Default Methodology for Analysis of Airborne Exposure to Mixtures of Chemicals in Emergencies:

The User's Guide for the Chemical Mixture Methodology

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FOREWORD

This document provides a user's guide for the Chemical Mixture Methodology (CMM) Workbook. It presents an introduction to the CMM, a description of the CMM Workbook and each of its worksheets, and instructions on how to use the CMM Workbook.

The CMM provides recommended default emergency exposure guidelines for mixtures of chemicals. The CMM makes extensive use of Health Code Numbers (HCNs) to examine the additive impact that each chemical component in a chemical mixture may have on specific target organs. The CMM is a more realistic predictor of potential human health impacts than can be obtained using the (1) nonconservative method of separately analyzing the consequences of each chemical component or the (2) overly conservative method of adding the exposures from each chemical together, regardless of the human organ targeted by the chemical.

The CMM is designed to support U.S. Department of Energy emergency planning hazards assessments (EPHAs), safety analyses, and assessments during emergency response situations. Development of the CMM and the preparation of this user's guide were sponsored by the U.S. Department of Energy Office of Emergency Management and Policy.

ACRONYMS AND ABBREVIATIONS

AEGL	Acute Exposure Guideline Level
AIHA	American Industrial Hygiene Association
CASRN	Chemical Abstracts Service Registry Number
CFR	Code of Federal Regulations
C_i	airborne concentration
CMM	Chemical Mixture Methodology
DOE	U.S. Department of Energy
EPA	U.S. Environmental Protection Agency
EPHA	Emergency Planning Hazards Assessment
ERPG	Emergency Response Planning Guideline
HCN	health code number
HI	hazard index
PAC	Protective Action Criteria
PEL	permissible exposure limit
SCAPA	Subcommittee on Consequence Assessment and Protective Actions
TEEL	Temporary Emergency Exposure Limits
TWA	time-weighted average

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SECTION 1. INTRODUCTION

The Chemical Mixture Methodology (CMM) Workbook is set up to automatically apply the U.S. Department of Energy (DOE) Subcommittee on Consequence Assessment and Protective Actions (SCAPA) recommended default methodology for a user-supplied mixture of chemicals. This methodology is originally published in *Applied Occupational and Environmental Hygiene* (Craig et al., 1999) and updated in the *Journal of Applied Toxicology* (Yu et al., 2010). Both research articles are available at http://orise.orau.gov/emi/scapa/chem-mixture-methodolgy/background.htm.

The CMM provides recommended default emergency exposure guidelines for mixtures of chemicals. The CMM provides more realistic and conservative estimates of potential human health impacts than can be obtained by analyzing the consequences of each chemical component without considering their combined impact. The CMM also provides more realistic estimates than can be obtained by adding the exposures from each chemical together regardless of the organ targeted by the chemical (an overly conservative approach). The CMM is recommended by SCAPA for potential use in Emergency Planning Hazards Assessments (EPHAs) (see DOE O 151.1C, DOE, 2005), Documented Safety Analyses (see 10 CFR 830, DOE, 2001), and for consequence assessments supporting emergency response exercises or actual accident situations.

Radioactive chemicals are provided in the CMM Workbook only when the chemical toxicity is significant compared to the radiological health effects. Currently, this is limited to the following low-specific-activity radioactive isotopes:

- "Uranium of low enrichment in the form of compounds that are relatively soluble in body fluids (e.g., carbonates, nitrates, fluorides, sulfates). Depending on the exact proportions of the different uranium isotopes, the chemical toxicity concern becomes dominant as the nominal enrichment (^{235}U weight percent) decreases through the range from about 16% to 5%" (DOE-HDBK-1046-2008, 2008).

- Thorium and some of its compounds.

When the CMM is used, a hazard index (HI) is calculated for each component of a chemical mixture at the chosen receptor point. The "HI_i" is the concentration of chemical "i" ($Conc_i$) divided by the concentration limit for chemical "i" ($Limit_i$). The appropriate concentration limit for a chemical is determined based on its Protective Action Criteria (PAC). The PAC values have been developed to assist in emergency planning of chemical release events and are composed of Acute Exposure Guideline Levels (AEGLs) (Rusch *et al.*, 2000; Rusch *et al.*, 2002), Emergency Response Planning Guidelines (ERPGs) (Rusch, 1993), and Temporary Emergency Exposure Limits (TEELs) (Craig *et*

al., 1995, Craig et al., 2000).[1] Four different PAC benchmark values are developed for each chemical. Each successive benchmark is associated with an increasingly severe effect that involves a higher level of exposure. The four benchmarks present threshold levels as follows:

> 0 - no adverse health effects (always based on a TEEL value because AEGLs and ERPGs do not report a level for no adverse effects)
>
> 1 - mild, transient health effects
>
> 2 - irreversible or other serious health effects that could impair ability to take protective action
>
> 3 - life-threatening health effects.

The PAC values are presented in a searchable database and as lists of tables and spreadsheets (see http://www.atlintl.com/DOE/teels/teel.html).

For a given chemical, an HI_i less than or equal to 1.0 means that the applicable PAC concentration limit (i.e., either effect levels 0, 1, 2, or 3) for that single chemical "i" has not been exceeded. However, if the hazard indices for all chemicals in a mixture are summed and the cumulative hazard index is greater than 1.0, then an unacceptable condition may exist for human health and safety, and mitigating strategies may need to be considered. Unless the health effects of the components are known to be independent in their mode of toxicity, the toxic consequences of all components should, as an initial step in an assessment, be considered to be additive. This represents the most conservative upper-bound approach for assessing exposures to chemical mixtures.[2]

If this upper-bound approach produces unacceptable results (HI_i>1.0), the next step is to classify the chemicals in the mixture according to their toxic consequences. The toxicological classification of specific chemicals can be done using the health code numbers (HCNs) established for each chemical.

HCNs are used in the CMM to identify the target-organ effects of each chemical in the mixture. Any chemicals that target the same or similar organs or operate by the same acute (i.e., short-term, 7 days or fewer) or chronic (i.e., long-term, more than 7 days) mode of toxicity should be considered additive to that target organ or by that same mode

[1] The AEGLs are developed by the U.S. Environmental Protection Agency (EPA) National Advisory Committee and the National Research Council AEGL Subcommittee; ERPGs are produced by the American Industrial Hygiene Association (AIHA) Emergency Response Planning Committee; and TEELs are developed by DOE.

[2] The CMM does not consider reactions between the chemicals in the mixture that in some cases could generate new chemicals, alter the chemical mixture, or change the mixture's dispersion properties. This level of complexity is beyond the current scope of the CMM.

of toxicity. For simplicity in this discussion, target-organ effects and modes of toxicity are considered simply as target-organ effects.

Summation of the HIs for all chemicals in a mixture having the same toxic consequences (i.e., the same or similar HCNs) enables determination of the acceptability or unacceptability of exposure to any specific mixture of chemicals using this more discerning and realistic approach.

The HCNs offer a convenient way of performing this exposure addition by numerically binning identical or similar target-organ effects. All of the individual exposure HIs categorized into the same or similar HCN bin are added together to yield an HI sum for that target-organ bin.

Any of the individual HI sums that exceed a value of 1.0 ($\Sigma HI_i > 1.0$) indicate that the exposure limit has been exceeded and that some kind of mitigating action should be taken to reduce the exposure to that target organ below the applicable limit.

SECTION 2. THE CMM WORKBOOK

Two versions of the Microsoft Excel-based CMM Workbook are offered to meet user needs. The first version of the CMM Workbook is intended for most users and allows a maximum of 15 chemicals in a mixture. It is downloadable from the CMM webpage at http://orise.orau.gov/emi/scapa/hcn.htm. The second version allows a maximum of 30 chemicals in a mixture. A disadvantage in using the 30-chemical version is that in half of the workbook's worksheets, the additional rows reserved to display information for the extra set of 15 chemicals will drop the presentation of a key row of summary information out of the default display window (the user will need to manually scroll down to view this summary information). The 30-chemical version of the CMM Workbook can be obtained by sending an email request to the CMM development team at PACDevelopment@listserv.orau.gov. Except for the minor differences associated with doubling the maximum number of chemicals permitted in a mixture, both versions of the CMM Workbook are identical.

The CMM workbook employs six worksheets:

1. *Input*
2. *Import*
3. *HIs by mode*
4. *HIs by target organ*
5. *Output*
6. *HCN-PAC*.

To use the CMM Workbook, the user enters information on a mixture of chemicals into the *Input* worksheet. This information includes the name of each chemical in the mixture, an identification number for each chemical, the specific PAC of concern, and the concentration of each chemical at a user-selected receptor location common to all chemicals in the mixture.

The *Input* worksheet has room for the entry of a maximum of either 15 or 30 chemicals in a given mixture, depending on the version of the CMM workbook that is being used.

To provide the user with ready access to the chemical-specific information required to complete the *Input* worksheet, reference information for each chemical is included in the *HCN-PAC* worksheet. This information includes the name of each chemical and its Chemical Abstracts Service Registry Number (CASRN), HCN values, and PAC values.

Information on the chemical concentrations at the user-specified receptor location, as required in the *Input* worksheet, must be provided by the user. This information typically

is obtained from hand calculations or atmospheric dispersion modeling results (e.g., EPICode,[3] ALOHA[4]).

The CMM Workbook is designed to execute calculations automatically once data are entered or removed from the *Input* worksheet. However, in some cases it may be necessary to manually start the calculations. To execute the CMM worksheet calculations on a personal computer, simultaneously press **Ctrl** and **=** on the keyboard or simply press the **F9** key. *(On an Apple computer, simultaneously press **Apple** or **Command** and **=** on your keyboard.)* After the calculations are executed, HI information for each chemical in the input mixture and the sum of all HIs for the entire mixture will be provided in the *Output* worksheet. In addition, intermediate and supplementary information are provided in three other worksheets: *Import*, *HIs by mode*, and *HIs by target organ*.

Figure 1 provides an overview of the steps followed to use the CMM Workbook.

Note that only the *Input* worksheet is used to enter information. The *HCN-PAC* worksheet also can be modified by the user (e.g., to add new chemicals or updated HCN or PAC data), but the other four worksheets are password-protected to maintain the integrity of the CMM software.

[3] EPICode is a software tool designed to aid emergency response personnel, emergency planners, and health and safety professionals in evaluating the atmospheric release of toxic substances. For information on EPICode, see http://www.epicode.com/.

[4] ALOHA is an atmospheric dispersion model used for evaluating releases of hazardous chemical vapors. It is part of the CAMEO suite of tools. CAMEO is used to plan for and respond to chemical emergencies. For information on ALOHA, see http://www.epa.gov/emergencies/content/cameo/what.htm.

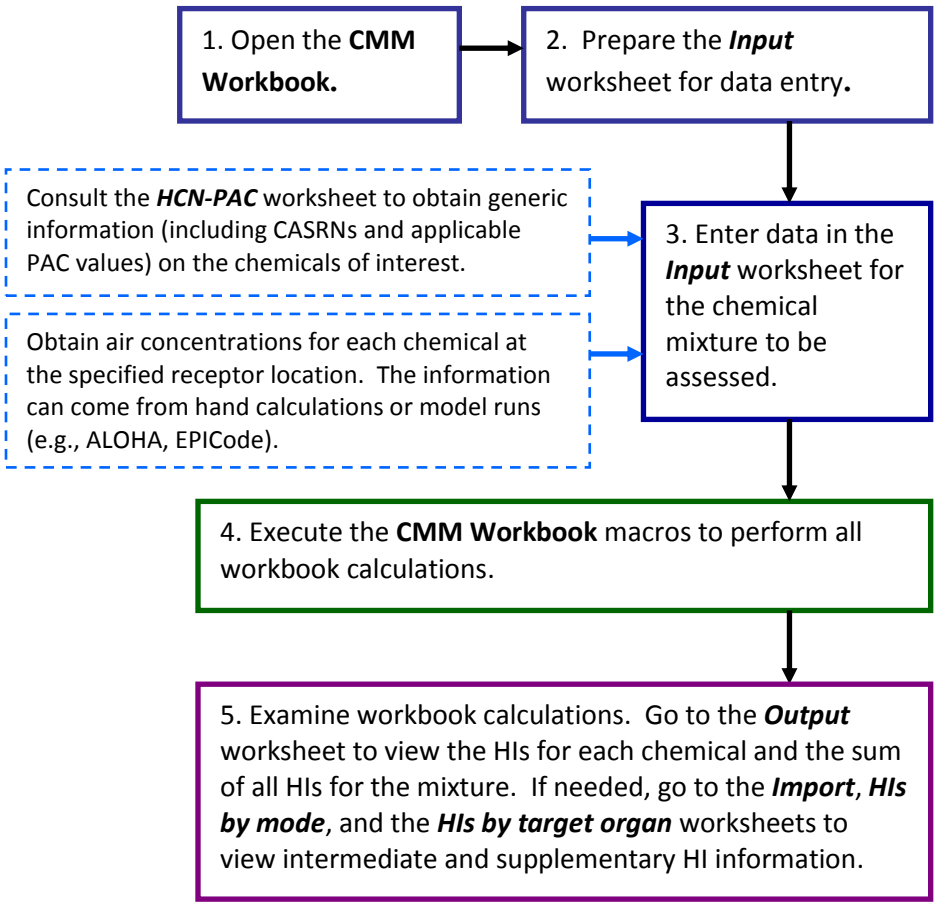

Figure 1. How to Use the CMM Workbook.

SECTION 3. USING THE CMM WORKBOOK

In this section, the steps that are followed when using the Microsoft Excel-based CMM Workbook are presented. Basic instructions on how to manipulate the workbook are provided for users of both Excel 2003 and Excel 2007 where appropriate.

STEP 1. Open the Workbook.

When opening the CMM Workbook, macros must be enabled. The CMM Workbook uses macros to perform all of its data lookups and calculations. To guard against macros that may have a malicious function, Excel offers its users four levels of security (Very High, High, Medium, and Low) for workbooks that use macros. If your version of Excel has its macro security level set to Very High or High, your computer likely will block execution of the CMM Workbook macros. To enable the macros in the CMM Workbook, the Excel security level should be set no higher than Medium. To check the Excel security level using Microsoft Excel 2003, open the CMM Workbook and go to **Tools → Macro → Security → Security Level** (see Figure 2).

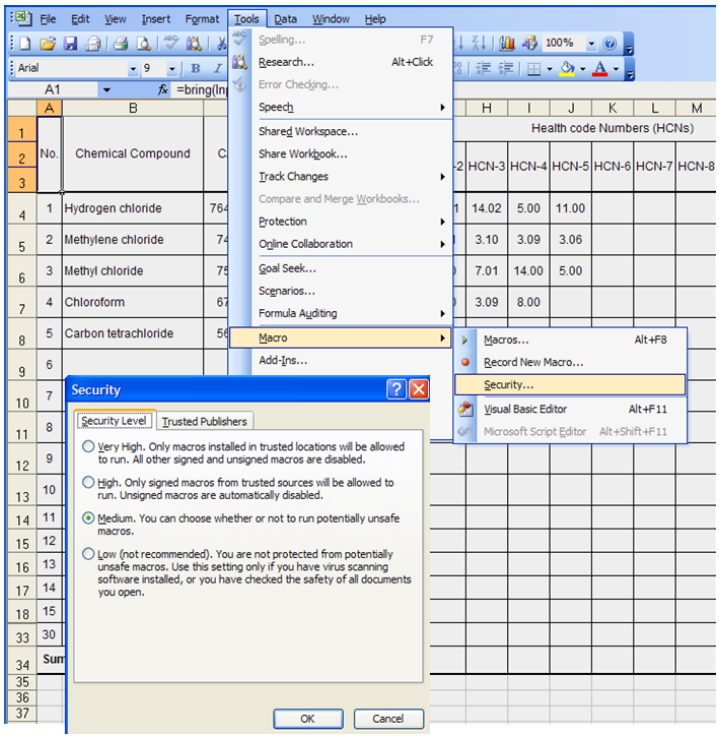

Figure 2. Setting the Security Level for Macros. Shown for Microsoft Excel 2003.

Once the security level in any Excel workbook is set, it will stay at that level for all Excel files until changed. At the Medium security level, a security warning (Figure 3) will be displayed when the user opens the CMM Workbook; the user can choose to either enable

or disable the workbook macros. Clicking the **Enable Macros** button will allow the workbook to execute its macros.

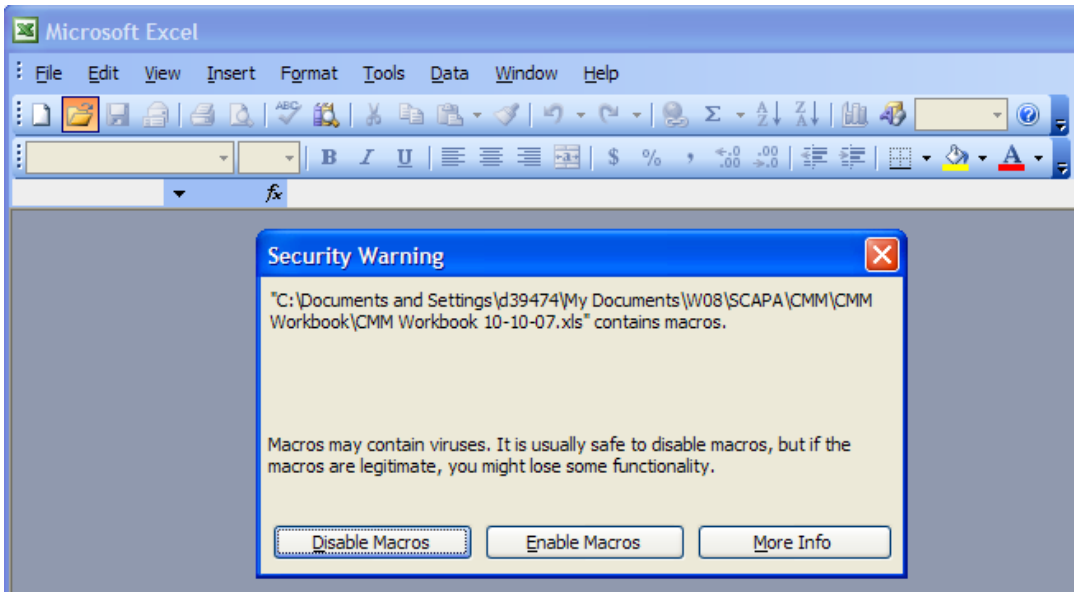

Figure 3. The Microsoft Excel 2003 Security Warning about Macros.

For users running Excel 2007, the macro security settings can be changed in the Trust Center to enable the workbook's macros to run. *Note: in some organizations, only a system administrator may be empowered to make these changes.* To access the Trust Center, click the **Microsoft Office Button** and then click **Excel Options**. Next, click the **Trust Center** option on the left side of the pop-up Excel Options window, then click the **Trust Center Settings** button on the right side of the window to open the Trust Center window. Click the **Macro Settings** category on the left side of the **Trust Center** window, select either the **Disable all macros with notification** or **Enable all macros** option, then click the **OK** button on both the **Trust Center** and **Excel Options** windows to lock-in this change.

If **Disable all macros with notification** is enabled, a Security Warning ribbon will be displayed above the worksheet each time the CMM Workbook is opened. Click the **Options** button on this ribbon. In the **Security Options** pop-up window (with a heading of "Security Alert – Macro"), select the **Enable this content** option, then click the **OK** button. The workbook macros will now be operational.

STEP 2. Prepare the Input Worksheet for Data Entry.

When the *Input* worksheet is accessed, information for a sample mixture of chemicals is likely to be displayed. This mixture may be the scenario example that came preloaded with the workbook, or it may be input data from the last time the workbook was saved.

These old entries should be cleared from the worksheet before a new chemical mixture is entered. First, highlight the data entered in Columns B through F.

Next, if using Excel 2003:

- Right-click this selection and select **Clear Contents** (as shown in Figure 4);
- Select **Edit** on the toolbar, select **Clear** on the drop-down menu, and select the **All** option; or
- Click the **Delete** key on the keyboard.

Do not delete or cut cell contents using the *Edit* menu or by using the right mouse button *delete* function.

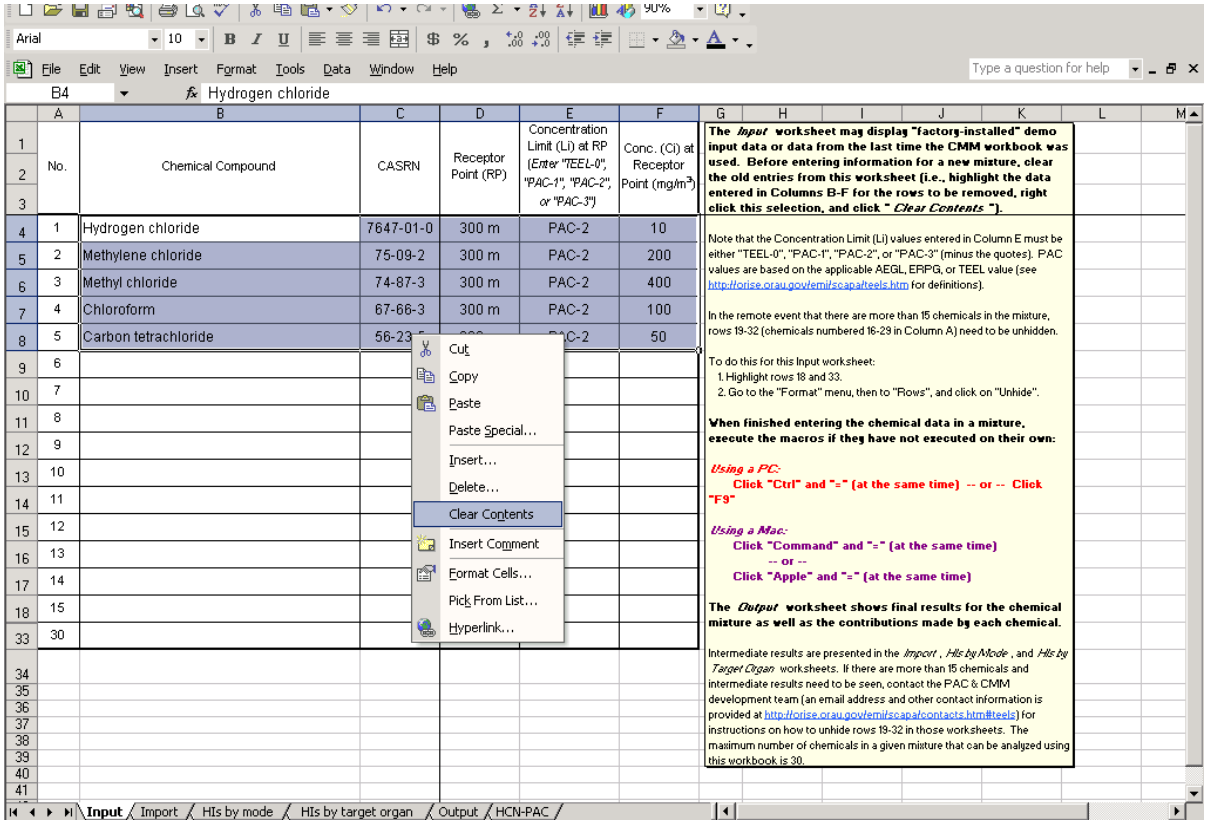

Figure 4. Clearing Old Data from the *Input* Worksheet.

Or, if using Excel 2007, on the **Home** tab, in the **Editing** group, click the arrow next to the **Clear** button, then click **Clear Contents**.

Note: As chemical names and other information are entered into the *Input* worksheet, this input is shared and displayed in the other worksheets.

STEP 3. Enter Data in the Input Worksheet.

Before entering data in the *Input* worksheet, users should check the *HCN-PAC* worksheet lookup table to ensure that each chemical in the subject mixture is listed in the *HCN-PAC* worksheet. The workbook will not execute any calculations for chemicals not listed in the *HCN-PAC* worksheet. In addition, it is recommended that users copy and paste chemical names and CASRNs from the *HCN-PAC* look-up worksheet to the *Input* worksheet to avoid entry errors.

3.1. In the *Input* worksheet, insert in Column B (using the paste function or manually enter using the keyboard) the names of each chemical in the mixture. Enter one chemical name per row. This information is used to label output products. The chemical names, CASRNs, HCNs, and PAC values for all chemicals supported in the workbook are provided in the *HCN-PAC* worksheet.

3.2. Insert in Column C the CASRN for each chemical listed in Column B. The CASRNs should be obtained from Column C of the *HCN-PAC* worksheet. In cases where a listed chemical does not have a CASRN, a substitute or alternative CASRN (e.g., z-0001) has been provided. The workbook will treat it as a CASRN for fetching and importing purposes. If a CASRN is not entered in the *Input* worksheet for a given chemical or does not exist in the *HCN-PAC* worksheet, the workbook cannot calculate HIs for that chemical.

3.3. Enter location information for the receptor point of interest (e.g., *offsite at 600 m*, *onsite at 300 m*, *local at 400 m*) in Column D. This information is **not** used in workbook calculations but is helpful to the user in selecting input values for other *Input* worksheet parameters and for documentation purposes.

3.4. Determine the governing concentration limit at the receptor point and enter this information in Column E. The governing concentration limit is the applicable PAC. The PAC data in the *HCN-PAC* worksheet incorporate applicable AEGL, ERPG, and TEEL values.[5] Acceptable inputs for the concentration limit are TEEL-0, PAC-1, PAC-2, or PAC-3 (note that an entry of PAC-0 will **not** work; use TEEL-0 instead). Input must be in this five- or six-character format (e.g., TEEL-0, PAC-2).

[5] The definitions for TEEL-0, -1, -2, and -3; AEGL-1,-2, and -3; and ERPG-1, -2, and -3 are provided at http://www.atlintl.com/DOE/teels/teel/teeldef.html.

If the chemical entered in the *Input* worksheet is listed in the *HCN-PAC* worksheet, the workbook uses the TEEL-0 or PAC-n (where n = 1, 2, or 3) entry in Column E to obtain the actual concentration limit value from the appropriate PAC column in the *HCN-PAC* worksheet. The value obtained is automatically inserted as the concentration limit (in units of milligrams per cubic meter [mg/m^3]) in Column D of the *Import* worksheet.

3.5. Calculate or otherwise obtain the airborne concentration (C_i) of each chemical "i" at the receptor point (from Column D of the *Input* worksheet) and enter this value in Column F of the *Input* worksheet. This concentration must be in units of **mg/m^3**. Concentrations may be obtained using values from existing data tables, manual calculations of atmospheric dispersion, or output from atmospheric dispersion models (e.g., ALOHA, EPICode).

3.6. Once the CASRN, concentration limit, and concentration data are entered for a given chemical in Columns C, E, and F, respectively, the workbook should automatically perform its calculations and update output data in the other worksheets. The user can also manually execute the workbook calculations. On a personal computer, this is done by simultaneously pressing **Ctrl** and **=** on your keyboard or by pressing the **F9** key. On an Apple computer, simultaneously press **Apple** or **Command** and **=** on your keyboard.

STEP 4. Workbook Performs Calculations.

The following describes the process used by the workbook's macros in performing mixture methodology calculations.

4.1. The hazard index (HI_i) for each chemical (see Eqn. 1) at the receptor point of interest is reported in the *Import* worksheet in Column E and also in the *Output* worksheet in Column D.

$$HI_i = C_i / PAC_i \qquad \text{Eqn. 1}$$

An HI_i that is greater than 1.0 indicates that a concentration limit (i.e., PAC limit value) has been exceeded.

4.2. Initially, the workbook sums all the HI_i values (see Eqn. 2) to determine acceptability of the scenario being evaluated and whether protective actions or administrative controls should be applied.

$$\sum_{i=1}^{n} HI_i = HI_1 + HI_2 + \ldots + HI_n \qquad \text{Eqn. 2}$$

The sum of the HI_i values is provided in the *Import* worksheet in the last row of Column E and also in the *Output* worksheet in Column E. If the sum of the HI_i values is less than or equal to 1.0 (as shown in Eqn. 3), *there is no need to proceed with a further assessment*.

$$\sum_{i=1}^{n} HI_i \leq 1 \qquad \text{Eqn.3}$$

If the sum of the HI_i values is greater than 1.0, then HCNs need to be employed to provide a more realistic, although still somewhat conservative, assessment of the hazard. To do this, the workbook continues with the following calculations.

4.3. The workbook determines the toxicological classification of each chemical (i.e., its HCNs) from the values provided in the *HCN-PAC* worksheet (Columns E through N). Up to 10 HCN values may be entered for each chemical. These values were derived by the CMM Workbook development team. If a chemical has more than 10 HCNs, only the 10 most significant were entered by the development team in this worksheet. The ranking of the HCNs is based on their relevance to emergency preparedness and response. The workbook copies the HCN data for each chemical entered in the *Input* worksheet into the *Import* worksheet (Columns F through O).

The category of each chemical is provided in the *HCN-PAC* worksheet in Column O and is copied into Column P of the *Import* worksheet. The category gives the concentration-limit classification used to determine whether the toxicological consequences of exposure to a chemical are concentration-dependent, dose-dependent, acute, cumulative, or other (see Table 1). Although the category is used in HCN and TEEL determination, it is not used explicitly in the mixture methodology. However, it may aid the user in determining whether a time period longer or shorter than the recommended 15-minute duration may logically be used in measuring or modeling the user-supplied concentration at the receptor point of interest (Column F in the *Input* worksheet).

4.4. The workbook sums the HIs of all chemicals having the same HCNs. For example, the HIs for those chemicals that are carcinogens (HCNs 1 and 2) are summed; chronic, systemic toxins (HCN = 3.00, 3.01–3.12) are summed separately; acute systemic toxins (HCN = 4.00, 4.01–4.12) also are summed separately. These summations are done automatically by the workbook. Results for each major HCN grouping are presented in Columns D through S in the *HI by mode* worksheet and in Columns D through AN of the *HIs by target organ* worksheet. The results of the *HIs by mode* and *HIs by target organ* worksheets are summarized in Columns G through J of the *Output* worksheet. The sum of the HIs for each HCN must be less than or equal to 1.0 for the exposure to be within prescribed limits. For the user's convenience, all summed HIs greater than or equal to a generally accepted 0.5 action level are presented in bolded **red** font.

Table 1. Chemical Categories Used in the *Import* Worksheet: Column P.
This table is adapted from Craig et al. (1999).

Category[A]	Concentration-limit Classification[A]	Exposure duration treatment[B]
1A	Ceiling standard	Concentration-dependent[D]
1B	Irritants	Concentration-dependent[D]
1C	Technologic feasibility[C]	Concentration-dependent[D]
2	Acute toxicants	Dose-dependent[E] (exposure limits for 8 hours/day)
3	Cumulative toxicants	Dose-dependent[E] (exposure limits for 40 hours/week)
4	Both acute and cumulative	Dose-dependent[E] (exposure limits for 8 hours/day and/or 40 hours/week)

Notes:

A These categories are taken directly from Table 6.7 in *Patty's Industrial Hygiene and Toxicology* (Cralley and Cralley, 1985).

B For release durations less than 15 minutes, concentrations may be calculated over a shorter time period but for not less than 1 minute if the chemical is known to exert immediate toxic effects.

C Permissible exposure limits (PELs) for substances in this category have been set (by the U.S. Department of Labor Occupational Safety and Health Administration) either by technological feasibility or good hygiene practices. No adjustments should be made based on the length of exposure; that is, these PELs are treated as ceiling limits (see reference in Note A).

D For concentration-dependent chemicals, the concentration at the receptor point of interest is calculated as the peak 15-minute time-weighted average (TWA) concentration.

E For dose-dependent chemicals, the concentration at the receptor point of interest may be calculated as the peak 60-minute TWA concentration.

4.5. In performing summations, irritants are a special case. Irritants may be denoted as severe (HCN = 14.00), moderate (HCN = 15.00), or mild (HCN = 16.00). These are added together and weighted by severity (i.e., multiplied by 1.0 for severe, 0.5 for moderate, 0.25 for mild). Irritants that affect only one target organ also can be considered separately. For example, irritants affecting only the eyes are indicated by HCN = 14.01, 15.01, and 16.01; and irritants affecting only the skin are indicated by HCN = 14.02, 15.02; and 16.02.

The CMM Workbook carries out computations for all chemicals that have HCN and PAC values listed in the *HCN-PAC* worksheet. If a chemical is not listed in the *HCN-PAC*

worksheet, it may be added in the row after the last chemical on the list. The user will have to supply applicable HCNs and PACs for such chemicals.

STEP 5. Examine Workbook Calculations.

The *Output* worksheet presents summary information on the HIs computed by the workbook. This information includes

- the Individual HIs for each chemical in the mixture
- the Sum of all HIs for all the chemicals in the mixture
- the Sum of the Toxic Mode or Endpoint HIs (i.e., summation for all the chemicals in the mixture of the HIs for each key HCN category)
- the Sum of Target Organ HIs category (i.e., summation for all the chemicals in the mixture of the HIs for each key target organ category).

If the sum of all HIs is less than or equal to 1.0, the exposure to the chemical mixture is within established emergency preparedness limits. If the sum of all HIs is greater than 1.0, the Sum of Toxic Mode or Endpoint HIs and Sum of Target-Organ HIs should be examined. If all the HI sums presented for the Toxic Mode or Endpoint are less than or equal to 1.0 **and** all the HI sums for the Target-Organ are less than or equal to 1.0, the exposure to the chemical mixture is within established limits.

The *Import, HIs by mode, and the HIs by target organ* worksheets provide supplementary information beyond what is summarized in the *Output* worksheet. The *Import* worksheet provides a convenient summary of key input information, HCN data, and HI results. The *HIs by mode* worksheet provides detailed HI results for each chemical and 16 HCN categories. The *HIs by target organ* worksheet provides detailed HI results for each chemical and up to 37 target organ or endpoint HCN categories.

The display of the CMM Workbook has been optimized for PCs at a zoom setting of 100%. Typical of the Excel workbook software, if a column is too narrow to display a cell's contents, the symbol ###### will appear in that cell. To remedy this problem on worksheets that have not been password-protected, the column width can be manually expanded to display the worksheet contents. On password-protected worksheets, the column width cannot be adjusted; however, increasing the zoom percentage (e.g., from 75% to 100%) should allow the worksheet contents to be displayed. If the problem persists or if the printout also shows ###### for some or all of the data, please send an email stating the problem to the CMM development team at PACDevelopment@listserv.orau.gov.

SECTION 4. CMM WORKSHEET DESCRIPTIONS

In this section, summary descriptions are provided of each of the CMM Workbook worksheets and for each worksheet column.

Worksheet 1 – *Input* (requires user input)
Chemical Compounds, Receptor Point, Concentration Limit, and Concentrations of Chemicals in the Mixture

Column	Heading	Information in the Column
A	No.	Sequential numbering of the chemicals in the mixture
B	Chemical Compound	Names of the chemicals in the mixture
C	CASRN	CASRNs of the chemicals in the mixture. Includes alternative Z number IDs for chemicals that do not have CASRNs. NOTE: It is suggested that the user copy the chemical name and CASRN for each chemical from the *HCN-PAC* worksheet and paste them into the *Input* worksheet to avoid entry errors.
D	Receptor Point (RP)	Receptor Point
E	Concentration Limit (Li) at RP (Enter "TEEL-0", "PAC-1", "PAC-2", or "PAC-3")	Concentration Limit at Receptor Point. This is the applicable PAC, provided in the form of a "TEEL-0" or "PAC-n" (minus the quotation marks); where n is 1, 2, or 3.
F	Conc. (C_i) at Receptor Point (mg/m^3)	Concentration at Receptor Point (in units of mg/m^3)

Note: The chemicals that initially appear in the *Input* worksheet are for illustrative purposes only. These data should be replaced with the user's chemicals.

Worksheet 2 – *Import* (calculations performed automatically)
HI Calculation and HCNs for Chemicals in Mixture

Column	Heading	Information in the Column
A	No.	Sequential numbering of the chemicals in the mixture
B	Chemical Compound	Names of the chemicals in the mixture
C	CASRN	CASRNs of the chemicals in the mixture. Includes alternative Z number IDs for chemicals that do not have CASRNs.
D	Conc. Limit PAC-n (mg/m^3)	Concentration Limit – a PAC (mg/m^3). This is the actual concentration limit value for the "TEEL-0" or "PAC-n" specified in the *Input* worksheet, Column E. The concentration limit value, in units of mg/m^3, is obtained from the *HCN-PAC* worksheet, Columns P, Q, R, or S for TEEL-0, PAC-1, PAC-2, or PAC-3, respectively.
E	Hazard Index (HI)	Hazard Index (HI), *Input* Column F divided by *Import* Column D
Health Code Numbers (HCNs)		
F	HCN-1	Column E from *HCN-PAC* worksheet – 1st listed HCN for the indicated chemical
G	HCN-2	Column F from *HCN-PAC* worksheet – 2nd listed HCN for the indicated chemical
H	HCN-3	Column G from *HCN-PAC* worksheet – 3rd listed HCN for the indicated chemical
I	HCN-4	Column H from *HCN-PAC* worksheet – 4th listed HCN for the indicated chemical
J	HCN-5	Column I from *HCN-PAC* worksheet – 5th listed HCN for the indicated chemical
K	HCN-6	Column J from *HCN-PAC* worksheet – 6th listed HCN for the indicated chemical
L	HCN-7	Column K from *HCN-PAC* worksheet – 7th listed HCN for the indicated chemical
M	HCN-8	Column L from *HCN-PAC* worksheet – 8th listed HCN for the indicated chemical
N	HCN-9	Column M from *HCN-PAC* worksheet – 9th listed HCN for the indicated chemical
O	HCN-10	Column N from *HCN-PAC* worksheet – 10th listed HCN for the indicated chemical
P	Category	Column O from *HCN-PAC* worksheet -- the concentration-limit classification used to determine whether the toxicological consequences of exposure to a chemical are concentration-dependent or dose-dependent. Other information is provided as well; see Table 1 for details.

Check to see if all of the HI values in Column E are less than or equal to 1.0. If the sum is less than or equal to 1.0, then the exposure is within established limits and there is no need to consult the next worksheet. Row 34 presents the Sum of the HIs for all chemicals in the mixture.

Worksheet 3 - *HIs by mode* (calculation performed automatically)
Summation of HIs by Mode of Toxic Action for Chemicals in Mixture

Column	Heading	Information in the Column
A	No.	Sequential numbering of the chemicals in the mixture
B	Chemical Compound	Names of the chemicals in the mixture
C	CASRN	CASRNs of the chemicals in the mixture. Includes alternative Z numbers for chemicals without CASRNs.
Hazard Indices (HIs) for Chemicals		
D	HCN = 1 or 2 Carcinogens	Cumulative HI for Carcinogens
E	HCN = 14, 15, or 16 Irritants	Computed HI for Irritants
F	HCN = 3 Chronic Systemic Toxins	Cumulative HI for Chronic Systemic Toxins
G	HCN = 4 Acute Systemic Toxins	Cumulative HI for Acute Systemic Toxins
H	HCN = 5 Reproductive Toxins	Cumulative HI for Reproductive Toxins
I	HCN = 6 Cholinesterase Toxins	Cumulative HI for Cholinesterase Toxins
J	HCN = 7 Nervous System Toxins	Cumulative HI for Nervous System Toxins
K	HCN = 8 Narcotics	Cumulative HI for Narcotics
L	HCN = 9 Respiratory Sensitizers	Cumulative HI for Respiratory Sensitizers
M	HCN = 10 Chronic Respiratory Toxins	Cumulative HI for Chronic Respiratory Toxins
N	HCN = 11 Acute Respiratory Toxins	Cumulative HI for Acute Respiratory Toxins
O	HCN = 12 Blood Toxins - Anemia	Cumulative HI for Blood Toxins - Anemia
P	HCN = 13 Blood Toxins - Methemoglobinemia	Cumulative HI for Blood Toxins - Methemoglobinemia
Q	HCN = 17 Asphyxiants	Cumulative HI for Asphyxiants
R	HCN = 18 Explosive, flammable safety	Cumulative HI for Explosive, flammable safety
S	HCN = 19, 20 Other & nuisance	Cumulative HI for Other & nuisance

All Sums of Toxic Mode or Endpoint-specific HIs are provided at the bottom of the worksheet (e.g., Row 34, Columns D through S). The sum of HIs for each toxic mode or endpoint-specific effect must be equal to or less than 1.0 to be within established limits. If not, individual HIs need to be examined to pinpoint the chemicals in the mixture that are contributing most to the sum(s).

Worksheet 4 – *HIs by target organ* (calculation performed automatically)

Summation of Hazard Indices by Target Organ for Chemicals in Mixture

Note: (C) = Chronic, (A) = Acute

Column	Heading	Information in the Column
A	No.	Sequential numbering of the chemicals in the mixture
B	Chemical Compound	Names of the chemicals in the mixture
C	CASRN	CASRNs of the chemicals in the mixture. Includes alternative Z numbers for chemicals without CASRNs.
Hazard Indices for Chemicals By Target Organ		
D	Carcinogens unspecified target organ (C)	Cumulative HI for HCN = 1.00, 2.00
E	Bladder cancer (C)	Cumulative HI for HCN = 1.01, 1.00, 2.00
F	Kidney cancer (C)	Cumulative HI for HCN = 2.01, 1.00, 2.00
G	Liver cancer (C)	Cumulative HI for HCN = 1.02, 2.02, 1.00, 2.00
H	Bladder toxin (C)	Cumulative HI for HCN = 3.01, 3.00
I	Bladder toxin (A)	Cumulative HI for HCN = 4.03, 4.00
J	Hematological system unspecified effects (C)	Cumulative HI for HCN = 3.02, 3.00
K	Hematological system unspecified effects (A)	Cumulative HI for HCN = 4.06, 4.00
L	Bone toxin (C)	Cumulative HI for HCN = 3.03, 3.00
M	Bone toxin (A)	Cumulative HI for HCN = 4.13, 4.00
N	Bone marrow toxin (C)	Cumulative HI for HCN = 3.04,3.00
O	Bone marrow toxin (A)	Cumulative HI for HCN = 4.04, 4.00
P	Brain toxin (C)	Cumulative HI for HCN = 3.05, 3.00
Q	Brain toxin (A)	Cumulative HI for HCN = 4.05, 4.00
R	Eye toxin (chronic ocular effects) (C)	Cumulative HI for HCN = 3.06, 3.00
S	Eye toxin (acute, other than irritation) (A)	Cumulative HI for HCN = 4.01, 4.00
T	Gastrointestinal tract toxin (C)	Cumulative HI for HCN = 3.07, 3.00
U	Gastrointestinal tract toxin (A)	Cumulative HI for HCN = 4.07, 4.00
V	Heart, Cardiovascular system toxin (C)	Cumulative HI for HCN = 3.08, 3.00
W	Heart, Cardiovascular system toxin (A)	Cumulative HI for HCN = 4.08, 4.00
X	Kidney toxin (C)	Cumulative HI for HCN = 3.09, 3.00
Y	Kidney toxin (A)	Cumulative HI for HCN = 4.09, 4.00

Column	Heading	Information in the Column
Z	Liver toxin (C)	Sum of HIs for HCN = 3.10 and 3.00
AA	Liver toxin (A)	Cumulative HI for HCN = 4.10, 4.00
AB	Skin toxin, incl. dermatitis & sensitization (C)	Cumulative HI for HCN = 3.11, 3.00
AC	Skin toxin, other than irritation (A)	Cumulative HI for HCN = 4.11, 4.00
AD	Skin perforation (C)	Cumulative HI for HCN = 3.12, 3.00
AE	Skin perforation (A)	Cumulative HI for HCN = 4.12, 4.00
AF	Nose toxin, other than irritation (A)	Cumulative HI for HCN = 4.02, 4.00
AG	Reproductive system toxin (C)	Cumulative HI for HCN = 5.10, 3.00
AH	Reproductive system toxin (A)	Cumulative HI for HCN = 5.00, 4.00
AI	Nervous system, including CNS, narcosis, cholinesterase toxin (A)	Cumulative HI for HCN = 7.00, 7.01, 8.00, 6.00, 4.00
AJ	Nervous system, including CNS (C)	Cumulative HI for HCN = 7.10, 7.11, 3.00
AK	Respiratory system toxin, including sensitizers (C)	Cumulative HI for HCN = 9.00, 10.00, 3.00
AL	Respiratory system toxin, including severe & moderate irritation (A)	Cumulative HI for HCN = 11.00, 11.01, 4.00
AM	Blood toxin, anemia (C)	Cumulative HI for HCN = 12.00, 3.02, 3.00
AN	Blood toxin, Methemoglobinemia and asphyxiants (A)	Cumulative HI for HCN = 13.00, 17.00, 4.06, 4.00

All Sums of Organ-specific HIs are provided at the bottom of the worksheet (e.g., Row 34, Columns D through AN). The sum of HIs for each toxic target-organ effect must be less than or equal to 1.0 to be within established limits. If not, individual HIs need to be examined to pinpoint the chemicals in the mixture that are contributing most to the sum(s).

Worksheet 5 – *Output* (calculations performed automatically)
Mixture Methodology Output Summary

Column	Heading	Information in the Column
A	No.	Sequential numbering of the chemicals in the mixture
B	Chemicals in mixture	Names of the chemicals in the mixture
C	Chemical CASRN	CASRNs of the chemicals in the mixture. Includes alternative Z numbers for chemicals without CASRNs.
D	Individual Hazard Index (HI)	Summation of HIs for each chemical in the mixture
E	Sum of all HIs	Summation of all HIs for all chemicals
F	--	*(Blank column)*
Sum of Toxic Mode or Endpoint HIs		
G	Mode or Endpoint	Key categories of HCNs for which HI sums are ≥0.25
H	HI sum ≥ 0.25	HI sums that are ≥ 0.25 are shown. Information is not provided for those categories of HCNS with HI sums < 0.25. Values ≥ 0.5 are displayed using a **bolded red** font.
Sum of Target-Organ HIs		
I	Target Organ	Target organs or which HI sums are ≥0.25
j	HI sum ≥ 0.25	HI sums that are ≥ 0.25 are shown. Information is not provided for those target organs with HI sums < 0.25. Values ≥ 0.5 are displayed using a **bolded red** font.

This worksheet summarizes information in worksheets 2, 3, and 4. If the Sum of all HIs is less than or equal to 1.0 (Column E), there is no need to consult the results contained further to the right in this worksheet. If the Sum of all HIs is greater than 1.0 (Column E), then the Sum of Toxic Mode or Endpoint HIs (Columns G and H) and Sum of Target-Organ HIs (Columns I and J) should be consulted. If all Toxic Mode or Endpoint HI sums (Column H) **and** all Target-Organ HI sums are less than or equal to 1.0 (Column J), then exposure is within established limits.

Columns H and J present HI sums equal to or greater than 0.25. This value was chosen because it captures HI sums that are potentially significant. Values equal to or greater than 0.5 are further highlighted in a **bold red** font because the 0.5 value is a generally accepted action level and is within a factor of two of exceeding the exposure limit.

Worksheet 6 – *HCN-PAC*[6] (used by the workbook as a look-up table only)
HCNs and PACs (mg/m^3)

Column	Heading	Information in the Column
A	No.	Sequential numbering of chemicals
B	Chemical Compound	Names of the chemicals. For a given chemical, if any of the PAC values are AEGLS, then the name is in **12 point font and bolded**. Similarly, if any of the PAC values are ERPGs, then the name is in 1**0 point font and bolded**. And finally, if any of the PAC values are TEELs, then the name is in 10 point font and non-bolded.
C	CAS Registry Number (CAS RN)	CASRNs for each chemical. Includes alternative Z numbers for chemicals without CASRNs. For a given chemical, if any of the PAC values are AEGLs, then the CASRN is in **12 point font and bolded**. Similarly, if any of the PAC values are ERPGs, then the CASRN is in **10 point font and bolded**. And finally, if any of the PAC values are TEELs, then the CASRN is in 10 point font and non-bolded.
D	Sax Number (Lewis Sr., 2004)	SAX number for each chemical
Health Code Numbers (HCNs) for PAC Rev. 26 Chemicals		
E	HCN-1	1st listed HCN for the indicated chemical
F	HCN-2	2nd listed HCN for the indicated chemical
G	HCN-3	3rd listed HCN for the indicated chemical
H	HCN-4	4th listed HCN for the indicated chemical
I	HCN-5	5th listed HCN for the indicated chemical
J	HCN-6	6th listed HCN for the indicated chemical
K	HCN-7	7th listed HCN for the indicated chemical
L	HCN-8	8th listed HCN for the indicated chemical
M	HCN-9	9th listed HCN for the indicated chemical
N	HCN-10	10th listed HCN for the indicated chemical
O	Category	This gives the concentration-limit classification used to determine whether the toxicological consequences of exposure to a chemical are concentration-dependent or dose-dependent. Other information is provided as well; see Table 1 for details.

[6] The HCN-PAC worksheet was called the HCN-TEEL worksheet in all versions of the workbook released prior to October 2007.

Column	Heading	Information in the Column
PAC Rev 26 values based on AEGLs, ERPGs, and TEELs (mg/m^3)		
P	TEEL-0	Values are provided for each of the four PAC categories based on the data provided in Rev 26 of the PAC data set. If a PAC value is an AEGL, then it is in **12 point font and bolded**. If a PAC value is an ERPG, then it is in **10 point font and bolded**. TEELs are in 10 point font, regular non-bolded.
Q	PAC-1	
R	PAC-2	
S	PAC-3	

All PAC and TEEL values are given in units of milligrams per cubic meter. Some of these values were expressed originally in parts per million and were converted to milligrams per cubic meter.

Data in this worksheet are copied from other sources of information. The *HCN-PAC* worksheet is not intended to be printed as part of the mixture methodology results printout.

This worksheet will be updated periodically as PACs and HCNs are developed for new chemicals or as PACs are otherwise changed or HCNs updated (see http://orise.orau.gov/emi/scapa/teels.htm for more information).

SECTION 5. REFERENCES

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 J, TE. 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 J, T. E. 2000. Derivation of temporary emergency exposure limits (TEELs). *Journal of Applied Toxicology* **20**:11-20.

DOE (U.S. Department of Energy). 2001. Nuclear Safety Management. *Federal Register*. Code of Federal Regulations, Part 830. 10 CFR Part 830. 66(7): 1810Washington, DC. p 1810-1824.

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

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.

Lewis, RJ. Sr. 2004. Sax's Dangerous Properties of Industrial Materials. 11th Edition, Volumes 1 -3. John Wiley & Sons.

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.

Yu X-Y, Petrocchi AJ, Craig DK, Glantz CS, Trott DM, Ciolek J, Lu P-Y, Bond J-A, Tuccinardi J, TE. 2010. Development and applications of the chemical mixture methodology. *J. Applied Toxicology* **30**: 513-524.