, Brisbane, Toronto, Singapore: John Wiley & Sons. p 150-185.
- Craig DK, Baskett RL, Davis JS, Dukes L, Hansen DJ, Petrocchi AJ, Powell TJ, Sutherland PJ, Tuccinardi Jr., T. E. 1999. Recommended default methodology for analysis of airborne exposures to mixtures of chemicals in emergencies. *Applied Occupational and Environmental Hygiene* **14**(9):609-617.
- Craig DK, Davis JS, DeVore R, Hansen DJ, Petrocchi AJ, Powell TJ. 1995. Alternative guideline limits for chemicals without environmental response planning guidelines. *Am. Ind. Hyg. Assoc. J.* **56**:919-925.
- Craig DK, Davis JS, Hansen DJ, Petrocchi AJ, Powell TJ, Tuccinardi Jr., T. E. 2000. Derivation of temporary emergency exposure limits (TEELs). *Journal of Applied Toxicology* **20**:11-20.
- DOE (U.S. Department of Energy). 2004a. DOE-EH-4.2.1.3-EPIcode-gap analysis, auality assurance improvement plan: EPIcode gap analysis. Washington, DC: Department of Energy. 68 p.
- DOE (U.S. Department of Energy). 2004b. DOE-EH-4.2.1.4-EPIcode-Code Guidance, *EPIcode computer code application guidance for documented safety analysis*. Washington, DC: Department of Energy. 72 p.
- DOE (US Department of Energy). 2005. DOE O 151.1C. Comprehensive emergency management system November 2, 2005 ed. p 90.  
<https://www.directives.doe.gov/directives/current-directives/151.1-BOrder-c/view> [1 September 2009]
- DOE (US Department of Energy). 2007. DOE G 151.1-2. Technical planning basis: Emergency management guide. <https://www.directives.doe.gov/pdfs/doe/doetext/neword/151/g1511-2.html> [1 September 2009]
- DOE (U.S. Department of Energy). 2008. DOE-HDBK-1046-2008. Temporary emergency exposure limits for chemicals: Methods and practice. August 2008. Washington, DC. p 52.
- EPA (U.S. Environmental Protection Agency) 1986. Guidelines for the health risk assessment of chemical mixtures. In: Agency EP, editor. Washington, DC: Federal Register. p 34014-34025.
- EPA and NOAA (U.S. Environmental Protection Agency and National Oceanic and Atmospheric Administration). 2007. ALOHA user's manual. Version 5.4.  
<http://response.restoration.noaa.gov/> [1 September 2009]
- Homann S. 2003. EPIcode. Version 7.0.  
[http://www.hss.energy.gov/nuclearsafety/qa/sqa/central\\_registry/EPIcode/EPI.htm](http://www.hss.energy.gov/nuclearsafety/qa/sqa/central_registry/EPIcode/EPI.htm) [1 September 2009]
- Lewis, RA. 1998. Lewis Dictionay of Toxicology. 1<sup>st</sup> Edition. Informa Healthcare.
- Lewis, RJ. Sr. 2004. Sax's Dangerous Properties of Industrial Materials. 11<sup>th</sup> Edition, Volumes 1-3. John Wiley & Sons.

- [http://www.knovel.com/web/portal/basic\\_search/display? EXT\\_KNOVEL\\_DISPLAY\\_bookid=1332](http://www.knovel.com/web/portal/basic_search/display? EXT_KNOVEL_DISPLAY_bookid=1332) [1 September, 2009]
- NCHS. 2001. National Center for Health Statistics. <http://www.cdc.gov/nchs/> [1 September 2009]
- NIOSH (National Institute for Occupational Safety and Health). 2008. Registry of Toxic Effects of Chemical Substances (RTECS), Comprehensive Guide to the RTECS.
- Rusch GM, Garrett R, Tobin P, Falke E, Lu PY. 2000. The development of acute exposure guideline levels for hazardous substances. *Process Saf. Prog.* **19**(2):98-102.
- Rusch GM, Garrett R, Tobin P, Falke E, Lu PY. 2002. The development of acute exposure guideline levels for hazardous substances. *Drug Chem. Toxicol.* **25**(4):339-348.
- Rusch GM. 1993. The history and development of emergency response planning guidelines. *Journal of Hazardous Materials* **33**(2):193-202.
- SCAPA. 2009. Subcommittee on Consequence Assessment and Protective Actions. <http://orise.orau.gov/emi/scapa/> [1 September 2009]
- Thoman DC, O'Kula KR, Laul JC, Davis MW, Knecht KD. 2006. Comparison of ALOHA and EPIcode for safety analysis applications. *Journal of Chemical Health and Safety* **13**(6):20-33.

## Appendix

### List of Acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Limit
AIHA	American Industrial Hygiene Association
ALOHA	Areal Locations Of Hazardous Atmospheres
C	Concentration
CASRN	Chemical Abstract System Registry Number
CFR	Code of Federal Regulations
CMM	Chemical Mixture Methodology
CNS	Central Nervous System
DOE	U.S. Department of Energy
EPA	Environmental Protection Agency
ERP	Emergency Response Planning
ERPG	Emergency Response Planning Guideline
HCN	Health Code Number
HI	Hazard Index
LLC	Limited Liability Company
NNSA	National Nuclear Safety Administration
NOAA	National Oceanic and Atmospheric Administration
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criterion
PEL	Permissible Exposure Limit
PNNL	Pacific Northwest National Laboratory
SCAPA	Subcommittee on Consequence Assessment and Protective Actions
STEL	Short-Term Exposure Limit
TEEL	Temporary Emergency Exposure Limit
TLV	Threshold Limit Value
TWA	Time-Weighted Average
USA	United States of America

## Tables

The following pages present the Tables cited in the above sections of this paper. Immediately below are the captions for each of these Tables.

**Table 1.** Health Code Numbers (HCNs) used to classify toxic effects by target organ. The HCNs are listed in the order adapted from Craig et al. [1999]. New acute HCNs are presented in bold font; new chronic HCNs are italicized. Rank indicates the importance in terms of emergency response and planning.

**Table 2.** References used to develop HCNs.

**Table 3.** Comparison of target organ health code numbers (HCNs) and concentration limit classification ("Cat." or chemical category) for chemicals in the mixture between 1999 and 2009 versions of the CMM. Substantial differences are apparent in the top 10 HCNs, particularly in the marked expansion of HCNs.

**Table 4a.** Chemical concentrations, PACs, and HIs for a sample chemical mixture using the 1999 version of the CMM.

**Table 4b.** Chemical concentrations, PACs, and HIs for a sample chemical mixture using the 2009 version of the CMM.

**Table 5a.** Summation of HIs for chemicals in the mixture having the same toxic consequences (mode): chronic toxic effects in the 1999 version of the CMM. The chronic system codes are highlighted in bold font.

**Table 5b.** Summation of HIs for chemicals in the mixture having the same toxic consequences (mode): acute toxic effects in the 2009 version of the CMM. The acute system HCNs are highlighted in bold font.

**Table 6.** Summation of HIs for chemicals in the mixture having the same toxic consequences (mode): narcosis (i.e. HCN 8.00) and irritant (HCNs 14.xy, 15.xy, and 16.xy) or having the same toxic consequences (target organ): nervous system acute effects (i.e. HCNs 8.00, 6.00, 7.00, and 7.01) and respiratory (HCNs 11.00 and 11.01) in the 1999 and 2009 versions of the CMM.

**Table 7.** Source term and toxicological consequences analysis of a waste transfer leak scenario.

**Table 8.** Summary of CMM analysis of seven hypothetical waste mixtures.

**Table 1.** Health Code Numbers (HCNs) used to classify toxic effects by target organ. The HCNs are listed in the order adapted from Craig et al. [1999]. New acute HCNs are presented in bold font; new chronic HCNs are italicized. Rank indicates the importance in terms of emergency response and planning.

Rank	HCN	Target-Organ Effect
29	1.00	OSHA carcinogen (29 CFR 1910.1000) — chronic effect
30	1.01	Bladder carcinogen — chronic effect
31	1.02	Liver carcinogen — chronic effect
32	2.00	Suspect carcinogen or mutagen — chronic effect
33	2.01	Kidney carcinogen — chronic effect
34	2.02	Liver carcinogen — chronic effect
55	3.00	Systemic toxin—chronic effects
45	3.01	Bladder—chronic effects
41	3.02	Hematological effects—chronic, unspecified
46	3.03	Bone—chronic effects
42	3.04	Bone marrow—chronic blood-forming system and other chronic effects
35	3.05	Brain—chronic effects
47	3.06	Eye—chronic ocular effects
44	3.07	Gastrointestinal tract—chronic effects
28	3.08	Heart, Cardiovascular system—chronic effects
40	3.09	Kidney—chronic effects
43	3.10	Liver—chronic effects
52	3.11	Skin—chronic effects including dermatitis and sensitization
54	3.12	Skin perforation—nasal septum perforation and other chronic effects other than skin absorption
13	4.00	Systemic toxin—acute short-term high hazard effects
9	4.01	Eye—acute, other than irritation
<b>20</b>	<b>4.02</b>	<b>Nose—acute effects other than irritation</b>
<b>26</b>	<b>4.03</b>	<b>Bladder—acute effects</b>
<b>23</b>	<b>4.04</b>	<b>Bone marrow—acute blood-forming system and other acute effects</b>
<b>15</b>	<b>4.05</b>	<b>Brain—acute effects</b>
<b>22</b>	<b>4.06</b>	<b>Hematological effects—acute, unspecified</b>
<b>25</b>	<b>4.07</b>	<b>Gastrointestinal tract—acute effects</b>
<b>14</b>	<b>4.08</b>	<b>Heart, Cardiovascular system—acute effects</b>
<b>21</b>	<b>4.09</b>	<b>Kidney—acute effects</b>
<b>24</b>	<b>4.10</b>	<b>Liver—acute effects</b>
<b>51</b>	<b>4.11</b>	<b>Skin—acute effects other than irritation</b>
<b>53</b>	<b>4.12</b>	<b>Skin perforation—acute effects other than skin absorption</b>
<b>27</b>	<b>4.13</b>	<b>Bone—acute effects</b>
49	5.00	Reproductive toxin—acute effects
50	<i>5.10</i>	<i>Reproductive toxin—chronic effects</i>
4	6.00	Cholinesterase toxin—acute effect
18	7.00	Nervous system toxin—acute effects
16	7.01	Central nervous system—acute effects
37	<i>7.10</i>	<i>Nervous system toxin—chronic effects</i>

36	7.11	Central nervous system—chronic effects
17	8.00	Narcotic — acute effect
39	9.00	Respiratory sensitizer — chronic effect
38	10.00	Respiratory toxin — chronic effects
19	11.00	Respiratory toxin — acute effects other than irritation
<b>10</b>	<b>11.01</b>	<b>Respiratory irritant — acute severe or moderate but not mild irritant effects</b>
48	12.00	Blood toxin, anemia — chronic effect
3	13.00	Blood toxin, methemoglobinemia — acute effect
6	14.00	Severe irritant
5	14.01	Eye irritant— severe
11	14.02	Skin irritant — severe
8	15.00	Moderate irritant
7	15.01	Eye irritant — moderate
12	15.02	Skin irritant — moderate
57	16.00	Mild irritant
56	16.01	Eye irritant — mild
58	16.02	Skin irritant — mild
1	17.00	Asphyxiants, anoxiants — acute effect
2	18.00	Explosive, flammable safety (no adverse effects with good housekeeping)
59	19.00	Generally low risk health effects—nuisance particles, vapors or gases
60	20.00	Generally low risk health effects—odor

**Table 2.** References used to develop HCNs.

Order	Description of References
1	Acute Exposure Guideline Levels (AEGs), National Academy of Sciences (NAS) Documentation [NAS, 2000-2009]. These are eight volumes of documentation supporting development of the current final AEGL values for 34 chemicals as of fall 2009. In addition, some Interim AEGs have Technical Support Documents that are available only online at the AEGL website, <a href="http://www.epa.gov/oppt/aegl/pubs/chemlist.htm">http://www.epa.gov/oppt/aegl/pubs/chemlist.htm</a>
2	Emergency Response Planning Guidelines (ERPGs) Documentation, American Industrial Hygiene Association (AIHA)
3	CHEM-BANK Silver Platter CD ROM Toxicology Databases. The following are also available online through other proprietary databases such as ExPub. ( <a href="http://www.expub.com/">http://www.expub.com/</a> ) which was used here. <ul style="list-style-type: none"> <li data-bbox="316 745 1388 819">• Registry of Toxic Effects of Chemical Substances (RTECS), National Institute for Occupational Safety and Health (NIOSH)</li> <li data-bbox="316 819 1323 850">• Hazardous Substances Data Bank (HSDB), National Library of Medicine</li> <li data-bbox="316 850 1372 892">• Chemical Hazards Response Information System (CHRIS), U.S. Coast Guard</li> <li data-bbox="316 892 1356 966">• Pocket Guide to Chemical Hazards and ICSC International Chemical Safety Cards, NIOSH, National Institute for Occupational Safety and Health</li> <li data-bbox="316 966 1421 1039">• Oil and Hazardous Materials—Technical Assistance Data System (OHMTADS), Environmental Protection Agency, 1991</li> </ul>
4	Sax's Dangerous Properties of Industrial Materials, 11 <sup>th</sup> Edition (SAX) CD ROM; also available on the web via subscription <a href="http://www.knovel.com/web/portal/basic_search/display?_EXT_KNOVEL_DISPLAY_bookid=1332">http://www.knovel.com/web/portal/basic_search/display?_EXT_KNOVEL_DISPLAY_bookid=1332</a>
5	Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) (TLV Booklet), American Conference of Governmental Industrial Hygienists (ACGIH)
6	Documentation of TLVs, ACGIH
7	Guide to Occupational Exposure Values (OEV Guide), ACGIH
8	Patty's Industrial Hygiene and Toxicology, 2 <sup>nd</sup> edition, Volume 3, Part A, pages 153-185, Table of chemicals and their target organ HCNs.
9	Hawley's Condensed Chemical Dictionary
10	Handbook of Chemistry and Physics
11	Sigma Aldrich Material Safety Data Sheets (MSDSs) and other references.

**Table 3.** Comparison of target organ health code numbers (HCNs) and concentration limit classification (“Cat.”, or chemical category) for chemicals in the mixture between 1999 and 2009 versions of the CMM. Substantial differences are apparent in the top 10 HCNs, particularly in the marked expansion of HCNs.

	Chemical Name (CASRN)	Health Code Numbers in 1999					Cat.	Health Code Numbers in 2009										Cat.
		1	2	3	4	5		1	2	3	4	5	6	7	8	9	10	
1	Acetone (67-64-1)	16.00	8.00				1B	6.00	15.01	11.01	15.02	4.08	4.05	7.01	8.00	7.00	11.00	1A
2	Benzene (71-43-2)	2.00	12.00	3.00	14.01	14.02	1C	14.01	4.01	11.01	15.02	4.08	4.05	7.01	8.00	7.00	11.00	1A
3	Biphenyl (92-52-4)	15.00					1B	15.01	11.01	15.02	4.08	7.01	8.00	7.00	11.00	4.09	4.10	1B
4	Carbon tetrachloride (56-23-5)	3.10	2.00	5.00			1A	14.01	4.01	14.02	4.08	4.05	7.01	7.00	11.00	4.02	4.09	1A
5	Chlorobenzene (108-90-7)	3.00	8.00	5.00			4	6.00	4.01	11.01	4.08	7.01	8.00	7.00	11.00	4.09	4.10	1B
6	Diphenylamine (122-39-4)	3.10	3.09	3.01	5.00		3	13.00	15.01	11.01	15.02	4.08	8.00	11.00	4.09	4.06	4.03	1B
7	Ethylene glycol (107-21-1)	15.00	3.00	7.00			1B	15.01	4.01	11.01	4.08	4.05	7.01	8.00	7.00	11.00	4.09	1A
8	Methyl ethyl ketone (78-93-3)	15.00	8.00	3.00			1B	15.01	11.01	15.02	4.08	4.05	7.01	8.00	7.00	11.00	4.02	1A
9	Methylene chloride (75-09-2)	17.00	3.10	8.00			4	13.00	15.01	4.01	11.01	14.02	4.08	4.05	7.01	8.00	7.00	1A
10	Phenol (108-95-2)	14.00	4.00	2.00			1B	13.00	6.00	14.01	4.01	11.01	14.02	4.08	4.05	7.01	8.00	1B
11	Tetrachlorethylene (127-18-4)	3.10	7.01	8.00	2.00		1A	6.00	15.01	11.01	14.02	4.08	4.05	7.01	8.00	7.00	11.00	1A
12	Toluene (108-88-3)	15.00	8.00	7.01			2	15.02	16.01	7.01	4.01	3.02	5.10	3.08	11.00	3.10	8.00	1A
13	Trichloroethane, 1,1,1- (71-55-6)	16.00	8.00	3.00			1B	14.01	4.01	11.01	15.02	4.08	4.05	7.01	8.00	7.00	11.00	1A
14	Xylene (1330-20-7)	15.00	8.00	5.00			2	14.01	11.01	15.02	4.05	7.01	8.00	7.00	11.00	4.02	4.09	1A

**Table 4a.** Chemical concentrations, PACs, and HIs for a sample chemical mixture using the 1999 version of the CMM.

No.	Name	Chemical		PAC-2 mg/m <sup>3</sup>	PAC-3 mg/m <sup>3</sup>	HI based on			
		Concentration mg/m <sup>3</sup> @ 30 m	@ 100m			PAC-2 @ 30 m	PAC-3 @ 30 m	PAC-2 @ 100m	PAC-3 @ 100m
1	Acetone	5770	544	20100	20100	0.29	0.29	0.027	0.027
2	Benzene	417	43.2	479	3190	<b>0.87</b>	0.13	0.090	0.013
3	Biphenyl	50.1	4.72	7	100	<b>7.2</b>	<b>0.50</b>	<b>0.67</b>	0.047
4	Carbon tetrachloride	69.8	6.57	629	4720	0.11	0.015	0.010	0.0014
5	Chlorobenzene	206	19.4	920	4600	0.22	0.045	0.021	0.0042
6	Diphenylamine	34.1	3.21	50	500	<b>0.68</b>	0.068	0.064	0.0064
7	Ethylene glycol	24.8	2.34	102	152	0.24	0.16	0.023	0.015
8	Methyl ethyl ketone	3780	356	2950	8850	<b>1.3</b>	0.43	0.012	0.040
9	Methylene chloride	1220	115	2600	13900	0.47	0.088	0.044	0.0083
10	Phenol	7.37	0.693	193	770	0.038	0.0096	0.0036	0.00090
11	Tetrachlorethylene	122	11.5	1360	6780	0.090	0.018	0.0085	0.0017
12	Toluene	901	84.8	1130	3760	<b>0.80</b>	0.24	0.075	0.023
13	Trichloroethane, 1,1,1-	887	83.5	5450	16400	0.16	0.054	0.015	0.0051
14	Xylene	520	48.9	868	3910	<b>0.60</b>	0.13	0.056	0.012
<b>Summation of hazard indices for all chemicals:</b>						<b>13</b>	<b>2.2</b>	<b>1.2</b>	0.2

HI values  $\geq 0.5$  are bolded

**Table 4b.** Chemical concentrations, PACs, and HIs for a sample chemical mixture using the 2009 version of the CMM.

No.	Name	Chemical Concentration mg/m <sup>3</sup>		HI based on					
		@ 30 m	@ 100m	PAC-2 mg/m <sup>3</sup>	PAC-3 mg/m <sup>3</sup>	PAC-2 @ 30 m	PAC-3 @ 30 m	PAC-2 @ 100m	PAC-3 @ 100m
1	Acetone	5770	544	7600	13500	<b>0.76</b>	0.43	0.072	0.040
2	Benzene	417	43.2	550	12800	0.16	0.033	0.017	0.003
3	Biphenyl	50.1	4.72	60.5	100	<b>0.83</b>	<b>0.50</b>	0.078	0.047
4	Carbon tetrachloride	69.8	6.57	1190	3270	0.059	0.021	0.006	0.002
5	Chlorobenzene	206	19.4	690	1840	0.30	0.11	0.028	0.011
6	Diphenylamine	34.1	3.21	125	125	0.27	0.27	0.026	0.026
7	Ethylene glycol	24.8	2.34	100	150	0.25	0.16	0.023	0.016
8	Methyl ethyl ketone	3780	356	7960	11800	0.47	0.32	0.045	0.030
9	Methylene chloride	1220	115	1940	24000	<b>0.63</b>	0.051	0.059	0.005
10	Phenol	7.37	0.693	88.5	769	0.083	0.010	0.008	0.001
11	Tetrachlorethylene	122	11.5	1560	8130	0.078	0.015	0.007	0.001
12	Toluene	901	84.8	4520	16900	0.20	0.053	0.019	0.005
13	Trichloroethane, 1,1,1-	887	83.5	3270	22900	0.27	0.039	0.026	0.004
14	Xylene	520	48.9	3990	10800	0.13	0.048	0.012	0.005
<b>Summation of hazard indices for all chemicals:</b>						<b>4.5</b>	<b>2.1</b>	0.4	0.2

HIs ≥0.5 are bolded.

**Table 5a.** Summation of HIs for chemicals in the mixture having the same toxic consequences (mode): chronic toxic effects in the 1999 version of the CMM. The chronic system codes are highlighted in bold font.

No	Name	Health Code Numbers										HIs based on:			
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	PAC-2 @30m	PAC-3 @30m	PAC-2 @100m	PAC-3 @100m
1	Acetone	16.00	8.00									[0.76]	[0.43]	[0.072]	[0.040]
2	Benzene	2.00	12.00	<b>3.00</b>	14.01	14.02						0.16	0.033	0.017	0.003
3	Biphenyl	15.00										[0.83]	[0.50]	[0.078]	[0.047]
4	Carbon tetrachloride	<b>3.10</b>	2.00	5.00								0.059	0.021	0.006	0.002
5	Chlorobenzene	<b>3.00</b>	8.00	5.00								0.30	0.11	0.028	0.011
6	Diphenylamine	<b>3.10</b>	<b>3.09</b>	<b>3.01</b>	5.00							0.27	0.27	0.026	0.026
7	Ethylene glycol	15.00	<b>3.00</b>	7.00								0.25	0.16	0.023	0.016
8	Methyl ethyl ketone	15.00	8.00	<b>3.00</b>								0.47	0.32	0.045	0.030
9	Methylene chloride	17.00	<b>3.10</b>	8.00								<b>0.63</b>	0.051	0.059	0.005
10	Phenol	14.00	4.00	2.00								[0.083]	[0.010]	[0.008]	[0.001]
11	Tetrachlorethylene	<b>3.10</b>	7.01	8.00	2.00							0.078	0.015	0.007	0.001
12	Toluene	15.00	8.00	7.01								[0.20]	[0.053]	[0.019]	[0.005]
13	Trichloroethane, 1,1,1-	16.00	8.00	<b>3.00</b>								0.27	0.039	0.026	0.004
14	Xylene	15.00	8.00	5.00								[0.13]	[0.048]	[0.012]	[0.005]
<b>Sum of hazard indices for chemicals with chronic (cumulative) toxic effects:</b>											<b>2.5</b>	<b>1.0</b>	0.2	0.1	

HIs ≥0.5 are bolded; values in brackets are not used in computing the sum of hazard indices.

**Table 5b.** Summation of HIs for chemicals in the mixture having the same toxic consequences (mode): acute toxic effects in the 2009 version of the CMM. The acute system HCNs are highlighted in bold font.

No	Name	Health Code Numbers										HIs based on:			
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	PAC-2 @30m	PAC-3 @30m	PAC-2 @100m	PAC-3 @100m
1	Acetone	6.00	15.01	11.01	15.02	<b>4.08</b>	<b>4.05</b>	7.01	8.00	7.00	11.00	<b>0.76</b>	0.43	0.072	0.040
2	Benzene	14.01	<b>4.01</b>	11.01	15.02	<b>4.08</b>	<b>4.05</b>	7.01	8.00	7.00	11.00	0.16	0.033	0.017	0.003
3	Biphenyl	15.01	11.01	15.02	<b>4.08</b>	7.01	8.00	7.00	11.00	<b>4.09</b>	<b>4.10</b>	<b>0.83</b>	<b>0.50</b>	0.078	0.047
4	Carbon tetrachloride	14.01	<b>4.01</b>	14.02	<b>4.08</b>	<b>4.05</b>	7.01	7.00	11.00	<b>4.02</b>	<b>4.09</b>	0.059	0.021	0.006	0.002
5	Chlorobenzene	6.00	<b>4.01</b>	11.01	<b>4.08</b>	7.01	8.00	7.00	11.00	<b>4.09</b>	<b>4.10</b>	0.30	0.11	0.028	0.011
6	Diphenylamine	13.00	15.01	11.01	15.02	<b>4.08</b>	8.00	11.00	<b>4.09</b>	<b>4.06</b>	<b>4.03</b>	0.27	0.27	0.026	0.026
7	Ethylene glycol	15.01	<b>4.01</b>	11.01	<b>4.08</b>	<b>4.05</b>	7.01	8.00	7.00	11.00	<b>4.09</b>	0.25	0.16	0.023	0.016
8	Methyl ethyl ketone	15.01	11.01	15.02	<b>4.08</b>	<b>4.05</b>	7.01	8.00	7.00	11.00	<b>4.02</b>	0.47	0.32	0.045	0.030
9	Methylene chloride	13.00	15.01	<b>4.01</b>	11.01	14.02	<b>4.08</b>	<b>4.05</b>	7.01	8.00	7.00	<b>0.63</b>	0.051	0.059	0.005
10	Phenol	13.00	6.00	14.01	4.01	11.01	14.02	<b>4.08</b>	<b>4.05</b>	7.01	8.00	0.083	0.010	0.008	0.001
11	Tetrachlorethylene	6.00	15.01	11.01	14.02	<b>4.08</b>	<b>4.05</b>	7.01	8.00	7.00	11.00	0.078	0.015	0.007	0.001
12	Toluene	15.02	16.01	7.01	<b>4.01</b>	3.02	5.10	3.08	11.00	3.10	8.00	0.20	0.053	0.019	0.005
13	Trichloroethane,	14.01	<b>4.01</b>	11.01	15.02	<b>4.08</b>	<b>4.05</b>	7.01	8.00	7.00	11.00	0.27	0.039	0.026	0.004
14	1,1,1- Xylene	14.01	11.01	15.02	<b>4.05</b>	7.01	8.00	7.00	11.00	<b>4.02</b>	<b>4.09</b>	0.13	0.048	0.012	0.005
<b>Sum of hazard indices for chemicals with acute system toxic effects:</b>												<b>4.5</b>	<b>2.1</b>	0.4	0.2

Hazard indices exceeding 0.5 are bolded in red as appeared in the new CMM workbook Rev. 25.

**Table 6.** Summation of HIs for chemicals in the mixture having the same toxic consequences (mode): narcosis (i.e., HCN 8.00) and irritant (HCNs 14.xy, 15.xy, and 16.xy) or having the same toxic consequences (target organ): nervous system acute effects (i.e., HCNs 8.00, 6.00, 7.00, and 7.01) and respiratory (HCNs 11.00 and 11.01) in the 1999 and 2009 versions of the CMM..

<u>Toxic consequence by mode</u>	$\sum_{i=1}^n HI_{i(p)}$							
	1999 Version of CMM				2009 Version of CMM			
	@30m PAC-2	@30m PAC-3	@100m PAC-2	@100m PAC-3	@30m PAC-2	@30m PAC-3	@100m PAC-2	@100m PAC-3
Narcotic HCN=8.00	<b>2.8</b>	<b>1.1</b>	0.3	0.1	<b>4.4</b>	<b>2.1</b>	0.4	0.2
Irritant HCN=14.xy, 15.xy, 16.xy	<b>3.2</b>	<b>1.6</b>	0.3	0.1	<b>4.2</b>	<b>2.0</b>	0.4	0.2
Nervous System HCN=8.00, 6.00, 7.00, 7.01	N/A	N/A	N/A	N/A	<b>4.5</b>	<b>2.1</b>	0.4	0.2
Respiratory System HCN=11.00, 11.01	N/A	N/A	N/A	N/A	<b>4.5</b>	<b>2.1</b>	0.4	0.2

Hazard indices  $\geq 0.5$  are bolded.  
N/A=not available

**Table 7.** Source term and toxicological consequences analysis of a waste transfer leak scenario.

Chemical Name (CASRN)	Mass (kg)	Duration (min)	Peak 15-min TWA conc. (mg/m <sup>3</sup> ) @ 100 m <sup>a</sup>	Hazard Index based on PAC-2
Sodium Nitrite (7632-00-0)	24.6	480	26	26
Sodium chromate (7775-11-3)	1.97	480	2.1	2.8
Sodium nitrate (7631-99-4)	14.1	480	15	2.0
Trisodium phosphate (7601-54-9)	12.6	480	13	0.03
Sodium hydrogen metasilicate (z-0068) <sup>b</sup>	13.3	480	14	0.2
<b>Sum of Hazard Indices:</b>				31
<b>Limiting Toxic Mode/Endpoint or Organ-Specific Hazard Indices:</b>				31

<sup>a</sup> Calculated using EPICode

<sup>b</sup> No CASRN is assigned to this chemical, a temporary identification number is used instead.

**Table 8.** Summary of CMM analysis of seven hypothetical waste mixtures.

Scenario	$\sum_{i=1}^n HI_i$	Greatest HIs by mode		Greatest HIs by target organ	
Waste transfer leak from a single shell tank	31	31	Acute systemic toxin, Acute respiratory toxin	31	Respiratory system toxin(A) <sup>a</sup>
Fire in contaminated facility	41	39	Acute systemic toxin	39	Respiratory system toxin (A) <sup>a</sup>
Mixing incompatible materials	18	17	Acute systemic toxin	17	Respiratory system toxin (A) <sup>a</sup>
Flammable gas deflagration	7.4	6.0	Chronic systemic Toxins	6.0	Respiratory system toxin (C) <sup>a</sup>
Above ground structure failure	2.5	2.5	Acute systemic toxin, Acute respiratory toxin	2.5	Reproductive system toxins (A) <sup>a</sup>
Nuclear Criticality	0.00077	N/A <sup>b</sup>	N/A <sup>b</sup>	N/A <sup>b</sup>	N/A <sup>b</sup>
Solid aerosol release from tank failure due to excessive loads	0.089	N/A <sup>b</sup>	N/A <sup>b</sup>	N/A <sup>b</sup>	N/A <sup>b</sup>

<sup>a</sup> A=acute health effects; C=chronic health effects; <sup>b</sup> N/A=not applicable