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**CONSEXPO**

A Program to estimate Consumer Product  
Exposure and Uptake

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General Inspectorate for Health Protection and Directorate of Food and Product Safety.

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## Summary

The program and the manual presented in this report allow for the exposure assessment of compounds contained in consumer products. The main similarity between consumer products is their diversity. Consumer products range from shoe polish to household detergents to pesticides against aphids. All these products may contain hazardous compounds, both as wanted, active compounds and as unwanted contaminants. Assessing the exposure to these compounds urges for steps beyond simply measuring the concentration in the product. Most products release their compounds while being used and the concentrations that are contacted by people differ from the concentrations in the product.

The present report provides a modeling approach based on simple exposure and uptake models. In order to cope with the diversity in consumer products, it is based on a general model framework that provides a general setting for widely differing exposure situations, and, secondly, it offers a number of predefined exposure and uptake models, which the users can link to build a complete exposure and uptake model. The starting points are the inhalatory, dermal and oral routes of exposure. For each of these routes, a limited number of models is available to model exposure and uptake. Of course, multiple routes of entry are defined by defining a model for more than one route. In some cases, the program automatically uses multiple routes of entry, for example in the case of airborne compounds, which can enter via the inhalatory, dermal and oral routes !

The program reports several important exposure variables, namely the per event concentration, the yearly averaged concentration, the fraction taken up, the amount taken up during a year (per route and summed) and the uptake per kilogram body weight per day.

The program also allows for stochastic parameters, in order to propagate the effects of variable and/or uncertain parameters to the final exposure and uptake estimates. If there are stochastic parameters, the resultant distributions can be displayed and studied.

## Samenvatting

Het programma en de handleiding die tesamen dit rapport vormen, geven de mogelijkheid om de blootstelling te schatten en te beoordelen van stoffen die uit consumentenproducten komen. De voornaamste overeenkomst tussen consumentenproducten is eigenlijk de enorme diversiteit. Zo kunnen consumentenproducten bestaan uit schoensmeer, uit huishoudzeppen of uit bladluisbestrijdingsmiddelen. Al deze producten bevatten potentieel schadelijke stoffen, soms als de actieve ingredient, soms als een toevallige contaminant. Bij het beoordelen van de blootstelling aan deze stoffen is het noodzakelijk meer informatie te hebben dan alleen de concentratie in het product zelf. Veel producten staan immers tijdens gebruik stoffen af of worden voor gebruik verdund.

Het rapport biedt een modelbenadering voor het schatten van de blootstelling, gebaseerd op relatief simpele blootstellings- en opnamemodellen. Om de diversiteit in consumentenproducten te kunnen hanteren, zijn deze modellen gebaseerd op een algemeen modelraamwerk waarin het mogelijk is blootstellings- en opnamemodellen te vangen die in een serie van situaties bruikbaar zijn. Ten tweede biedt het programma een groot aantal voorgedefinieerde blootstellings- en opnamemodelmodules, die door de gebruiker achter elkaar gezet kunnen worden. Het beginpunt van deze modellen is de route van blootstelling, te weten de inhalatoire, de dermale of de orale route. Meerdere blootstellingsroutes tegelijkertijd zijn ook mogelijk door voor meerdere routes een blootstellings- en opnamemodel te definiëren. In sommige gevallen past het programma automatisch blootstelling via meerdere routes toe, zoals bij blootstelling via de lucht. In principe kan dan blootstelling via de inhalatoire, dermale én orale route plaatsvinden.

Als resultaat van de berekeningen rapporteert het programma een aantal blootstellings- en opnamevariabelen. Dit zijn achtereenvolgens de blootstelling per gebeurtenis, de jaargemiddelde blootstelling, de opgenomen hoeveelheid per route, de gesommeerde opgenomen hoeveelheid en de opgenomen hoeveelheid per kilogram lichaamsgewicht per dag.

Daarnaast laat het programma stochastische parameters in de modellen toe. Deze hebben tot gevolg dat de resultaten geen puntwaarde zijn, maar een verdeling van waarden volgen. Deze verdeling kan getekend en bestudeerd worden.

# Chapter 1

## Introduction

Consumers daily use products for their personal convenience. Part of these products is food, but another part is used for all kinds of purposes. Exposure to the latter category of products is characterized by a large diversity in chemical composition and usage of products. To assess the exposure to these consumer products, Van Veen (in prep.) has developed a general model framework to include contact, exposure and uptake. In this framework, exposure is defined as the concentration of a chemical compound in the medium touching the body. For example, the exposure to an airborne pollutant is expressed in terms of  $\text{mg}/\text{m}^3$ , a concentration measure. Uptake includes both the intake rate of the medium and the uptake rate of the compound by the body.

The full general exposure and uptake model is represented by the following equation (Van Veen, in prep.):

$$U_c = \int_0^{\infty} P(t)U(E(x_p(t), t), t) dt$$

where  $U_c$  is the total uptake (mg),  $P(t)$  is the contact function,  $x_p(t)$  is the path of a person,  $E(x_p(t), t)$  is the exposure ( $\text{mg}/\text{cm}^3$ ) as a function of time and the path of a person, and  $U(E(x_p(t), t), t)$  is the uptake rate ( $\text{mg}/\text{min}$ ) as a function of exposure and time. For the inhalatory and the oral routes, the uptake rate  $U(E(x_p(t), t), t)$  can often be written as medium intake rate  $I_m$  times absorbed fraction  $F$  times exposure  $E$ :

$$U(E(x_p(t), t), t) = I_m(t)F(E(x_p, t))E(x_p, t).$$

More generally,  $E(x, t)$  and  $U(E(x, t), t)$  represent, respectively, the potential exposure and uptake, which are converted to their actual counterparts by specifying  $x_p(t)$  for the path of a person and  $P(t)$  for the period of contact. In the CONSEXPO program, however, the spatial dependence of exposure is not yet included. This simplifies the potential exposure to a function only depending on time:  $E(t)$ . This restriction implies that the path of a person is not implemented in the present program, but it will be in the future.

Of course, the user does not have to memorize these equations before the program can be used. The CONSEXPO program takes the burden from your shoulders and

implements the general consumer product exposure and uptake model. It allows the user to specify the contact, exposure, and uptake parts of the general model. Then, it integrates contact, exposure, and uptake to calculate the time courses of exposure and uptake. Predefined contact, exposure, and uptake scenarios are available in the program. The user can browse through the scenarios and select the scenario that fits the assessment problem best. After selecting a scenario, the user has to provide the parameters that define the scenario. By changing parameter values, the scenario can be fitted to the problem of the user.

The models formed by the program are screening models, no more, no less. They allow the risk assessor to estimate exposure and uptake, but the accuracy of the model results heavily depends on the accuracy of the model scenario parameters. In addition, the models themselves are simplified representations of reality and can not be expected to mimic reality in all aspects and every occasion.

The program has been and is being developed in the framework of an RIVM project to improve risk assessment for consumer products. It contains the algorithms proposed by Vermeire et al. (1993), which are included in the Technical Guidance Document of the European Union for the risk assessment of existing chemicals. The present program can be used to perform the calculations mentioned in the Guidance Document. Along with the progress in this project, the program is most likely to be extended in the future. The most eminent extension will be the formation and inclusion of a database containing information on products and use scenarios. The eventual goal is to let the user select a product or a product category from a predefined list, which the program will use to find default scenarios and scenario parameters in the database.

I would like to thank Henk Derks, Martin Olling, Theo Vermeire, Tjalling Jager, Jan van Eijkeren, Rolaf van Leeuwen, Wim Mennes, Henk Roelfzema, Peter Bragt and Wout Slob for the many useful discussions and the time they took to test the program and to report the errors. The program gradually emerged under their comments. Jan van Eijkeren provided me with help on implementation problems and has prepared the dermal "diffusion in product" scenario.

This software is provided "as is" without express or implied warranty. Send your comments, questions and bug reports to the author, e-mail: [bftvee@rivm.nl](mailto:bftvee@rivm.nl).

## Chapter 2

# Installation

The program is distributed on a floppy containing two files: `conexv10.exe` and `install.bat`. `Conexv10.exe` is a self extracting ARJ-archive. `Install.bat` is an MS-DOS shell script and automates the installation procedure. Check the system requirements below before you start the installation procedure. Then, put the floppy in drive `a:` and enter `a:install` on the MS-DOS command line. The archive will be unpacked into the directory `c:\CONSEXPO` on your hard disk.

### 2.1 System requirements

The following system requirements apply:

1. Intel based PC, with MS-DOS as the operating system,
2. MS-Windows 3.1 installed and working,
3. 1 megabyte of hard disk capacity.

The requirement that MS-Windows 3.1 is installed and working implies that your machine has a 80386 processor or up, that you have at least 4 Mb of internal memory and that the free space on the hard disk is at least 5 Mb.

A mathematical coprocessor is not mandatory, but highly recommended. Otherwise, some of the computations will last awfully long.

### 2.2 Manual installation

The install script unpackes the `CONSEXPO` program in the `c:\CONSEXPO` directory. If you want to put the program in a different directory, you will have to reside to manual installation. Copy the archive `conexv10.exe` to the directory in which you want to create a subdirectory `CONSEXPO`. Then, change directory to that subdirectory and type `conexv10 -y`. The `-y` assumes yes on each question. Now the archive is unpacked, automatically creating a subdirectory `CONSEXPO` with the program and its

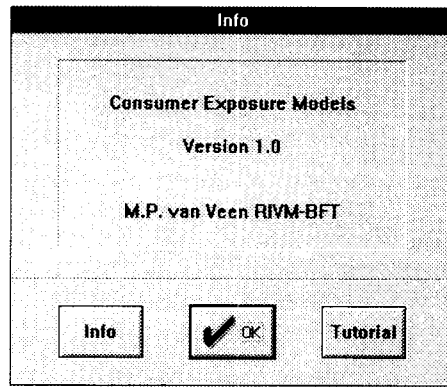


Figure 1. Opening dialog of the CONSEXPO program.

files. Be sure to include the path to the CONSEXPO program in the DOS PATH variable, otherwise the program is not able to find some of its files.

## 2.3 Installation problems

While running the installation script, a couple of problems can be encountered.

1. *Warning: you do not have a c:\windows subdirectory or it is incomplete.* This is a warning, installation will proceed, but be aware that if MS-Windows 3.1 is not installed on your system, CONSEXPO will not work.
2. *Directory c:\CONSEXPO exists, installation aborted!* There already is a c:\CONSEXPO directory, probably containing an earlier version of CONSEXPO. To prevent overwriting of files, the installation procedure is aborted. Copy all files from the CONSEXPO directory to a safe place (or delete them) and restart the installation script.
3. *Installation disk incomplete!* Contact the distributor of the program. There are files missing.
4. *Archive not unpacked!* For some reason, the archive was not unpacked. You can manually install the program as described in section 2.2.

## 2.4 Running the program

The program runs in the MS-Windows environment. First start MS-Windows, then start the file manager and start `c:\consexpo\consexpo.exe`. The program opens with a dialog that welcomes you and offers three buttons to choose from. The middle button, "Ok", will remove the welcome dialog to display the CONSEXPO program window. The other two buttons lead to information about the system. The "info" button shows an introduction to and general information about the system, such as its purpose, its author and acknowledgements. The "tutorial" button offers the possibility to guide you through a short tutorial. The tutorial explains the program in 6 steps. Novice users of the program ought to read the tutorial, otherwise the input of data and the retrieval of results remains somewhat of a mystery.

## Chapter 3

# Menu structure

The menu bar is displayed at the top of the CONSEXPO window (fig.2). It contains menu entries for handling files and for printing (*File*), for system wide settings (*System*), for getting help (*Help*) and for defining and analyzing an exposure and uptake model (*Report*, *Contact*, *Exposure*, *Uptake* and *Compound*). The latter entries are used to compose a full exposure and uptake model. The entries *Exposure* and *Uptake* are subdivided into the routes of exposure and uptake: the inhalatory, dermal and oral ones. The menu entry *Report* displays the results of calculations with the exposure and uptake model. If an incomplete model has been specified, many or all of these results will have the status "unknown".

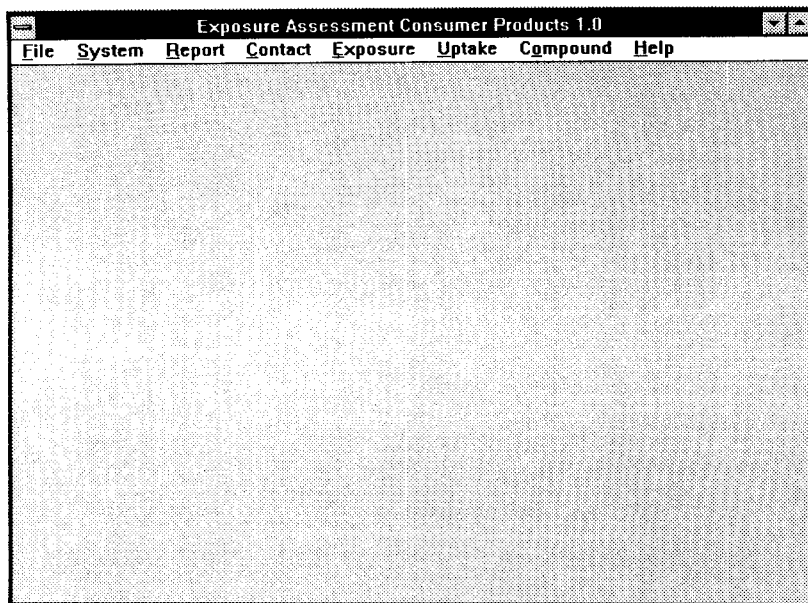


Figure 2. Workdesk of the CONSEXPO program.

Summarized, the menu bar contains eight main entries, which are explained in detail in the following sections:

**File** all commands concerning file handling and graphics printing, and the info and exit commands,

**System** all commands concerning the calculation routines as a whole,

**Report** all commands concerning the model results and the definition of models,

**Contact** all commands concerning contact,

**Exposure** all commands concerning exposure. It contains the routes contact, and for each route the appropriate exposure scenario can be selected,

**Uptake** all commands concerning uptake. It contains the routes of contact, and for each route the appropriate uptake model can be selected,

**Compound** all commands concerning the definition of the chemical compound of interest,

**Help** commands to display help information.

### 3.1 File menu

The *File* menu consists of the following entries:

**Info** displays general information about the program and enables the user to follow a short tutorial of the program.

**New** resets all parameter values and options in order to start a new risk assessment session.

**Open** opens a previously saved risk assessment session.

**Save** saves the present risk assessment session. If the session has not been named yet, a file name is requested.

**Save As** name the risk assessment session and save it.

**Print Graph** print the graph currently displayed on screen. It will be printed on the Windows standard printer.

**Printer Setup** change the settings of the standard printer. The type of printer can not be changed. Instead, use the Windows configuration utilities to change the standard printer.

**Exit** leave the program. All results will be lost unless saved.

## 3.2 System menu

The *System* menu is used to set some general model settings:

**Options** Displays a dialog box to set the number of bars of a histogram, the number of points that are calculated to compose a point graph, the number of Monte Carlo loops and the names of the text viewer and the calculator.

**Calculator** Shows a calculator which can be used to do additional calculations. The default calculator is the MS-Windows calculator, but it can be replaced by any other calculator in the Options entry. Replacement is highly recommended, because the MS-Windows calculator is not to be trusted. Try  $5.01 - 5$  and the answer will be 0.00 ! Therefore, the XCALC calculator, a freeware calculator, is included on disk. It is fast and accurate, but has the disadvantage that it is a polish stack calculator, such as the HP calculators.

**Units to Internal** Causes the units that have been set in the parameter dialog boxes to be recalculated to the units as used internally in the program. It is included to check parameter values that have been entered using a unit different from the default. Originally intended for debugging purposes, it appeared to be valuable in checking parameter values as well.

## 3.3 Report menu

The *Report* menu entry is used to view the results of the exposure and uptake model. There are four ways to view the results:

1. display the average or worst case value using point estimates,
2. display the distribution of the result,
3. display the time course of exposure or uptake, or,
4. print the results to a file in the form of a report.

### 3.3.1 Point estimates

If the entry Point is chosen, the results are given as a point estimate. The results are given in the form of a dialog, in which the values for the estimated exposure and uptake are shown (fig. 3). Depending on the choice made in the Exposure definition dialogs (which can be a choice for worst case or for average case calculations), this point estimate reflects the average or the worst case exposure. Which point estimate is shown is indicated to the right of the value, where WC=worst case and AC=average case. Initially, this sign reads NS=not set. Of course, if *ALL* parameters are point estimates, the worst case exposure is identical to the average case exposure. If multiple parameters have variation, the worst case estimation is cumulative worst case. Each

Report					
Routes					
	Exposure			Uptake [mg/year]	
Inhalation	6.00e-01	mg/m3	AC	6.21e-01	F
Dermal	6.00e-07	mg/cm3	NS	Unknown	D
Oral	Unknown	mg/cm3	NS	Unknown	NS
Integrated					
Year averaged exposure:			Uptake mg/year:		
1.37e-10 mg/cm3			6.21e-01		
			Uptake mg/kg/day:		
			2.43e-05		
Monte Carlo Percentiles					
		Print		Calculate	
				95	
OK		Help		Details	
				Uptake Fractions	

Figure 3. The point estimates report dialog. On the left the estimated exposures and on the right the estimated uptakes are shown. The top half of the dialog shows the route specific estimates, while in the lower half the integrated measures are shown.

parameter achieves its 95 percentile value and those values are used to calculate the worst case exposure and uptake results.

To circumvent the cumulative worst case estimates, the Monte Carlo Percentiles part in the dialog is used to calculate arbitrary percentiles from the eventual exposure and uptake distributions. It uses Monte Carlo sampling from the parameter distributions to achieve the exposure and uptake distributions and rounds the requested percentile to the nearest percentile available from the Monte Carlo sampling. The number of Monte Carlo samples is set in the *System* menu, using the *Options* entry. The accuracy of the percentiles can be increased by increasing the number of Monte Carlo samples. Using the Monte Carlo percentile, a worst case estimate can be calculated from the exposure and uptake distributions by selecting its 95 percentile (or any other percentile that is considered to be "worst case"). Thus, it is not based on a cumulative worst case situation, as is the case when selecting the Worst Case option in the exposure scenarios. Background information on this procedure and the method that is used for its calculation can be found in chapter 5.

The results in the uptake part are always based on the point estimates given in the exposure part. Depending on the uptake model, the amount taken up is based on a fraction model (sign right of value reads F), a flow model (sign reads P, available only for the inhalatory route) or a diffusion model (sign reads D). This choice is set in the uptake definition dialog boxes, which differ per route.

The lower entries give summary measures. On the left, the year averaged exposure is displayed. On the right, the integrated uptake is displayed, which is uptake summed

over all routes. The upper entry states uptake in mg/year. If the frequency of contact is once per year, this boils down to the uptake per event. The lower entry states uptake in mg/kg body weight/day, the toxicologists view of uptake. A year has 365.25 days, correcting for leap years.

In addition to the amount taken up, the absorbed fraction through the inhalatory, dermal and oral route can be inspected by choosing the "Uptake Fractions" button.

To inspect the exposure scenarios, uptake models, and their parameter values in more detail, the *Details* button is used. After choosing this button, details on the exposure and uptake estimates are displayed. These details consist of the contact scenario, the exposure scenario, the uptake model and the parameters used by the models. The worst case estimates given here reflect the cumulative worst case, not the Monte Carlo worst case estimates. The text viewer allows its contents to be printed. Quit the text viewer by choosing Exit from the file menu. The text viewer runs concurrent with CONSEXPO, so you can display the results of several scenario/model combinations in a number of text viewer sessions. The text viewer is the Notepad by default, but another text viewer can be set in the *Options* entry of the *System* menu. If you select a text viewer different from Notepad, then the use of that text viewer might deviate from the description in the above.

### 3.3.2 Distribution

If the Distribution entry is chosen, the Choose Graph dialog displays. This dialog allows you to display a single distribution from either the exposure or the uptake distributions. An exposure or uptake distribution appears if one or more parameters exhibit stochastic variation. The distributions are calculated and drawn for each route of exposure and entry separately. If all parameters are point estimates, if there are parameters with out of range values or if there are parameters with missing values, no graph will be shown.

The Choose Graph dialog is divided into an exposure and an uptake part, containing the choices for the distribution that will be shown. Only a single distribution can be displayed, so only one can be chosen from the list. After pressing the *Ok* button or pressing the *enter* key, the distribution of your choice is drawn on the screen. If, during the generation of the distribution, only one parameter appears to have variation, a point graph is composed, using direct calculations. If there are multiple parameters with variation, a Monte Carlo method is used. A histogram displays the results of Monte Carlo calculations. More information about the use and interpretation of these distributions is given in Chapter 5, Stochastic Parameters.

If the exposure or uptake model is changed after the graph is drawn, the results are **not** automatically updated on screen. The Distribution entry has to be chosen again to reflect the model changes in the graph. This way, you are allowed time to observe changes in exposure or uptake resulting from the model change. The number of bars in the histogram, the number of points in the graph and the number of Monte Carlo loops can be changed in the *Options* entry in the *System* menu.

### 3.3.3 Time plot

The *Time Plot* entry displays the exposure or uptake as a function of time. After choosing the entry, the Choose Time Plot dialog box will pop up, from which the time course of exposure or uptake to be displayed can be chosen. Of course, only exposures or uptakes which have been fully defined can be displayed. Investigating the time course of exposure or uptake is particularly useful for nonlinear exposure scenarios, such as the *inhalatory open can* scenario.

The time scale that will be used in the plot can be chosen from the lower part of the dialog. The time course of exposure or uptake can be given "per event" or "per year". If exposure or uptake is "per event", then the time course during a single exposure event is given. In this case, the dynamics of exposure or uptake during an exposure event can be studied, but information about the number of events is omitted. Viewing this time course is particularly recommended for scenarios which are nonlinear in time, such as the *open can* or *source and ventilation* scenarios of the inhalatory route and the *fixed amount* scenario of the dermal route.

If the exposure or uptake is "per year", then the number of events is also taken into account. In this case, the dynamics per event is hardly visible, due to the time scale. If uptake is plotted per year, the amount taken up is the total amount taken up during all exposure events. This is the amount entering the body. There is no toxicokinetic model beyond uptake, so this graph does not display anything about the body burden or internal concentrations. The plot will be shown after choosing the *Ok* button. To print the plot, choose the *Print Graph* option from the File menu while the graph is on screen.

### 3.3.4 Print report to file

The Print to File entry prints out a report to file. This report can be used as an appendix to exposure assessment reports and is essentially the same as the details that are shown in the *Point* entry.

### 3.3.5 Inspect models

The Inspect Models entry displays a summary of the scenarios and models that are defined in the program (fig. 4). In addition to the name of the scenario or model, the summary indicates if the parameters that are needed to calculate the scenario or model results are present. If one or more parameters are missing, the sign "Par. Missing" is displayed. If all parameters are known, the sign "Par. Known" is displayed. If no results are displayed at the report entries, the "Inspect Models" dialog is used to verify if models are set and if all parameters have been specified for those models.

## 3.4 Contact menu

The Contact menu entry specifies the contact part of the exposure and uptake model. It defines the function  $P(t)$  as defined in Van Veen (in prep.). It contains two subentries,

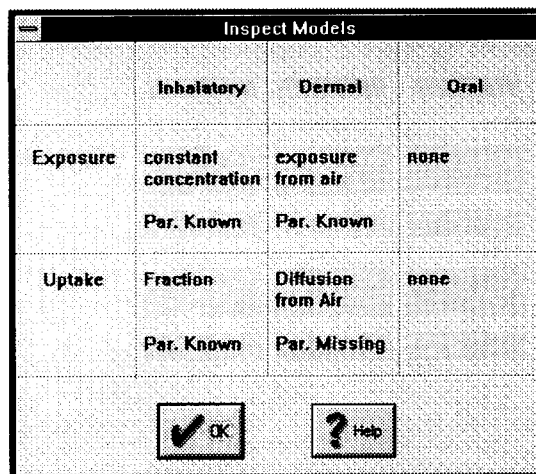


Figure 4. The “Inspect Models” dialog informs the user at any point in the program about the model scenarios that have been selected and if the parameters for the scenario’s have been set.

*Define* and *Human*. The *Define* entry is used to actually define the contact. The *Human* entry is used to specify the human body weight. The *Define* entry displays a dialog box, which allows you to choose a predefined contact scenario from a combobox, to read a contact scenario from file, and to define contact parameters.

### 3.5 Exposure menu

The Exposure menu entry defines the exposure part of the exposure and uptake model. Exposure is defined as the concentration of the chemical compound in the medium in contact with the body. It is the function  $E(x, t)$  as defined in Van Veen (in prep.). In the present version of the program, spatial differences in exposures are not allowed. Therefore, the exposure function reduces to a function depending only on time,  $E(t)$ .

The entry contains the routes of exposure as subentries. Choosing one of the routes displays a dialog box which allows you to set up the route, including the scenario of exposure and the parameters belonging to that scenario. If no scenario has been chosen and the scenario box displays "none", no parameters can be set and the "parameter" button does not react. It is possible to define exposure through multiple routes and the results of multi-route exposure will be shown in the Report menu entry.

### 3.6 Uptake menu

The Uptake menu entry defines the uptake part of the exposure and uptake model. Uptake is defined as both the intake rate of the medium and the uptake through the

body boundary. This is the function  $U(E(x, t), t)$  as defined in Van Veen (in prep). The entry has the routes of uptake as subentries. Choosing one of these routes displays an uptake definition dialog, which allows you to set up the uptake for that route. From the dialog box, the uptake model, the scenario of uptake, and the uptake parameters are chosen.

The uptake model can be a fraction model or a diffusion model. The fraction model calculates the uptake by means of the absorbed fraction. The diffusion model calculates the uptake by means of the two compartmental diffusional uptake model described in section 3 of Van Veen (in prep.). For inhalatory uptake a third model is available, the equilibrium flow model, as used by e.g. Ramsey and Andersen (1984) or McKone (1993). This model is based on equilibrium exchange in the lung.

### 3.7 Compound menu

The Compound menu entry is used to handle the parameters associated with the chemical compound of interest.

**Define:** define the compound parameters.

**Save:** save the parameters of the compound. Not only the molecular weight, octanol/water partition coefficient and the vapor pressure are saved, but also the dermal product/blood partition coefficient, the inhalatory air/blood partition coefficient and the inhalatory, dermal and oral permeabilities. If parameters has been assigned variation, the type and magnitude of the variation is also saved.

**Retrieve:** the parameter values saved in a file will be retrieved. This restores all compound associated parameters in the exposure and uptake model. To identify the compound which is retrieved from the file, the name of the compound is displayed in a message box.

### 3.8 Help menu

Accesses the help system of the program. The entry *Using Help* offers help to using the help system. The *Index* entry offers an index to the help, which might be useful if you want to browse through the help. The entries *Inhalatory*, *Dermal* and *Oral* explain the main routes of exposure and uptake, providing an overview of exposure and uptake models.

## Chapter 4

# Exposure and uptake routes

### 4.1 Contact

For all routes of exposure, the parameters to describe contact are frequency, duration of actual use, duration of contact and start of contact. The default values depend on the contact scenario that is selected. If no contact scenario is selected, i.e. scenario "none" is selected, the system defaults are displayed. The meaning of these parameters and the system defaults are defined as follows:

- Frequency: the frequency of use, in number of events per time interval. Default value: once per year, which implies that the report-point box shows the uptake resulting from a single contact.
- Total Duration: the total duration of contact per event. This duration is the time interval of contact, whether the product is actually used or not. Default value: 120 minutes. Status of default: guess. Range: duration of use- $\infty$ .
- Duration of use: the duration of actual use of the product per event. This is the time interval that the chemical compound is released from the product. Default value: 120 minutes. Status of default: guess. Range: As long as or shorter than Total Duration.
- Start: the start of contact relative to the onset of the exposure. This parameter is important when the exposure varies in time, for instance when the concentration is build up slowly. The start of contact defines which concentration is initially contacted. If the exposure is made up of a constant concentration, the start parameter is unimportant and should be 0. Default value: 0 minutes. Status of default: assumes that exposure does not change in time.

### 4.2 Inhalatory Route

Many products and the compounds therein reach our body via the air and enter the body via the inhalatory route. A simple example is a spray containing a volatile product.

After spraying the product, chemical compounds in the product fill the room and the inhaled air will contain these compounds.

The scenario's defined in the program are developed to describe exposure to consumer products. They do not adequately describe exposure to outdoor pollutants, for which day to day and hour to hour variations in the concentration are important in calculating the mean exposure.

#### 4.2.1 Contact

The contact with a compound is defined using the define subentry of the contact menu entry, see section 4.1.

#### 4.2.2 Exposure

To describe the inhalatory exposure, the program defines four exposure scenarios. The constant concentration scenario, the source and ventilation scenario, the pure substance scenario, and the open can scenario. Together, these scenario's allow for a wide range of situations.

*Constant Concentration.* In this scenario, the concentration in a single room is assumed to be constant. It is assumed that the amount of product that is released immediately fills the room and achieves an average concentration. This might be valid for volatile products with high diffusion rates. See Vermeire et al. (1993) for background information. The equation to calculate the exposure is

$$E = \frac{Aw_f}{V_r}$$

where  $A$  is the product amount released,  $w_f$  is the weight fraction of the compound in the product and  $V_r$  the volume of the room. The parameters are explained in further detail below.

*Code validation.* The computer code of the constant concentration scenario can be validated by entering the following parameter values: Amount released: 100 g, Weight fraction: 0.1, Room Volume: 10 m<sup>3</sup>. The concentration, as calculated by the program becomes 1000 mg/m<sup>3</sup> which is the same as 1000 mg/g \* 100 g \* 0.1 / 10 m<sup>3</sup>.

The parameters of the Constant Concentration scenario can be described as follows:

**Amount Released:** the amount of product released in the room. Default value: none. Range: 0-∞.

**Weight Fraction:** the weight fraction of the chemical compound in the product. Default value: none. Range: fraction from 0-1.

**Room Volume:** volume of the room in which the exposure occurs. Default value: 25 m<sup>3</sup>. Status of default: defines a room of 4 \* 2.5 \* 2.5 m<sup>3</sup>, which is a small room in Dutch social housing projects. Range: very small - ∞.

*Source and Ventilation.* This scenario describes a room where some source emits a chemical compound in the air, while the room is also ventilated with ambient air. The ambient air might be clean, but it also might contain the chemical compound of interest, emitted by other sources. This scenario generates exposures changing with time, making the contact start parameter (see contact menu entry) an important one. The formula is based on Sparks et al. (1994):

$$V_r \frac{dC}{dt} = S - Q_r(C - C_a) - eV_r C$$

where  $C$  is the exposure in the room,  $V_r$  is the room volume,  $S$  the generation rate of the compound,  $Q_r$  the effective ventilation rate,  $C_a$  the ambient air concentration and  $e$  the break down rate of the compound. This differential equation can be solved to give:

$$C = C_0 e^{-(e+Q_r/V_r)t} + \frac{S + Q_r C_a}{Q_r + eV_r} (1 - e^{-(e+Q_r/V_r)t})$$

*Code validation.* The computer code of the Source and Ventilation scenario can be validated by comparing the program results with a plot of the latter function by GNUPLOT (fig. 5), a simple function plotter.

The scenario is based on the following parameters:

**Generation Rate:** generation rate of the compound in weight per time released into the air. Default value: none. Range: 0-∞.

**Ventilation Rate:** amount of air that ventilates the room per unit of time. Default: none. Range: 0-∞.

**Ambient Concentration:** concentration of the compound that is released by the source in the ambient air which is used to ventilate the room. Default: none. Range: 0-∞.

**Break Down Rate:** the chemical break down rate of the compound in fraction per time unit. Default: none, a value of 0 would constitute a worst case situation. Range: 0-∞.

**Room Volume:** volume of the room in which the exposure occurs. Default value: 25 m<sup>3</sup>. Status of default: defines a room of 4 \* 2.5 \* 2.5 m<sup>3</sup>, which is a small room in Dutch social housing projects. Range: 0.001 - ∞, 0 not allowed.

*Pure Substance.* This scenario defines a situation in which a pure substance evaporates in a room. The evaporation rate depends on the difference in vapor pressure between the pure substance and the actual vapor pressure of the evaporated substance in air. Additionally, the room is ventilated with ambient air. Eventually, an equilibrium will be reached between the concentration in the substance and in air. This scenario is derived from Jayjock (1994). The scenario can only be calculated if the physicochemical properties of the compound are given in the *Compound* menu entry.

The equation given by Jayjock (1994) is slightly extended to incorporate initial concentrations which are not equal to 0:

$$C = C_0 e^{-\frac{K_t A + Q_r}{V_r} t} + \frac{1000 K_t M A P}{RT [K_t A + Q_r]} \left[ 1 - e^{-\frac{K_t A + Q_r}{V_r} t} \right]$$

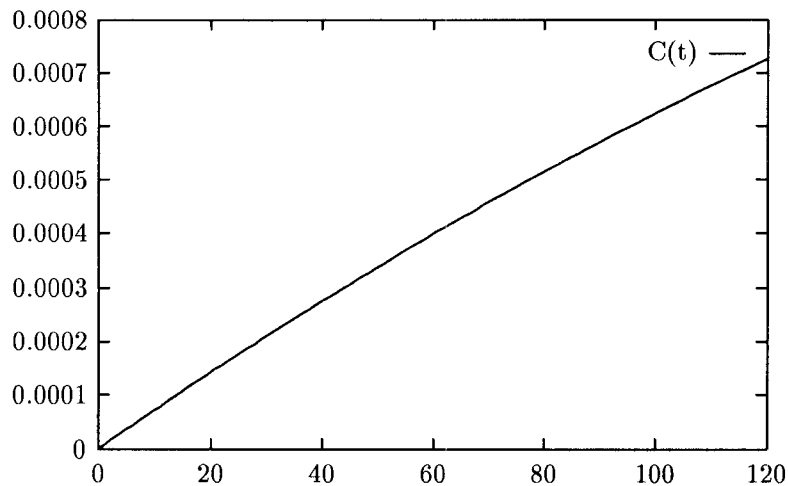
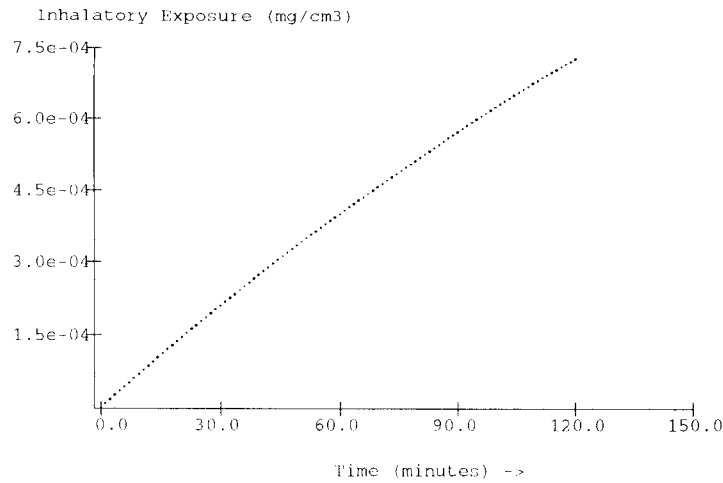


Figure 5. Validation of the source and ventilation scenario. A - result of the CONSEXPO program, B - result of the function plotted by GNUPLOT, units as in A. Parameters:  $V_r = 25 \text{ m}^3$ ,  $S = 100 \text{ mg/min}$ ,  $Q_r = 5 \text{ m}^3/\text{hour}$ ,  $C_a = 0.001 \text{ mg/cm}^3$ ,  $e = 0.000001 \text{ 1/min}$  and  $C_0 = 0$ .

where  $C_0$  the initial compound concentration in air,  $K_t$  a constant calculated from the molecular weight,  $A$  the area from which evaporation takes place,  $Q_r$  the effective ventilation rate,  $V_r$  the room volume,  $M$  the molecular weight,  $P$  the vapor pressure of the compound,  $R$  the universal gas constant, and  $T$  the absolute temperature.

*Code validation.* The code can be validated by comparing the time course with the figures presented by Jayjock (1994). Figure 6a displays the results of the CONSEXPO program, using propylene glycol (molecular weight 76.1 g/mole, vapor pressure 0.000175 atm) and the following parameters: release area:  $0.001 \text{ m}^2$ , room volume:  $27 \text{ m}^3$ , ventilation rate: 1 room volume air change per hour times a mixture coefficient  $0.3 = 0.3 * 27 = 8.1 \text{ m}^3/\text{hr}$ , and temperature: 25 C. Figure 6b shows the figure as given by Jayjock (1994), his figure 2.

Its parameters are:

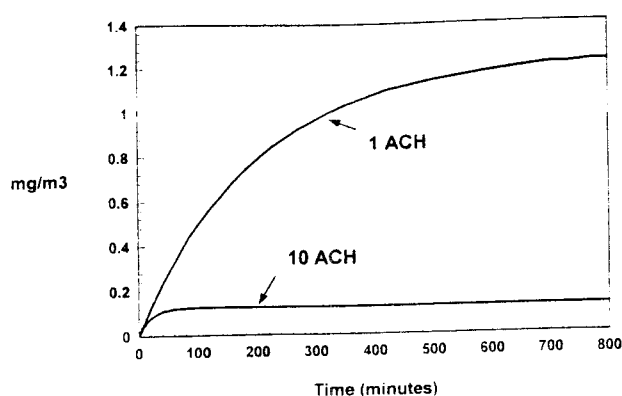
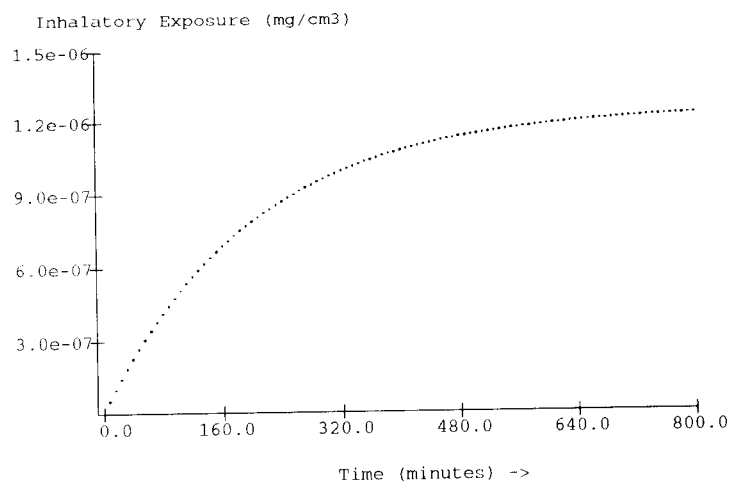


Figure 6. comparison of CONSEXPO-results and the results of Jayjock (1994). A - CONSEXPO results using the pure substance scenario, B - results published by Jayjock (1994), compare (A) with the line belonging to 1 ACH.

**Release Area:** the surface area of the canned product which is in contact with the air. Default value: 0.0025 m<sup>2</sup>. Status of default: guess, intended to described a small can. Range very small-∞.

**Temperature:** The temperature in the room. Default value: 298 kelvin = 25 Celsius. Status of default: rounded summer temperature in the Netherlands. Range: 0-∞.

**Room Volume:** volume of the room in which the exposure occurs. Default value: 25 m<sup>3</sup>. Status of default: defines a room of 4 \* 2.5 \* 2.5 m<sup>3</sup>, which is a small room in Dutch social housing projects. Range: 0.001 - ∞, 0 not allowed.

**Effective Ventilation Rate:** amount of air that ventilates the room per unit of time. Default: none. Range: 0-∞.

*Open Can.* This scenario defines a situation in which a can is left open in a room and compounds vaporize from the product inside the can. More generally it can be used for any mixture of chemicals from which a compound evaporates. The evaporation rate is driven by the difference of equilibrium vapor pressure and the actual vapor pressure

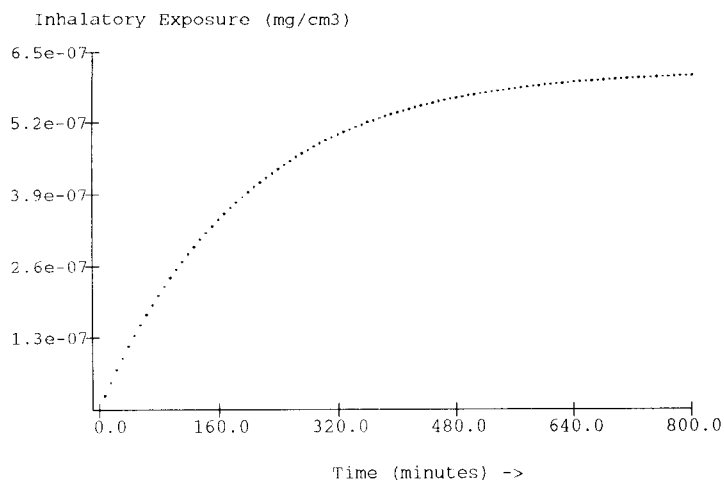


Figure 7. CONSEXPO result of the open can scenario, using the parameters from the pure substance scenario, extended with the values given in the text.

of the evaporated compound in air. The scenario is only valid for short periods of time, during which the concentration of the compound in the product hardly changes. The scenario will be expanded to a more general one in the future.

The room is ventilated with clean ambient air, and therefore the concentration of the compound in air will reach an equilibrium. This scenario is derived from Jayjock (1994), combined with Raoult's law. The open can scenario assumes that the product is a binary mixture, consisting of the chemical of interest and an "averaged chemical", replacing the other chemicals. The scenario can only be calculated when the properties of the compound are given in the the *Compound* menu entry.

The equation for the evaporation has already been given in the pure substance scenario. Raoult's law is expressed as:

$$P_{part} = \frac{X/M_x}{X/M_x + Y/M_y}$$

where  $P_{part}$  is the partial vapor pressure of compound  $x$  in the product,  $X$  is the concentration of the compound  $x$ ,  $M_x$  is the molecular weight of compound  $x$ ,  $Y$  is the concentration of the other compounds, and  $M_y$  is the average molecular weight of those compounds.

*Code validation.* The computer code can be validated by using propylene glycol and the same parameters as in the pure substance scenario, combined with the assumption that the compound of interest constitutes 50 % of the product and that the molecular weight of the other compounds is equal to the molecular weight of propylene glycol. The result should be exactly half of that of the pure substance scenario (fig. 6), which is the case (fig. 7).

Its parameters are:

**Release Area:** the surface area of the product which is in contact with the air. Default value: 0.0025 m<sup>2</sup>. Status of default: guess, intended to described a small can. Range very small-∞.

**Temperature:** The temperature in the room. Default value: 298 kelvin = 25 Celsius. Status of default: rounded average summer temperature in the Netherlands. Range: 0-∞.

**Room Volume:** volume of the room in which the exposure occurs. Default value: 25 m<sup>3</sup>. Status of default: defines a room of 4 \* 2.5 \* 2.5 m<sup>3</sup>, which is a small room in Dutch social housing projects. Range: 0.001 - ∞, 0 not allowed.

**Effective Ventilation Rate:** amount of air that ventilates the room per unit of time. Default: none. Range: 0-∞.

**Amount Product:** the amount of product inside the can. Default: none. Range: 0-∞.

**Weight Fraction:** the weight fraction of the compound in the product. Default: none. Range: 0-1.

**Molecular weight solvent:** the average molecular weight of the matrix which contains the chemical of interest. If this matrix is a combination of compounds, use the weighted average of the molecular weights, where each compound is weighted by its concentration in the matrix. Default: none. Range: very small – very large.

### 4.2.3 Uptake

To define the uptake of a compound in the lung, three models can be used, the fraction model, the equilibrium flow model and the diffusion model. Background information on the models is given in Van Veen, Olling and Vermeire (1994).

*Fraction Model.* The fraction model is based on the formula

$$U_c = T * Q_l * F * R * E$$

to calculate the total amount taken up  $U_c$ .

*Code validation.* Code validation is simple. If the fraction taken up is set at 0.75, then the program reports a fraction of 0.75 taken up in the *report-point* dialog.

The scenario contains the following parameters:

*T:* contact time (defined in the contact menu)

*Q<sub>l</sub>:* inhalation rate, the volume of air that passes the lungs in a certain amount of time. Default value: based on the body weight defined in the contact menu. If the body weight is not defined, there is no default value. Status of default: it is calculated using a formula proposed by Guyton (1947):  $Q_l = 460W^{0.7579}$  cm<sup>3</sup>/minute, where *W* is body weight in kg. Range: 0-∞.

*F:* absorbed fraction, i.e. that fraction of the total amount of the compound that is actually absorbed by the body. Default value: 1. Status of default: worst case situation, where there is total uptake. Range: 0-1.

*R:* respirable fraction, that fraction of the compound that enters the lung and is not deposited in the throat. the fraction 1-R is deposited in the throat and enters the oral route of uptake. Default value: 1. Status of default: It is a worst case assumption with regard to the inhalatory route. It is valid for gaseous compound which are hardly deposited. For aerosols, the value is too high and should be adjusted according to the mean droplet size.. Range: 0-1.

*E:* exposure, defined in the exposure-inhalation menu entry.

*Diffusion Model.* The diffusion model is based on the concentration difference between the lung air and lung blood (Van Veen, in prep.). The uptake rate is defined as:  $U = A_l P_l (C_l - K_{ab} C_b)$ , where  $U$  is the uptake rate,  $A_l$  the area of the lung wall,  $P_l$  the permeability of the lung wall,  $C_l$  the compound concentration in lung air,  $K_{ab}$  is the air/blood partition coefficient, and  $C_b$  the compound concentration in lung blood. The initial concentration in lung air is calculated from the concentration in the ambient air and the fraction of lung air that is refreshed per breath. That fraction is approximately 0.25 (Silbernagel and Despopoulos, 1993). The initial average concentration in the lung, just after inspiration, is then approximated by:

$$C_l(t = 0) = \frac{V_e + (1 - f)V_r}{V_e + V_r} C_a$$

where  $C_a$  is the ambient concentration,  $f$  is the fraction of the compound taken up during a breath,  $V_e$  is the expired amount of air,  $V_r$  is the residual volume in the lung, and  $V_l = V_e + V_r$ ,  $V_e = 0.25V_l$ ,  $V_l$  being the total volume of the lung.

During a breath, when the air inside the lung forms a compartment that is relatively closed from the outside, the concentration in lung air decreases as a function of uptake, whilst lung blood takes up the compound from the lung air and is continuously diluted by inflow of clean blood. The program calculates the amount of compound taken up from a single breath, and sums all these amounts taken up during the period of exposure.

*Code validation.* The code can be validated using an implementation of the differential equations (Appendix A; eq. 8 in Van Veen, in prep.) in SIMUSOLV (fig. 8). The result can be compared with the fraction taken up as calculated by CONSEXPO. Using an air/blood partition coefficient of 0.01, a blood flow of 6000 cm<sup>3</sup>/min, a blood volume of 750 cm<sup>3</sup>, a permeability of 0.1, an area of 60 m<sup>2</sup>, a volume of 2.5 liter, a dead space of 0, an inhalation rate of 10000 cm<sup>3</sup>/min, and a respirable fraction of 1, the fraction taken up as predicted by CONSEXPO becomes 0.77. The fraction calculated by the SIMUSOLV implementation is: 0.77 (estimating the duration of a breath as  $V_e/Q_i = 0.0625$  min., fig. 8).

It is based on the following parameters:

**Air/Blood Partition Coefficient:** The ratio between the equilibrium concentration of the compound in air and in blood:  $PC = C_a/C_b$ . Default value: none. Range: 0-∞.

**Blood Flow:** The flow of blood through the lungs. Default value: 6000 cm<sup>3</sup>/min. Status of default: it is the cardiac output of an adult. Range: 0-∞.

**Blood Volume:** The volume of blood that is present in the lungs. Default value: 750 cm<sup>3</sup>. Status of default: guess. Range: 0-∞.

**Lung Wall Permeability:** permeability of the wall between the lung air and the lung blood, predominantly the permeability of the alveolar wall. Default value: none. Range: 0-∞.

**Lung Area:** Area of the contact surface between lung air and blood. Default value: 600000 cm<sup>2</sup> = 60 m<sup>2</sup>. Status of default: literature value for adult. Range: 0-∞.

**Lung Volume:** total volume of the lung. Default: 2500 cm<sup>3</sup> = 2.5 liter. Status of Default: approximated from Silbernagl and Despopoulos (1993). Range: 0-∞.

**Dead Space:** fraction of lung air that is not involved with air/blood exchange. Default value: 0.2. Status of default: guess. Range 0-1.

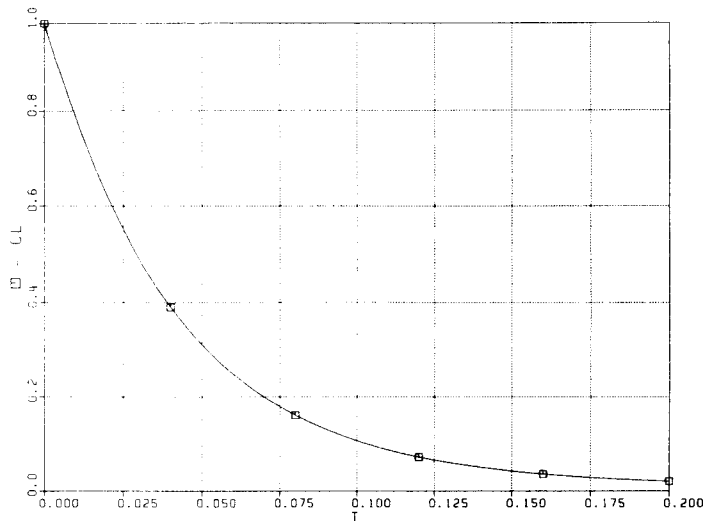


Figure 8. Time course of the two compartment diffusion model describing uptake in the lung using the SIMUSOLV implementation. For parameter values, see text.

**Inhalation Rate:** the volume of air that passes the lungs in a certain amount of time. Default value: based on the body weight defined in the contact menu. If the body weight is not defined, there is no default value. Status of default: it is calculated using a formula proposed by Guyton (1947):  $Q = 460W^{0.7579}$  cm<sup>3</sup>/minute, where  $W$  is body weight in kg. Range: 0-∞.

**Respirable Fraction:** that fraction of the compound that enters the lung and is not deposited in the throat. the fraction 1-R is deposited in the throat and enters the oral route of uptake. Default value: 1. Status of default: It is a worst case assumption with regard to the inhalatory route. It is valid for gaseous compound which are hardly deposited. For aerosols, the value is too high and should be adjusted according to the mean droplet size. Range: 0-1.

*Flow Model.* The flow model is based on equilibrium exchange between a compound in the lung air and the lung blood. This involves the air/blood partition coefficient and the blood flow as transport determining parameters. The permeability of the lung wall  $P_l$  is assumed to be very large, such that passage of the lung wall is by far not the rate limiting step. It is also assumed that there is no body burden of the compound, resulting in clean venous blood with a zero compound concentration. This assumption will overestimate the amount taken up. The model is used and described by e.g. Ramsey and Anderson (1984). It expresses the fraction taken up as:

$$F = \frac{K_{ba}}{(K_{ba} + Q_l/Q_b)}$$

where  $K_{ba}$  the blood/air partition coefficient,  $Q_l$  the inhalation rate and  $Q_b$  the blood flow through the lung.

*Code validation.* The fraction taken up can be calculated from the equation given in the above. Assuming a blood/air partition coefficient of 10, a blood flow rate of 6000 cm<sup>3</sup>/minute and a inhalation rate of 10000 cm<sup>3</sup>/min, the fraction taken up becomes

0.857, equal to the fraction calculated by the CONSEXPO program in the *point* entry of the *report* menu.

The parameters of the model are a subset of the parameters used in the diffusion model. Therefore, no separate input dialog has been made. Simply neglect the blood volume, lung volume, lung area, death space and permeability parameters of the diffusion model. The parameters of the flow model are:

**Air/Blood Partition Coefficient:** The ratio between the equilibrium concentration of the compound in air and in blood:  $PC = Ca/Cb$ . Default value: none. Range: 0-∞.

**Blood Flow:** The flow of blood through the lungs. Default value: 6000 cm<sup>3</sup>/min. Status of default: it is the cardiac output of an adult. Range: 0-∞.

**Inhalation Rate:** the volume of air that passes the lungs in a certain amount of time. Default value: based on the body weight defined in the contact menu. If the body weight is not defined, there is no default value. Status of default: it is calculated using a formula proposed by Guyton (1947):  $Q = 460W^{0.7579}$ , where  $W$  is body weight in kg. Range: 0-∞.

**Respirable Fraction:** that fraction of the compound that enters the lung and is not deposited in the throat. the fraction 1-R is deposited in the throat and enters the oral route of uptake. Default value: 1. Status of default: It is a worst case assumption with regard to the inhalatory route. It is valid for gaseous compound which are hardly deposited. For aerosols, the value is too high and should be adjusted according to the mean droplet size. Range: 0-1.

## 4.3 Dermal route

Dermal contact with consumer products occurs when we handle things, when we spill fluids or when we contact products dissolved in water. Compounds from the product will pass the skin and enter the blood. Dermal exposure also occurs concurrently with inhalatory exposure because our skin is always exposed to air. Therefore, setting inhalatory exposure automatically sets a dermal exposure of the same magnitude. Uptake from exposure to volatile compounds can only be calculated using the diffusion model of uptake.

### 4.3.1 Contact

Dermal contact with products is defined in the *Contact* menu entry, see section 4.1.

### 4.3.2 Exposure

There are two exposure scenarios defined, which essentially differ in the way the distribution of a chemical compound inside the product is handled. The "Fixed Volume" scenario assumes that the product is well mixed, such that no diffusion gradients can occur. The name of the scenario refers to a second assumption, namely that the volume of product is constant during the time interval of exposure. The "Diffusion in Product" scenario assumes that the product is not mixed at all, and transport of a chemical compound takes place by means of diffusion. Then, a concentration gradient of the

chemical will be formed inside the product. Therefore, these scenarios describe two extremes with regard to assumptions about transport inside the product.

Initially, the exposure scenario "None" is displayed, denoting that no dermal exposure is present.

*Fixed Volume.* The fixed volume scenario describes uptake from a fixed volume of product that contacts a certain area of skin. This fixed volume can be either a small volume that is spilled on the skin, or a large volume, contacted for example during dish washing. The finite volume of the product sets the maximal amount of compound that can be taken up to the total amount present in the product. The scenario assumes that the product is well mixed, and gradients inside the product do not occur.

The exposure is given by:

$$C = \frac{Aw_f}{DV_p}$$

where  $A$  is the amount of product,  $w_f$  is the weight fraction,  $D$  is the dilution and  $V_p$  is the product volume.

*Code validation.* The concentration of a compound in a product can be calculated using an amount of 1 gram, a volume of 1 cm<sup>3</sup>, a weight fraction of 0.25 and a dilution of 2. The concentration becomes 125 mg/cm<sup>3</sup>, which is equal to the concentration reported by the program in the point entry of the report menu.

The parameters to describe this scenario are:

**Amount of Product:** the weight of the undiluted product that contacts the skin. Default value: none. Range: 0-∞.

**Volume of Product:** the volume of the product that contacts the skin. If the dilution factor, see below, is set to 1, then this volume reflects the volume that is contacted. If the dilution factor is set to some other value, this volume reflects the volume in which the product was contained before dilution. Default: none. Range: 0.001-∞, 0 not allowed.

**Weight Fraction:** the weight fraction of the chemical compound in the product. If the product is diluted before use, the weight fraction in the original product is used and the dilution factor is set. If you fill in the weight fraction in the diluted product, set the dilution to 1 to indicate that no further dilution takes place. Default: none. Range: a fraction between 0 and 1.

**Dilution:** the dilution factor after the weight fraction of the chemical in the product has been established. If the weight fraction is the weight fraction in the diluted product, please set the dilution to 1. If the weight fraction is determined before the product is diluted, set the dilution to the number of times that the product is diluted. This will occur in assessing products like dish washing or all purpose detergents. The dilution is expressed in the number of times that a product has been diluted. Default value: 1.0. Status of default: implies no dilution. Range: very small to ∞, 0 not allowed. Values below 1 imply concentration of the product, values above 1 dilution.

*Diffusion in Product.* The "Diffusion in Product" scenario describes dermal exposure to and uptake from products for which the diffusion gradient in the product can not be neglected. This will often be the case for solid products and for liquid products with a high viscosity. In these cases, one has to model the gradient inside the product

to be able to calculate the uptake. The diffusion model is developed in Van Eijkeren (in prep.). The present model also takes the possibility into account that evaporation of the chemical compound decreases the exposure.

The diffusion gradient inside the product is described by:

$$\frac{\partial C_p(x, t)}{\partial t} = D \frac{\partial^2}{\partial x^2} C_p(x, t)$$

where  $D$  is the diffusion coefficient of the compound inside the product and  $C_p(x, t)$  is the compound concentration at depth  $x$  and time  $t$ . The border between product and skin defines  $x = 0$ .

At the product–air border, the loss of material from the product is proportional to the concentration difference between the surface of the product and air

$$\phi_{air} = K_l(C(H, t) - C_a(t))$$

where  $\phi_{air}$  is the evaporation rate to air,  $K_l$  is the exchange coefficient,  $C(H, t)$  is the compound concentration in the product at the borderlayer, and  $C_a(t)$  is the air concentration. Momentarily, the air concentration is supposed to be zero.

At the product–skin border, the uptake is governed by the concentration difference between product and skin blood, the skin itself acting as a resistance between product and blood

$$\phi_{skin} = P_d(C(0, t) - K_{pb}C_b(t))$$

where  $\phi_{skin}$  is the dermal uptake rate,  $P_d$  is the dermal permeability,  $C(0, t)$  is the concentration in product at the skin border,  $K_{pb}$  is the product/skin partition coefficient, and  $C_b(t)$  is the dermal blood concentration.

The equations are numerically solved using a second order Runge–Kutta algorithm. In order to use this algorithm, the user has to provide the number of segments into which the product is divided during the calculations. The default of 10 segments will do in most circumstances.

By modeling the diffusion gradient inside the product explicitly, while modeling the skin simply as a resistance, one implies that the permeability of the skin for the compound is much larger than the permeability of the product for the compound. If not, the compound is more slowly transported by the skin and concentration gradients inside the product are of less importance.

*Code validation.* The code in the CONSEXPO program was validated by comparing its results with the FORTRAN program of Van Eijkeren (in prep.), see fig. 9.

The parameters in the scenario are:

**Concentration compound:** The concentration of the chemical compound in the product. Default: none. Range: 0 -  $\infty$ .

**Diffusion product:** The diffusion rate of the chemical compound in the product. Default: none. Range: 0 -  $\infty$ .

**Evaporation rate constant:** The exchange coefficient between product and air. It can be calculated by measuring the evaporation rate in weight per time, and dividing this value by concentration times exposed area. Default: none. Range: 0 -  $\infty$ .

t (min.)	CONSEXPO uptake (mg)	FORTTRAN uptake (mg)
1	91.503	91.503
5	335.85	335.85
10	498.31	498.31
15	597.43	597.43
20	670.96	670.96
25	732.37	732.37
30	786.86	786.36
35	836.68	836.68
40	882.99	882.99
45	926.48	926.48

Figure 9. Comparison between the results calculated by CONSEXPO and the results calculated by the FORTRAN program of J. van Eijkeren. The parameters in both programs were: product diffusion: 1 cm<sup>2</sup>/min, product thickness: 55 cm, evaporation rate: 0.1 cm/min, skin permeability: 1 cm/min, partition coefficient product blood: 1, exposed area: 100 cm<sup>2</sup>, blood volume: 5500 cm<sup>3</sup>, blood flow: 360000 cm<sup>3</sup>/min, number of product segments in calculation: 10, concentration compound at start: 1 mg/cm<sup>3</sup>.

**Thickness product:** The thickness of the layer of product, measured perpendicular to the skin.  
Default: none. Range: very small - ∞.

**Product segments:** A parameter specifying into how many segments the product is divided by the numerical routine. If this number is very low, the gradient in the product is approximated by a few segments and the calculations can be inaccurate. Setting a very large number, however, slows down the calculations considerably. A number in between 10 and 50 will do for most products. Default: 10. Status of default: Allows for quick calculations, which are not very inaccurate. Range: Do not use values beyond 5 – 50.

### 4.3.3 Uptake

Two models can be used to describe the uptake of a compound from the product, the fraction model and the diffusion model. The fraction model is a simple model, when knowledge about the product is scarce. The diffusion model is a more advanced model, which uses the concentration difference between the product and the blood in the skin (see appendix A). The uptake is proportional to this concentration difference, with the skin permeability as the proportionality coefficient. In case of exposure to gases or vapours, the diffusion equation is simplified by assuming that the blood concentration of the compound is negligible. In the latter case, the uptake rate is proportional to the concentration of the compound in air.

The skin permeability can be estimated by empirical formula's which use the  $K_{ow}$  and the molecular weight to predict permeability. Four of these empirical formula's have been implemented in the program, those from Fiserova-Bergerova et al. (1990), Guy and Potts (1992), McKone and Howd (1992), and Robinson (pers. comm.). The equations for the dermal permeability  $P_d$  are derived from the octanol/water partition coefficient  $K_{ow}$  and the molecular weight  $MW$ :

- Fiserova-Bergerova (1990):

$$P_d = \frac{1}{15}(0.038 + 0.153K_{ow})e^{-0.016MW} \text{ cm/hr.}$$

- Guy and Potts (1992)

$$P_d = 0.0018 K_{ow}^{0.71} e^{-0.014MW} \text{ cm/hr.}$$

- McKone and Howd (1992)

$$P_d = MW^{-0.6} \left( 0.33 + \frac{h}{0.0000024 + 0.00003 K_{ow}^{0.8}} \right)^{-1} \text{ cm/hr,}$$

where  $h$  is the thickness of skin, taken to be 0.0025 cm.

- Robinson (pers. comm.)

$$P_d = \frac{1}{1/(P_{sc} + P_{pol}) + 1/P_{aq} + 1/P_{cap}} \text{ cm/hr,}$$

$$P_{pol} = 10^{-6} \frac{300}{MW^{0.5}},$$

$$\log P_{sc} = -2.74 + 0.62 \log K_{ow} - 0.0054MW,$$

$$P_{aq} = 0.15 \frac{300}{MW^{0.5}},$$

$$P_{cap} = 0.93(1 - e^{-P_{cw}A/F}) \approx 0.93,$$

where  $P_{sc}$  is the permeability of the, hydrophobic, stratum corneum,  $P_{pol}$  is the permeability of the hydrophilic (or polar) pathway through the stratum corneum,  $P_{aq}$  is the permeability of the epidermis,  $P_{cap}$  is the permeability of the capillaries,  $P_{cw}$  is the permeability of the capillary wall,  $A$  is the surface area of capillary wall and  $F$  is the capillary blood flow.

Ten Berge (pers. comm.) evaluated these empirical equations against measured permeabilities and reported that they predict the dermal permeability within approximately an order of magnitude.

*Fraction Model.* The fraction model uses the equation

$$U_t = V * E * F$$

to calculate the total amount  $U_t$  taken up.

*Code validation.* Validation is done by setting a fraction taken up of 0.75 in the parameter dialog. The point entry of the report menu reports a fraction taken up of 0.75.

The definition of the parameters is:

**V:** volume of product. Defined in one of the exposure scenarios.

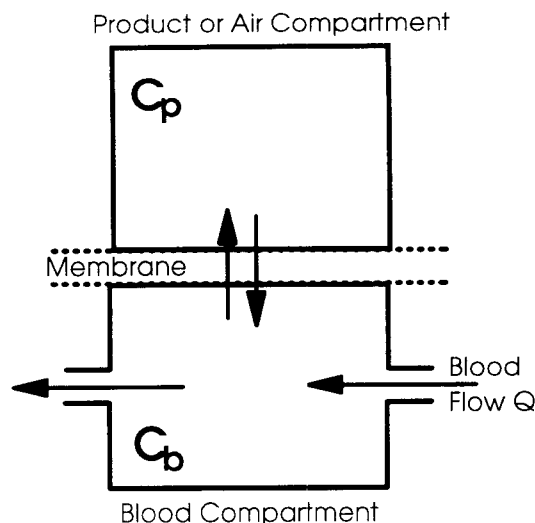


Figure 10. Schematic representation of the dermal diffusional uptake model. Diffusional transport between the product and the blood compartment defines the uptake rate. The skin is modeled as a membrane with a resistance. This overall resistance is derived from the resistances of the separate components of the skin, the stratum corneum, the epidermis and the dermis.

**E:** exposure. Defined with the dermal exposure menu entry.

**F:** absorbed fraction. Fraction of the total amount of compound that is taken up by the body.  
Default value: 1.0. Status of default: worst case assumption. Range: 0-1.

*Diffusion Model.* The diffusion model is based on the concentration difference between the product and skin blood (see appendix A, Van Veen, in prep.). The uptake rate is defined as  $U = A_d P_d (C_a - K_{pb} C_b)$ , where  $U$  is the uptake rate,  $A_d$  the area of dermal contact,  $P_d$  the dermal permeability,  $K_{pb}$  is the product/blood partition coefficient,  $C_p$  the compound concentration in the product and  $C_b$  the compound concentration in blood. Figure 10 depicts a schematic representation of the model. During contact, the concentration in the product decreases as a function of uptake, while the blood is continuously diluted by inflow of clean blood.

In case of exposure to airborne compounds, the diffusion equation is simplified by assuming that the concentration in the blood compartment is negligible in comparison to the air concentration. In that case, the uptake rate is given by  $U = A_d P_d C_a$ .

*Code validation.* The model is the same as the model used to calculate diffusional inhalatory uptake. Therefore, the validation of that part is also a validation for the dermal model.

The parameters which are used in this model are the following:

**Exposed Area:** The skin area exposed to the product. Default value: 4340 cm<sup>2</sup>, unless the exposure parameter "product volume" has been defined. Status of default: 4340 cm<sup>3</sup> is the area of hands, underarm, face and neck, together forming the area that is not covered

by clothes in summer. For activities like dish washing, the surface of the hands is more appropriate. Skin surface areas are tabulated by Vermeire et al. (1993). For focal contacts, a much smaller area will be necessary and the default will be based on the product amount. If the product volume is defined, the exposed area is estimated as product volume divided by 10, assuming a layer of 1 mm on the skin. range: very small -  $\infty$ .

**Blood Volume at Area:** The volume of blood underneath the area of exposure. Default: depends on the exposed area. Status of default: A layer of 1 mm blood inside the skin is assumed and the blood volume is estimated from the exposed area by  $\text{area} * 0.1$ . Range: very small -  $\infty$ , but  $5000 \text{ cm}^3$  is the average blood volume of an adult.

**Skin Blood Flow:** the blood flow through the skin at the site of exposure. Default value: depends on the exposed area. Status of default: The default is estimated by assuming that the blood flow at the site of exposure is proportional to the area of exposure. The flow is estimated by  $2500 * \text{area} / 19400$ , where  $19400 \text{ cm}^2$  is the total body surface and  $2500 \text{ cm}^3/\text{min}$  is the total adult blood flow through the skin. Range: 0 -  $\infty$ , but  $6000 \text{ cm}^3/\text{min}$  is the cardiac output of adult.

**Partition Coefficient Product/Blood:** the partition coefficient is the ratio between the equilibrium concentrations in the product and in blood. In case of aeral exposure, product can also be air. Default value: none. If the product is dissolved in water a value of 1 is recommended because blood is also a solution in water. Range: very small -  $\infty$ .

**Permeability Skin:** a rate parameter which defines how fast the skin is passed. It can be estimated from the molecular weight and the octanol/water partition coefficient, both to be set in the *Compound* menu entry. The dermal uptake dialog allows for selecting an estimation equation for the permeability, or to set your "own value". The empirical equations to estimate the permeability have been discussed in the above. Default value: if molecular weight and octanol/water partition coefficient are known, the default is estimated from these parameters using the Potts and Guy equation. Otherwise there is no default. Status of default: an article on the estimations is being prepared by W. ten Berge and colleagues (DSM). Range: 0 -  $\infty$ .

## 4.4 Oral route

Oral exposure and uptake from consumer products will occur when products are swallowed. There are two main categories of products that enter the body this way. Firstly, there is accidental swallowing of products like toothpaste, which are used in or around the mouth. Secondly, droplets or dust in the air will be partly deposited in the throat during inhalation. This fraction will be swallowed after a while. The program is neither intended to estimate exposure to compounds in food (see e.g. Slob (1993) for an overview of food exposure estimation) nor to estimate the acute, local effects of corrosive or reactive products.

### 4.4.1 Contact

The contact part of the oral exposure and uptake model is defined in the Contact menu entry. Due to the definition of the oral models, the duration and start of the exposure are not used. As explained in Van Veen (in prep.), the duration of exposure is defined as the duration of swallowing (not the travel time in the gut!) and this parameter vanishes in the computations.

## 4.4.2 Exposure

There are two single exposure scenarios to describe oral exposure. The Single Ingestion scenario describes uptake resulting from ingestion of some amount of product. The Daily Intake scenario describes uptake on a more daily basis and uses measured exposure data. The default when starting the program is the scenario "None", which means that there is no oral exposure. If the respirable fraction, defined in inhalatory uptake, is smaller than 1, a part of the inhaled particles is swallowed, causing an oral exposure to be present in the reports.

*Single ingestion.* The scenario describes uptake from an amount of product that is swallowed. The compound is taken up from this limited amount, which sets the maximal amount of compound that can be taken up to the amount initially present in the product.

The concentration is given by:

$$C = \frac{Aw_f}{DV_p}$$

where  $A$  is the amount of product,  $w_f$  is the weight fraction,  $D$  is the dilution and  $V_p$  is the product volume.

*Code validation.* The code can be validated by entering the following parameter values in the program: amount of product: 1 gram, volume of product: 1 cm<sup>3</sup>, weight fraction: 0.25, dilution: 2. The exposure should be 125 mg/cm<sup>3</sup> according to these parameters, which is in accordance with the value reported by the program.

The parameters which describe this scenario are:

**Amount Product:** the amount of product that is swallowed. This is the amount that is actually swallowed, whether it is diluted or not. Default value: none. Range: 0–∞.

**Volume Product:** the volume of product that is swallowed. In case the dilution is set to 1, this is the actual volume that is swallowed. In case the dilution is set to some other value, it is the volume of the product before dilution.

Default: none. Range: 0.001–∞, 0 not allowed.

**Weight Fraction:** the weight fraction of the chemical compound in the product. If this weight fraction is determined before the product is used, the original weight fraction can be filled in, and the dilution has to be set to a value different from 1. If the weight fraction has been determined in the diluted product, the dilution has to be set to 1. Default: none. Range: 0–1.

**Dilution:** the dilution of the product before it was swallowed. This parameter is included in order to be able to use the original weight fraction of a compound in the product, while including pre-use dilution, diminishing the weight fraction. If the weight fraction has been determined in the diluted product, please set dilution to 1, to indicate that no further dilution takes place. The dilution is expressed as the number of times that the product has been diluted. Default value: 1.0. Status of default: implies no dilution. Range: very small to ∞, negative values and 0 not allowed. Values below 1 imply concentration of the product, values above 1 dilution.

*Daily Intake.* If a daily intake rate can be specified, together with measured data on the concentration of the chemical compound in the product, the daily intake scenario can be used. It sets the duration of intake to 1 day, and takes the contact frequency as the number of days during which ingestion occurs.

*Code validation.* The code can be validated by making an input file with concentrations given in mg/kg, with a known mean. Compare that mean with the average case given by CONSEXPO, correcting for the difference in dimension.

The parameters of the model are:

**Amount per day:** the amount of product ingested per day. The number of days that ingestion takes place is defined by the frequency variable in the contact-define menu. Default: none. range: small to large.

**Concentration:** the measured concentrations in the medium that is ingested. The concentrations are defined by means of an input file. The name of the file can be given in the edit box, or can be selected from a list after selecting the 'browse' button. The input file has to contain the measured concentrations and the dimension of the concentrations. Each line of the file may contain either of the following:

1. a dimension specifier, in the form of:  
dim:xx  
where xx is one of the following specifications: mg/kg, microg/kg, fraction, %.  
Please adhere literally to these specifiers. A dimension specifier is obligatory.
2. a concentration, which has to be a number starting on the beginning of the line.
3. a multiple of concentrations, to specify a concentration that occurs more than once. Its specification is:  
yy\*zz  
where yy is the number of occurrences and zz the concentration, eg 5\*10.3.
4. each line not starting with a number and not containing 'dim:' is considered to be a comment. If the very first line contains a comment, this comment is displayed in a message box while reading the file. This comment can be used for a general identifier of the file.

Example:

```
Example data
dim:mg/kg
3
5.7
4*2.1
10.6
more comments
20.4
```

#### 4.4.3 Uptake

Two models can be chosen to describe the uptake from the lumen of the gut into the blood, the fraction and the diffusion model. Because of the lack of available parameter

value estimates, active uptake is excluded from the models and only passive diffusion is considered in the diffusion model. There are two variants of the diffusion model, the mixing tank model and the complete radial mixing model. The choice between these variants is made in the uptake definition dialog.

*Fraction Model.* The fraction model uses the equation  $\text{Uptake} = V * E * F$  to calculate the amount taken up.

*Code validation.* The code can be validated by entering 0.75 for the oral fraction taken up in the program. The point entry of the report menu indeed displays a fraction taken up of 0.75.

The definition of the parameters is:

**V:** volume of product. Defined in one of the exposure scenarios.

**E:** exposure. Defined with the oral exposure menu entry.

**F:** absorbed fraction. Fraction of the ingested amount of compound that is taken up by the body. Please mark the difference between fraction taken up and bioavailability. In the latter case the first pass effect is included, which is not included in the fraction taken up. Default value: 1.0. Status of default: worst case assumption. Range: 0-1.

*Diffusion Model.* The diffusional uptake model of the intestinal tract is based on a tube model proposed by Sinko, Leesman and Amidon (1991). In this model, the intestine is described as a long tube. Two variants of the model can be used in the program: the complete radial mixing model and the mixing tank model.

The complete radial mixing model assumes that the product travels through the intestine and releases the compound radially into the wall of the gut. The mixing tank model assumes that the intestine is one well mixed compartment from which uptake occurs. Generally, the complete radial mixing model is a better approximation of the gut and tends to result in a larger fraction taken up.

Both models can be expressed in terms of an absorption number  $A_n$ :

$$A_n = \frac{LP_e}{Rv}$$

where  $L$  is the length of the gut,  $P_e$  is the overall permeability of the gut wall,  $R$  is the radius of the gut, and  $v$  is the mean axial fluid velocity in the gut. Using the assumptions for the mixing tank model, the fraction taken up is expressed as:

$$F = F_{migr} \frac{2A_n}{1 + 2A_n},$$

where  $F_{migr}$  is the fraction of the compound that migrates from the product to the lumen of the gut and becomes available for diffusion. If the assumptions for the complete radial mixing model are used, the fraction taken up is expressed as:

$$F = F_{migr}(1 - e^{-2A_n}).$$

*Code validation.* The code can be validated using the following parameter values to calculate the absorption number: length of gut: 400 cm, permeability of the gut wall:

0.1, radius of gut: 4 cm, and axial velocity of of the fluid in the gut: 1.67 cm/minute. The absorption number becomes 5.988. Using this absorption number and a fraction migrated to lumen of 1.0, the fraction taken up as predicted from the mixing tank model becomes 0.9229. For the complete radial mixing model, the fraction taken up becomes 0.99999. Both values are also calculated by the program in the point entry of the report menu.

Both models share their parameters, which are defined as follows:

**Permeability:** a rate constant which defines how fast the intestinal wall is permeated. Default value: none. Range: 0 -  $\infty$ .

**Migration to Lumen:** the fraction of the compound that migrates from the product inside the intestine to the contents of the intestine. This parameter is included to allow for matrix effects. Default value: 1.0. Status of default: the default value implies that the compound is fully available inside the intestine. It is a worst case assumption. Range: 0-1.

**Lumen Flow:** The velocity of the intestinal contents, defining the flow through the lumen of the intestine. Default value: 1.67 cm/min. Status of default: the default value is based on the assumption that an intestine with a length of 4 m is traveled in 4 hours. Range: 0 -  $\infty$ .

**Intestinal Blood Flow:** The flow rate of blood in the wall of the intestine. Default: 1500 cm<sup>3</sup>/min. Status of default: a value frequently encountered in pharmacokinetic literature. Range: 0 -  $\infty$ .

**Intestine Length:** The length of that part of the intestine where uptake takes place. Default value: 400 cm. Status of default: approximates the length of the small intestine in an adult, the small intestine being that part where uptake usually takes place. Range: 0 -  $\infty$ .

**Intestine Radius:** Radius of the small intestine. Default value: 2 cm. Status of default: guess. Range: 0 -  $\infty$ .

## **Chapter 5**

# **Stochastic parameters**

### **5.1 Introduction**

Parameters are seldom undisputed point values. Almost always they tend to be disputed and they tend to follow a distribution of values. How to cope with these uncertainties and variabilities? First, what is the difference between uncertainty and variability? Variability is the notion that a parameter might follow a distribution of values instead of being a single value. A good example is body weight, which varies across persons, although the weight of a particular person can be accurately measured. Uncertainty describes how sure we are about a certain value or distribution. Long series of measurements have led to a good understanding of the distribution of body weight, reducing uncertainty about the shape of the body weight distribution. Uncertainty is quantified by specifying a distribution around the most likely value or by specifying a distribution for the mean and standard deviation of the parameter distribution.

The CONSEXPO program allows each contact, exposure, and uptake parameter to assume a single stochastic distribution, to express both the variability and the uncertainty of a parameters. Therefore, it convolutes variability and uncertainty into one distribution. There are three distributions available at the moment, the normal, lognormal and uniform distribution.

The type of distribution that is chosen to represent a particular parameter distribution severely affects the eventual distributions of exposure and uptake. Therefore, the parameter distributions should as much as possible be based on measured data. If you guess the distribution of a parameter, then the distribution of the exposure or uptake will reflect this guess! Fortunately, more and more sources for parameter distributions become available, for example the exposure factors handbook of the AIHC (1994) and an increasing number of papers in Risk Analysis.

### **5.2 Worst case calculations**

A well known approach in worst case exposure assessment is to take worst case estimates of the model parameters and to perform the calculations with these worst case parameter

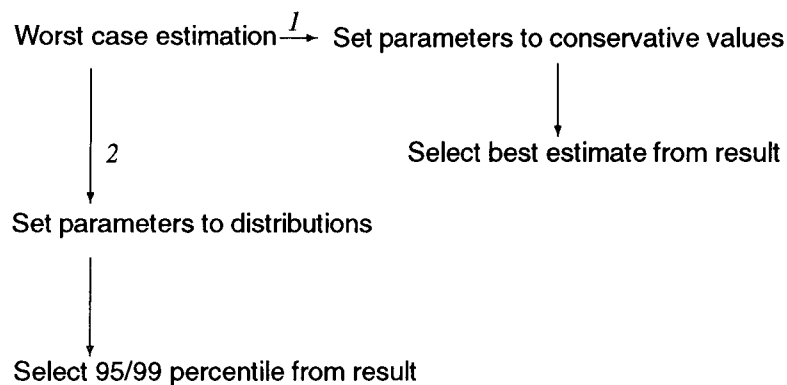


Figure 10. Routes for implementing a worst case approach. Route 1 implements the cumulative worst case, while route 2 selects the worst case from the eventual result distribution.

values (Fig. 10, route 1). In the program this route can be chosen by selecting the worst case option in the exposure definition dialogs, see section 3.3.1. The exposure and uptake estimates taken from these calculations are referred to as worst case estimates.

This approach has been given the nickname "cumulative worst case", because of a problem associated with the approach. Say there are two independent parameters, both having a distribution. If each of these parameters is set at its 95 percentile value, then the probability of exceeding that value is, per parameter, 0.05. However, the probability to simultaneously exceed the 95 percentile values of both parameters is  $0.05^2 = 0.0025$ , 0.25%, assuming the parameters are uncorrelated. For  $n$  independent parameters, this probability is  $0.05^n$ , a very small number if  $n$  is large. Thus, the combination of all parameters being at their 95 percentile values will seldom be met in the real world! A typical result is that "safe values" derived from such a cumulative worst case estimate of exposure are usually well below the background concentrations of the compound. In order to deal with this problem, exposure assessors tend to use "reasonable worst case" estimates for the parameters: estimates that are conservative, but not too conservative. If a reasonable worst case estimate would be the 75 percentile, then the probability of two uncorrelated parameters simultaneously exceeding their 75 percentiles is  $0.25^2 = 0.0625$ , 6.25%. Still,  $0.25^n$  is a small number if  $n$  is large.

A second approach to calculate worst case exposures and uptakes circumvents this problem (Fig. 10, route 2). Firstly, uncertain and variable parameters are given an appropriate stochastic distribution. Then, these distributions are used to calculate the distributions of exposure and uptake. Once the exposure and uptake distributions are established, the 95 percentile values from these distributions are taken. In contrast with the cumulative worst case situation, the probability of exceeding that exposure and uptake value is known, being 5%.

The benefit of being able to specify the probability of exceedance is gained at the cost of finding parameters distributions and calculating the distribution of exposure and uptake from the parameter distributions. In CONSEXPO, two approaches are used, the discrete probability approach and the Monte Carlo approach. The discrete probability

approach assumes that exposure (and identically uptake) is given by a function  $f(p)$  that depends monotonically on a parameter  $p$ . For a monotonically increasing function  $f(p)$ , the following relation holds:

$$Pr [p^* - \Delta \leq p \leq p^* + \Delta] = Pr [f(p^* - \Delta) \leq f(p) \leq f(p^* + \Delta)]$$

where  $\Delta$  is a small deviation from  $p^*$ . If  $f(p)$  is a monotonically decreasing function of  $p$ ,  $\leq$  is replaced by  $\geq$  at the right hand of the equality sign. If the probability density function of the parameter values is denoted by  $P(p)$ , and the probability density function of exposure and uptake is denoted by  $F(f(p))$ , then the following equality can be derived from the above:

$$\left| \int_{f(p-\Delta)}^{f(p+\Delta)} F(f(p)) df(p) \right| = \int_{p-\Delta}^{p+\Delta} P(p) dp,$$

where  $\Delta$  is a small deviation from a value  $p$ . The average probability density of the exposure as calculated from the parameter probability density is

$$\overline{F(f(P = p))} = \frac{\int_{p-\Delta}^{p+\Delta} P(p) dp}{|f(p + \Delta) - f(p - \Delta)|}.$$

If  $\Delta$  is a small value, this approach approximates the true probability density function  $F(f(p))$  very well. For simple probability density functions  $P(p)$  and simple functions  $f(p)$ , the probability density function  $F(f(p))$  can be derived from the probability density function  $P(p)$  analytically, see Mood et al (1980) and Press et al. (1991) for an overview of techniques.

The second approach to propagate the distribution of the parameter through the exposure and uptake models is to use Monte Carlo simulation. First, all parameters which attain a distribution achieve a value randomly taken from that distribution. Then, exposure and uptake are calculated, using those parameter values. This process is repeated many times, typically in the order of 1000 – 5000 times. During the Monte Carlo simulation, as many exposure and uptake values as there are repetitions are gathered. The frequency histogram of these exposure and uptake values approximates the shape of the probability density functions of exposure and uptake. The more repetitions, the more accurate the approximation.

Using Monte Carlo simulation implies that a good random generator is needed. The one implemented in the program is the `ran1` random generator from Press et al. (1991). The procedure to transform the uniformly distributed values from this random generator into normally distributed values is also taken from Press et al. (1991). The program does not use latin hypercube sampling, a variation of the Monte Carlo technique. Latin hypercube allows for a much more efficient sampling of the parameter distributions, gaining insight into the exposure and uptake distributions in less iterations than the Monte Carlo approach. However, the same accuracy can be reached with Monte Carlo sampling, although the number of iterations has to be large. Latin hypercube is top 3 on the to do list.

## 5.3 Distributions

The program allows parameters to attain three standard distributions, the normal, log-normal and uniform distribution. The dialog to set the stochastic distributions is reached by selecting the parameter name in any of the parameter definition dialogs.

### 5.3.1 Normal distribution

The parameters in this program are all restricted to positive values. If their mean value and their standard deviation are given, and the standard deviation is much smaller than the mean (say, a coefficient of variation not larger than 20%), the normal distribution might be a good choice as parameter distribution. The normal distribution specifies a symmetric distribution around the mean.

### 5.3.2 Lognormal distribution

If a parameter is restricted to positive values, as e.g. concentrations are, and the standard deviation is of the same order of magnitude as the mean, the lognormal distribution might be a good choice. The lognormal distribution is described by the median and the coefficient of variation (C.V.). The median is that value that is exactly in the middle of the distribution, with 50% of the distribution before and 50% after it. The coefficient of variation is the mean divided by the standard deviation.

### 5.3.3 Uniform distribution

If the only thing that is known about a parameter is a plausible lower and upper bound, the uniform distribution is a good choice. It assumes that every value in between the lower and upper bound has an equal probability of occurrence.

## 5.4 Displaying exposure or uptake distributions

Using the *Distribution* entry of the *Report* menu, exposure or uptake distributions can be drawn on the screen. The distributions are calculated and drawn for each route of exposure and entry separately. If all parameters are point estimates, if there are parameters with out of range values or if there are parameters with missing values, then no graph will be shown. The Choose Distribution dialog box, which displays after selecting the *Distribution* entry, is divided in an exposure and an uptake part, containing the exposure and uptake distributions respectively. Only one of these distributions can actually be displayed on screen, so only one can be chosen from the list. After selecting the *Ok* button or pressing *enter*, the distribution of your choice is drawn on the screen.

If, during the generation of the distribution, only one parameter appeared to have variation, a point graph is composed, using the discrete probability function approach. If there are multiple parameters with variation, the Monte Carlo approach is used. A histogram displays the results of Monte Carlo calculations.

If the exposure and uptake model is changed after the graph is drawn, then the results are **not** automatically updated on screen. The *Distribution* entry has to be selected again to reflect the model changes in the graph. This way, you are allowed the time to observe changes in exposure or uptake resulting from the model change. The number of bars in the histogram, the number of points in the graph and the number of Monte Carlo loops can be changed in the options dialog in the system menu.

## 5.5 Sensitivity analysis

The implementation of the uniform distribution and the procedures to display exposure and uptake variation as a result of parameter variation also allow the user to perform simple, local sensitivity analysis. Sensitivity analysis tries to relate changes in parameter values to changes in the result. If a large change of a parameter value results in but a minor change of the outcome, the model is said to be insensitive to that parameter. If, on the other hand, a small change in a parameter value causes a large change in the outcome, the model is said to be sensitive to that parameter.

The uniform distribution is useful to analyse how sensitive exposure and uptake estimates are to small variations in the value of a single parameter. Instead of a point value, one of the parameters in the model is given a uniform distribution, to specify a small, symmetric interval around the point value. Then, the resulting distributions of exposure and uptake are calculated. From these distributions, the lower and the upper bounds are determined. Using the upper and lower bounds of the parameter too, the following measure  $S$  can be calculated

$$S = \frac{f(u) - f(l)}{u - l},$$

where  $f(u)$  and  $f(l)$  are the exposure or uptake function  $f(p)$ , using the upper bound  $u$  and lower bound  $l$  of the parameter. As one can verify, it is an approximation to  $df(p)/dp$ , the derivative of the model with respect to the parameter. This measure can be calculated for each of the parameters, setting a uniform distribution for each parameter in turn. To achieve a relative measure instead of an absolute one,  $S$  can be divided by the value of the result  $f(p)$  at the point estimate of the parameter  $p$

$$S_r = \frac{S}{f(p)} 100\%.$$

The relative measure  $S_r$  facilitates comparison between models where the results differ in one order of magnitude or more.

These measures of sensitivity are only local measures. Firstly, all parameters achieve their best estimate and then each parameter achieves its sensitivity measure, the others being at their best estimate. In another assessment problem, where the best estimates of parameters differ, the parameter sensitivity measures will differ from the earlier estimates. A global sensitivity analysis, on the other hand, would determine the sensitivity of a model for the parameter regardless of the values of the other parameters. This is not possible with the present program.

## Chapter 6

# Tutorial

The use of the program will be demonstrated with the following exposure situation: Assume someone is cleaning his bicycle with a product that contains 50% tetrachloroethane as a solvent. The person cleans the bike inside a room which is ventilated. The can with the solvent is left open in the room. Question: What is the exposure to tetrachloroethane and how much of it is taken up in the person cleaning the bike ?

### 6.1 Step 1.

Start the CONSEXPO program by double clicking its icon. The welcome dialog box displays. Choose the *Ok* button of the welcome dialog. The dialog will disappear and the CONSEXPO window will appear on screen.

Now you are ready to use the program.

### 6.2 Step 2.

Choose the *Compound* entry from the menu bar. A submenu will pop up with the entries *Define*, *Save*, and *Retrieve*. Choose the *Define* entry. Here, you have to define the chemical compound of interest. The characteristics of tetrachloroethane are:

- Molecular weight: 167.85 g/mol;
- Log octanol/water partition coefficient: 2.39 (10log);
- Vapor pressure: 5.95 mm Hg.

If the dimension of the dimension box is not the dimension you want, click on the arrow in the dimension box, and choose the appropriate dimension. Now, choose *Ok* to accept the compound parameters.

Now, the compound has been defined.

### 6.3 Step 3.

No exposure without contact. Next, the contact entry will be filled in. From the menu bar, choose the *Contact* entry. Two subentries are displayed, *Define* and *Human*. Choose the *Define* entry. The Define Contact dialog is now displayed.

In this tutorial, a predefined scenario will be chosen. Click on the arrow in the scenario box. A large number of alphabetically ordered scenarios is shown in the box. A limited number is shown, but other entries can be reached via the scroll bar on the right. Our person cleans a bike. Find the scenario "Cleaning Bicycle" and click on it. Now it is displayed in the scenario box. Inspect the parameters by choosing the *parameters* button. All contact parameters are defined. Now, choose *Ok* to accept the parameters and once again *Ok* to accept the contact definition.

That is it for contact, neglect the average/worst case choice and continue.

### 6.4 Step 4.

No Uptake without exposure. Next, the exposure scenario and its parameters have to be defined. Choose the *Exposure* entry from the menu. A submenu will pop up containing the routes of exposure. In the situation sketched in the above, the route of exposure will be the inhalatory one. Choose *Inhalatory* from the routes.

A dialog is displayed which contains three points of interest: options, scenarios and the parameters button. In this exposure assessment, the primary interest is in the worst case option. Click on *Worst Case* to check that option.

Next, choose the *parameters* button. Eehh ?? Nothing happens !! That is because a scenario has to be chosen first. Click on the arrow in the scenario box, and pick the "open can" scenario from the possibilities. This scenario describes a situation in which a compound evaporates from a product and it is the closest to the exposure situation given in the above. Once again, choose the *parameters* button. Now, a dialog will appear in which the values of the parameters can be given. A number of parameters have default values. Set the ventilation rate to a value of 2.5 m<sup>3</sup>/hr. Remember, if this dimension is not the one displayed, click on the dimension box and choose the right one (use the scroll bar !). Set the amount of product to 200 gram, the weight fraction of the compound in the product to 50% and the molecular weight of the other compounds to 500 g/mol.

Suppose, we also do not agree with the release area. Moreover, we are uncertain about the actual area, we only know that it is in between 0.5 and 1.5 dm<sup>2</sup>. First, set the right dimension, dm<sup>2</sup>, in the dimension box. Then, click on the parameter name. A dialog appears which allows us to set a distribution for the parameter instead of a point value. First choose "uniform distribution" (watch the check !), then give an upper bound of 1.5 and a lower bound of 0.5.

That's all we know. Choose *Ok* to return to the parameter dialog. Choose *Ok* to accept the parameters and once again *Ok* to accept the exposure definition.

**intermezzo.** People are curious (so are exposure assessors). What is the exposure ? To

view this, go to the *Report* menu and choose *Point* from the submenu. A dialog displays where, apart from all the "unknown" entries, two entries display information, both with the same value (although they have a different dimension). This is the mean exposure from the scenario that you have set in the exposure definition (step 4), using the contact duration from the contact definition (step 3). The "WC" right of the inhalatory exposure denotes that you have selected a worst case in the exposure options.

## 6.5 Step 5.

Last but not least: uptake. The uptake model and parameters can be reached via the *Uptake* menu entry (suprise!). As in *exposure*, the submenu contains the routes of exposure. We are assessing the inhalatory route, so the *Inhalation* entry is chosen from the submenu. Now the uptake definition dialog is displayed. This dialog lets you choose the uptake model in the *options* part and lets you set the parameters of the uptake model with the *parameter* button. Because the blood/air partition coefficient of tetrachloroethane is known (being 18), we'll choose the flow model first and then press the parameter button. Now, all uptake parameters are shown, but we'll only need a few. Set the air/blood partition coefficient to 0.05291 (=1/18) and accept the defaults for the other parameters. We don't need the permeability. Choose *Ok*. And once again *Ok* to leave the uptake definition.

That's it for uptake.

## 6.6 Step 6.

What about the results ?

If we choose from the *Report* menu the *Point* entry once again, the report dialog is show. Now, the inhalatory uptake is also defined (with a "P" on the right to denote the flow model, which is mainly based on the Partition coefficient). Also multiroute uptake estimates are shown, which are sumvalues over all routes of uptake. One is set in terms of mg/kg body weight/day and the other in mg/year.

But graphs are more beautiful. To view exposure as a function of time, leave the report dialog (*Ok*) and choose *Time plot* from the *Report* menu. From the dialog, select inhalatory exposure and press *Ok*. The exposure is drawn on screen. If you would have selected inhalatory uptake, uptake would have been drawn. Other entries do not result in a graph, because they are "unknown" in the *Point* entry dialog.

What about the effect of variation in the release area in the open can scenario ? In step 4, a uniform distribution was chosen. To investigate how this variance propagates through the model, select the *Distribution* entry from the *Report* submenu. Now, choose *inhalation* from the exposure part (at the top). Then press *Ok*. Now, a graph is shown which shows the distribution of the exposure model results. The exposure varies around a value of  $1.8 \cdot 10^{-4} \text{ mg/cm}^3 = 180 \text{ mg/m}^3$ .

Finally, the results can be written to file. To achieve that, choose the *Print to File* entry from the *Report* submenu. Type a filename in the selector box and press *Ok*.

A file will be created (as an ASCII-file) which contains the results of the exposure assessment.

## Chapter 7

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# Appendix A

## A.1 Compartmental Uptake Model

The compartmental uptake model assumes a situation in which some amount of product, water or air contacts the body, the compound contained therein permeates the body boundary and is taken away from the site of contact by blood flow. Such a situation can be modeled by a well stirred outer compartment, a well stirred inner compartment with a through flow refreshing the compartment and a permeable membrane in between (fig. 10).

The equations describing this situation are (Van Veen, in prep.):

$$V_p \frac{dC_p}{dt} = -AP(C_p - K_{pb}C_b)$$

$$V_b \frac{dC_b}{dt} = AP(C_p - K_{pb}C_b) - QC_b$$

where  $V_p$  is the product volume,  $V_b$  is the blood volume at the site of exposure,  $C_p$  is the compound concentration in the product,  $C_b$  is the compound concentration in blood,  $A$  is the surface area of contact,  $P$  is the permeability of the body boundary,  $K_{pb}$  is the product/blood partition coefficient and  $Q$  is the blood flow at the site of contact.

In the program, this model is used to describe two situations:

1. Dermal uptake. If some amount of product is spilled on the skin or if contact with some amount of fluid is made, the compartmental model is used if the diffusion model is selected.
2. Inhalatory uptake. The compartmental uptake model can be used as a very simplified model for uptake of volatile or gaseous compound within the lung during a single breath. The model is used if the user selects the diffusion model of uptake.

## A.2 Input files

### A.2.1 Contact files

The contact parameters can be defined by reading an input file. At the moment, only the parameters duration, frequency and start can be defined by the file. In the future, it will be possible to read in a time series of contact. The latter feature will allow the user to specify irregular contacts.

The syntax for the input file is:

```
duration=xx  
start=xx  
frequency=xx
```

where xx is replaced by the appropriate value. If an unknown command is encountered (caused by a typing error or not reading this information) all file settings are discarded.

### A.2.2 Oral exposure files

The oral exposure input file is used in the daily intake scenario. It has to contain the measured concentrations and the dimension of the concentrations. Each line of the file may contain either of the following:

1. a dimension specifier, in the form of:

```
dim:xx
```

where xx is one of the following specifications: mg/kg, microg/kg, fraction, %. Please adhere literally to these specifiers. A dimension specifier is obligatory.

2. a concentration, which has to be a number starting on the beginning of the line.
3. a multiple of concentrations, to specify a concentration that occurs more than once. Its specification is:

```
yy*zz
```

where yy is the number of occurrences and zz the concentration, eg 5\*10.3.

4. each line not starting with a number and not containing 'dim:' is considered to be a comment. If the very first line contains a comment, this comment is displayed in a message box while reading the file. This comment can be used for a general identifier of the file.

Example:

```
Example data  
dim:mg/kg  
3  
5.7
```

4\*2.1  
10.6  
more comments  
20.4