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CONSEXPO 2

Consumer Exposure and Uptake Models

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Summary

The program and the manual presented in this report allow for the exposure assessment of chemical compounds contained in consumer products. Consumer products comprise a large diversity of products, ranging from shoe polish to detergents to pesticides. All these products may contain hazardous compounds, both active compounds and contaminants. Exposure assessments for these products are not equal to measuring product concentrations. Products will release their compounds during use and the concentration in air, water or a diluted product determines the exposure. The duration of use and residence times in a room or house determine the duration of exposure.

The present report provides a modelling approach based on mathematical contact, exposure and uptake models. For each route of exposure, a number of exposure and uptake models are included. A general framework joins the particular exposure and uptake models selected by the user. By joining different models and different routes, the program copes with the consumer product diversity. The program allows for stochastic parameters, to include variability and uncertainty. The program calculates the resulting exposure and uptake distributions, and allows any percentile to be calculated.

This program is linked to a database, which is to contain predefined exposure and uptake models for product categories. The exposure assessment of a product then starts with the default models and model parameters for its product category. These can be adjusted to fit the assessment to existing knowledge.

The program reports several important exposure variables, including the mean 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.

Samenvatting

Het programma en de achtergronden in het rapport zijn bedoeld voor de blootstellingsschatting van chemische stoffen in consumentenproducten. Consumentenproducten omvatten een grote diversiteit aan producten, zoals schoenpoetsmiddel, detergenten en pesticiden. Al deze producten bevatten mogelijkerwijs gevaarlijke stoffen, zowel actieve ingredienten als verontreinigingen. Een blootstellingsschatting voor dergelijke producten omvat meer dan het meten van productconcentraties. Stoffen uit de producten komen in lucht of in water en producten worden mogelijk verdund. Ook de duur van contact en de verblijftijd in huis bepalen de blootstelling.
Het voorliggende rapport bevat een modelmatige benadering, gebaseerd op contact-, blootstellings- en opnamemodellen. Voor elke blootstellingsroute zijn mathematische modellen aanwezig. Een algemeen raamwerk verbindt de modellen zoals ze door een gebruiker geselecteerd zijn. Door verschillende modellen te combineren wordt de blootstelling aan een product beschreven. In het programma kunnen ook stochastische parameters gegeven worden, die verdelingen van blootstelling en opname opleveren. Hieruit kan een willekeurig percentiel opgevraagd worden.
Het programma is verbonden met een database, waarin voorgedefinieerde blootstellings- en opnamescenarios komen te staan. De beoordeling van een product begint dan met de standaardmodellen en standaardparameters voor de productcategorie. Deze kunnen worden aangepast om de huidige stand van zaken in de beoordeling te betrekken.
Het programma rapporteert diverse blootstellingsmaten, waaronder de gemiddelde blootstelling gedurende contact, de jaargemiddelde blootstelling, de opname en de opname per kilogram lichaamsgewicht.

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 (1996) 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 mg/m^3, a concentration measure. Uptake includes both the intake rate of the medium and the uptake rate of the compound by the body.
To summarize the general model framework, $E(x, t)$ 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. The cumulative amount U_c taken up in the body is

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

where U_c is the cumulative 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 (mg/cm^3) as a function of time and path of a person, and $U(E(x_p(t), t), t)$ is the uptake rate (mg/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:

$$U(E(x_p(t),t),t) = I_m(t)FE(x_p(t),t)$$

In the CONSEXPO program the spatial dependence of exposure is not included at the moment. This simplifies potential exposure to a of time: $E(t)$.
Of course, the user does not have to memorize the exposure and uptake equations before the program can be used. The CONSEXPO implements the general consumer product exposure and uptake model in a user friendly software package. It allows the user to specify contact, exposure, and uptake by selecting the appropriate scenarios and models from predefined lists. Then, it integrates contact, exposure, and uptake to calculate time courses of exposure and uptake.
The models included in the program range from screening models to models predicting actual exposure. The screening models provide a quick and dirty examination of exposure, while the actual exposure models aim to predict the time course of exposure. All models, screening and actual exposure, depend heavily on the applicability of the model assumptions and the accuracy of the model parameters. In addition, models are simplified representations of reality and can not be expected to mimick reality in all aspects and every occasion.
The program 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 (EU, 1996) and the European Union System for the Evaluation of Substances EUSES (ECB, 1996). The general context of the CONSEXPO program within the RIVM is sketched by Vermeire and Van Veen (1996). They also describe other exposure models of the RIVM, covering direct exposure and exposure through the environment and food chain.

I would like to thank Peter Bragt, Harry Bremmer, Henk Derks, Jan van Eijkeren, Jan Freijer, Tjalling Jager, Rolaf van Leeuwen, Wim Mennes, Henk Roelfzema, Gert Steentjes, and Theo Vermeire for the many useful discussions and the time they took to test the program , to develop the database, and to report 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.

2. INSTALLATION

2.1. System requirements

The following system requirements apply:
- Intel based PC, with MS-DOS as the operating system,
- MS-Windows 3.1 installed and working,
- 5 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. CONSEXPO 2 will also run on Windows 95, Windows NT 4, and OS/2 with support for MS-Windows, because these 32 bit operating systems run 16 bit programs.

2.2. Installation

The installation procedure installs the CONSEXPO software and the defaults database. The defaults database is under development. At the moment it only contains a test entry, but in the future products and product categories will be added. Updates of the database will be made available electronically.
The program is supplied with one or two diskettes: 1. the CONSEXPO diskette, 2. the Borland database engine diskette. If the Borland database engine diskette is not provided or not installed, CONSEXPO will function, but the database is not available for the program. Users who have already Borland IDAPI tools installed (eg Paradox for windows or DBase V users) may have the IDAPI tools installed. There is no need to reinstall the engine.

2.2.1. Installation with one diskette

Only the CONSEXPO diskette is provided. Copy the self extracting archive `ce_distr.exe` to your harddisk to speed up extraction. Then start the archive, by double clicking it in the file manager or by using the program manager: File->Run. The archive will ask where the consexpo program must be placed. Select the directory of your choice, or accept the default.

2.2.2. Installation with two diskettes

Install the CONSEXPO diskette as above. Install the database engine by running INSTALL.EXE. Be sure to install the CONSEXPO diskette before installing the Database Engine. The latter may need the file bwcc.dll. This file is provided in the CONSEXPO distribution. If the database engine can not be installed, copy bwcc.dll to the windows\system directory.

3. THE PROGRAM

3.1. Displays

The program uses two displays to show its information, one for model overview and one for plotting graphs. The model overview is present at start-up. To toggle between the two displays, use the last two entries in the Options menu or use the rightmost buttons in the button bar. If exposure can be calculated, the graph display will automatically show the time course of exposure when selected.

3.1.1. The model overview

The model overview summarises all models that have been set and tests whether all parameters have been defined. The overview offers a short cut to model and parameter definition dialogues by double clicking the grey fields. For monitors with big fonts selected, this may not work.

3.1.2. The graphic display

The graph display displays distributions and time courses of exposure and uptake. Selecting the graph display enables those menu items that plot to the graph display in the Report menu.

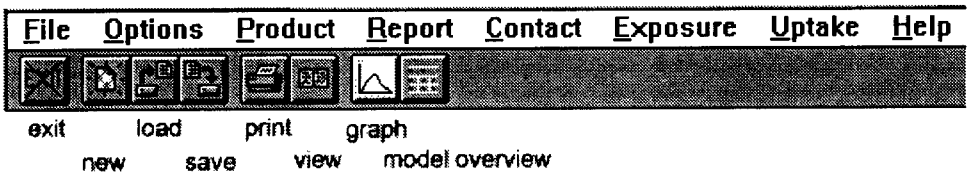

Figure 1. Menu and tool bar of CONSEXPO. Tool bar buttons are explained with keywords.

3.2. Menu and toolbar

The menu and toolbar bar is displayed at the top of the CONSEXPO window (fig. 1). The menu contains entries for handling files and printing (File), system wide settings (Options), getting help (Help) and defining and analysing exposure and uptake models (`Report`, `Contact`, `Exposure`, `Uptake` and `Product`). The toolbar contains shortcuts to a number of menu entries (fig. 1). Menu entries and toolbar buttons are explained in the lower bar of the program when the mouse is on top of an entry or button. Summarised, the menu bar contains eight main entries.

- **File** all commands concerning file handling and graphics printing, and the info and exit commands,
- **Options** all commands concerning the calculation routines as a whole,
- **Product** all commands concerning the retrieval of information from the defaults database, including product category defaults and chemical properties

- **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,
- **Help** commands to display help information.

3.2.1. File menu

The File menu consists of the following entries:

- **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 preview** preview the graph currently displayed on screen as it will be printed;
- **Print** print the graph currently displayed on screen. It will be printed on the Windows standard printer.
- **Print set-up** set the printer and change the settings of the printer.
- **Exit** leave the program. All results will be lost unless saved.

3.2.2. Options menu

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

- **System**. Displays a dialogue box to set system wide properties, including 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 database properties.
- **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.
- **Graph display**. Switch to the graph display screen. The options `distribution` and `time course` in the `Report` menu become available.
- **Model overview**. Switch to the model overview screen

3.2.3. Product menu

The product menu contains entries to read the database.

- **Select category** Select the product category from the defaults database and read default models and parameter values.
- **Select compound** Select or set the physico-chemical properties of the chemical compound.

3.2.4. Report menu

The `Report` menu entry is used to view the results of the exposure and uptake model. The `Distribution` and `Time course` entries that use graphical output are only enabled when the graph display is selected, see section 3.1. Otherwise, these entries are greyed out.

- **Point estimates**. Show point estimates of exposure and uptake.

- **Distribution**. Show the variability of exposure or uptake in case one or more parameters are variable.
- **Time course**. Show the time course of exposure or cumulative uptake.

3.2.5. Contact menu

The Contact menu entry specifies the contact part of the exposure and uptake model. The contact parameters define the function *P(t)* as defined in Van Veen (1996). The body weight or body weight distribution of the exposed persons is also defined here.

- **Define** to actually define the contact parameters,
- **Human** to specify the human body weight.

3.2.6. 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 (1996). In the present version of the program, spatial differences in exposure are not allowed. Therefore, the exposure function reduces to a function depending on time, *E(t)*.
The entry contains the routes of exposure as subentries. Choosing one of the routes displays a dialogue 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.

3.2.7. 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 (1996). The entry has the routes of uptake as subentries. Choosing one of these routes displays an uptake definition dialogue, which allows you to set up the uptake for that route. From the dialogue 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 a two compartimental diffusional uptake model, described in section 3 of Van Veen (1996). 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.

3.2.8. Help menu

Accesses the help system of the program.

- **Info**. General information on the CONSEXPO 2 program.
- **Routes of exposure**. Information on the routes of exposure and the available models for the routes.
- **Database**. Information on the defaults database and its use.
- **Menu**. Information on the menu of the program and the meaning of its entries. In fact the on line version of this chapter.
- **Tutorial**. The on-line version of the tutorial.

3.3. Reporting exposure and uptake results

Exposure and uptake results are displayed using the entries of the `report` menu. The subentries allow for a numerical (`Point`) or graphical (`Distribution; Time course`) representation of exposure and uptake. The latter are only available when the graphical display is in use, see section 3.1.

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 dialogue, in which the values for the estimated exposure and uptake are shown (fig. 3). Depending on the choice made in the Exposure definition dialogues (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 parameter achieves its 95 percentile value and those values are used to calculate the worst case exposure and uptake results.

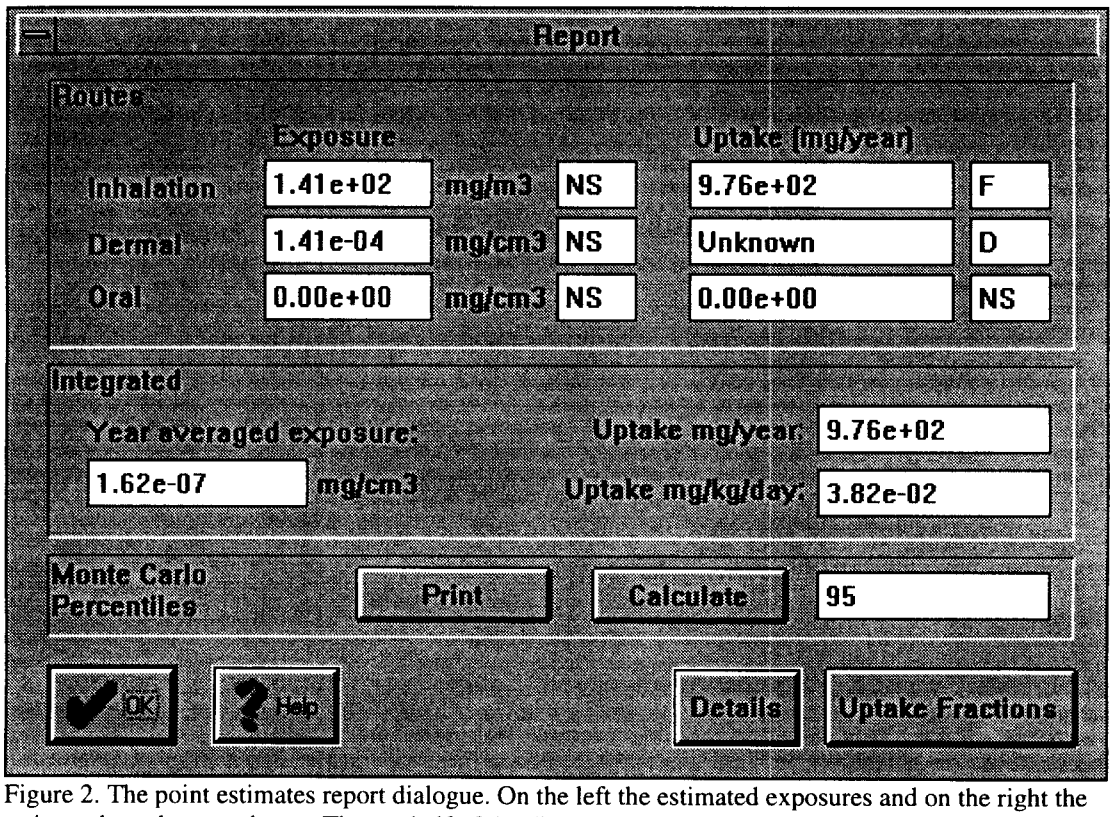

Figure 2. The point estimates report dialogue. On the left the estimated exposures and on the right the estimated uptakes are shown. The top half of the dialogue shows the route specific estimates, while in the lower half the integrated measures are shown.

To circumvent the cumulative worst case estimates, the Monte Carlo Percentiles part in the dialogue 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 dialogue 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 selecting 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 saved or 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 System entry of the Options menu. If you select a different text viewer, then the use may deviate from the description in the above.

3.3.2. Distribution

An exposure or uptake distribution can be displayed if one or more parameters exhibit stochastic variation. 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 dialogue to select a distribution is divided into an exposure and an uptake part, containing the distributions 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 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.

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 course

The Time course entry displays the exposure or uptake as a function of time. The menu entry is only enabled if the graph display is set. To set it, select Options->Graph Display or press the white button with the graph in the button bar. After choosing the Time course entry, a dialogue box will appear, from which the route of exposure or uptake to be displayed can be selected. 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 non-linear exposure scenarios, such as the inhalatory open can scenario which shows a saturating exposure concentration during long exposures. The plot will be displayed after choosing the Ok button. To print the plot, choose the Print Graph option from the File menu while the plot is on screen.

4. EXPOSURE AND UPTAKE MODELS

4.1. Introduction

CONSEXPO 2 is a multiroute, single compound modelling tool. Exposure and uptake models can be defined for each route of contact. The models and their parameters are presented here. First, contact is discussed. Second, exposure and uptake models are presented per route of exposure.
An overview of European data sources is prepared by Van Veen and Vermeire (in prep.) for the Residential Exposure Assessment Project of the Society for Risk Analysis, the International Society for Exposure Analysis and the US Environmental Protection Agency. It will be a useful starting point for more data and model sources.

4.2. 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 full time interval of contact, whether the product is actually used or not. Default value: 120 minutes. Status of default: guess. Range: duration of use-1.

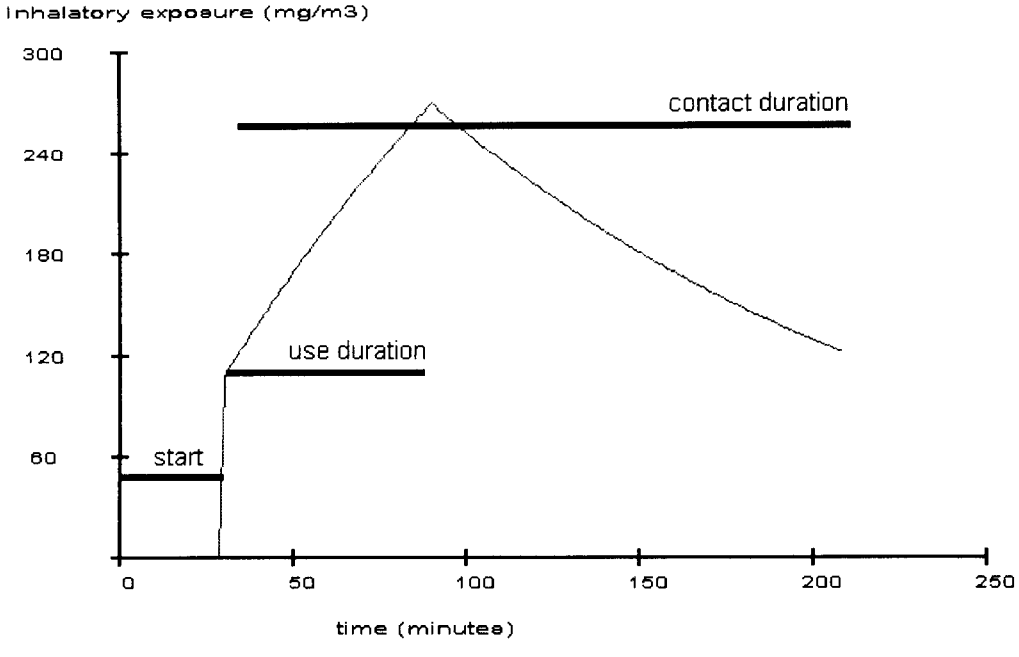

Figure 3. Definition of contact parameters.

- **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.

4.3. 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.
In comparison to CONSEXPO 1, two complicated models are added. The painting model extends the evaporation from mixture model and models evaporation from a finite source of compound in a certain amount of product. The indoor exhaust gas model predicts carbon monoxide concentrations in a single room, using a three compartment system to describe the different air layers that are separated by temperature gradients.

4.3.1. Inhalatory contact

The contact with a compound is defined using the `define` subentry of the `contact` menu entry, see section 4.2.

4.3.2. Inhalatory exposure

To describe the inhalatory exposure, the program defines six exposure scenarios. The constant concentration scenario, the source and ventilation scenario, the evaporation from pure substance scenario, the evaporation from mixture scenario, the indoor exhaust gas scenario, and the paint 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

$$E = \frac{w_f q}{V_{room}}$$

where A is the product amount released, w_f is the weight fraction of the compound in the product and V_{room} the volume of the room.

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.

Weight Fraction:the concentration (weight fraction) of the chemical compound in the product. Default value: none.

Room Volume: volume of the room in which the exposure occurs. Default value: 25 m^3. Status of default: defines a room of 4 * 2.5 * 2.5 m^3, which is a small room in Dutch social housing projects.

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):

$$V_{room}\frac{dE(t)}{dt} = S - Q_{room}(E(t) - C_{ambient}) - eV_{room}E(t)$$

where $E(t)$ is the exposure in the room, V_{room} is the room volume, S the generation rate of the compound, Q_{room} the effective ventilation rate, $C_{ambient}$ the ambient air concentration and e the break down rate of the compound. This differential equation can be solved with initial concentration E_0 to give:

$$E(t) = E_0 e^{-\left(e+Q_{room}/V_{room}\right)t} + \frac{S + Q_{room}C_{ambient}}{Q_{room} + eV_{room}}\left[1 - e^{-\left(e+Q_{room}/V_{room}\right)t}\right]$$

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.

Ventilation Rate: amount of air that ventilates the room per unit of time. Default: none.

Ambient Concentration: concentration of the compound in ambient air which is used to ventilate the room. Default: none.

Break Down Rate: the break down rate of the compound in fraction per time unit. Default: none.

Room Volume: volume of the room in which the exposure occurs. Default value: 25 m^3. Status of default: defines a room of 4 * 2.5 *2.5 m^3, which is a small room in Dutch social housing projects.

Evaporation from 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 fysicochemical 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.

$$E(t) = E_0 e^{-\frac{K_t A + Q_{room}}{V_{room}}t} + \frac{1000K_t MAP}{RT(K_t A + Q_{room})}\left[1 - e^{-\frac{K_t A + Q_{room}}{V_{room}}t}\right]$$

where E_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_{room} the effective ventilation rate, V_{room} the room volume, M the molecular weight, P the vapor pressure of the compound, R the universal gas constant, and T the absolute temperature.

Its parameters are:

Release Area:the surface area of the canned product which is in contact with the air. Default value: 0.0025 m^2. Status of default: guess, intended to described a small can.

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

Room Volume: volume of the room in which the exposure occurs. Default value: 25 m^3. Status of default: defines a room of 4 * 2.5 * 2.5 m^3, which is a small room in Dutch social housing projects.

Effective Ventilation Rate:amount of air that ventilates the room per unit of time. Default: none.

Evaporation from Mixture. This scenario defines a situation where compounds evaporize 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 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 Compound menu entry. The equation for the evaporation has already been given in the pure substance scenario. Raoults 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.

Its parameters are:

Release Area:the surface area of the product which is in contact with the air. Default value: none.

Temperature: The temperature in the room. Default value: 298 kelvin = 25 Celsius. Status of

default: rounded average summer temperature in the Netherlands.

Room Volume: volume of the room in which the exposure occurs. Default value: 25 m^3. Status of default: defines a room of 4 * 2.5 * 2.5 m^3, which is a small room in Dutch social housing projects.

Effective Ventilation Rate:amount of air that ventilates the room per unit of time. Default: none.

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.

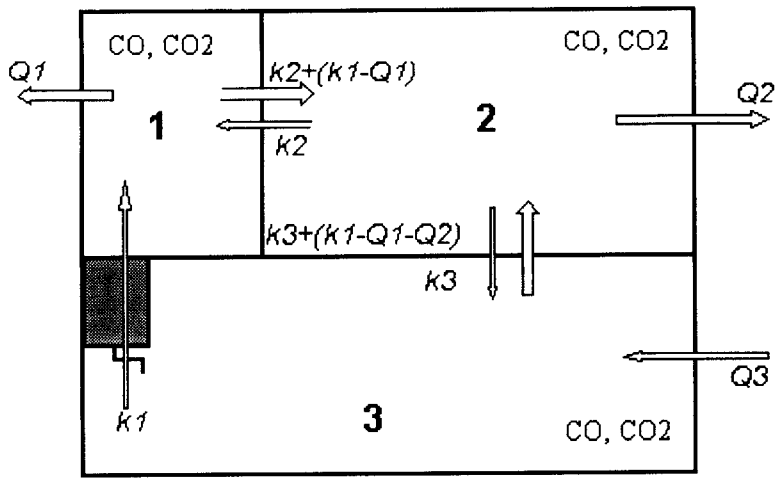

Figure 4. Scheme of the CO-model. A single room is subdivided in three layers when the burner is switched on. Parameters Q define the ventilation and parameters k define mixing between air layers.

Indoor Exhaust Gas. The scenario predicts carbon monoxide concentrations in a room from combustor and room characteristics. A pictural scheme of the model is displayed in figure 3. A single room is modelled, where a natural gas combustor (eg a stove, heater, or geyser) emits exhaust gas containing CO into the room. The CO_2 content of the air used for combustion determines the CO production of the combustor (De Vries and Bartelomeus, 1973).

Experiments (De Vries and Bartelomeus, 1973) have shown that hot exhaust gas separates the room air in a warm upper and a cold lower layer. Exchange between both layer decreases with increasing temperature gradient. The model distinguishes three air layers in the room: 1) the air directly above the combustor; 2) the air in the warm upper layer; 3) the air in the cold lower layer.

Ventilation is separated into outgoing and incoming components. Outgoing ventilation is forced by (mechanical) ventilation located above the combustor and/or outer wall. Incoming ventilation is situated near the bottom, in the cold lower layer. It suppletes the air removed by outgoing ventilation.

These considerations lead to a three compartment model for both CO and CO_2 (see fig. 4), which is numerically solved by CONSEXPO by fourth order Runga-Kutta. Because the CO and CO_2 concentrations differ for the different layers, the direction of air flow matters. Therefore, the following boolean variables are defined, which are 1 if the condition following the = is true and 0 otherwise.

$I_1 = k_1 > Q_1$

$I_2 = k_1 - Q_1 > Q_2$

For CO_2, the following mass balance equations apply, where subscripts 1,2, and 3 refer to the compartment as depicted in figure 4.

$$V_1 \frac{dC_1^{CO_2}}{dt} = S^{CO_2} + k_1 C_3^{CO_2} + k_2\left(C_2^{CO_2} - C_1^{CO_2}\right) - I_1 k_1 C_1^{CO_2} - (1-I_1)((k_1 - Q_1)C_2^{CO_2} + Q_1 C_1^{CO_2})$$

$$V_2 \frac{dC_2^{CO_2}}{dt} = I_1(K_1 - Q_1)C_1^{CO_2} + (1-I_1)(K_1 - Q_1)C_2^{CO_2} + k_2 C_1^{CO_2} + f_3 k_3 C_3^{CO_2}$$

$$-(k_2 + f_3 k_3)C_2^{CO_2} - I_2(k_1 - Q_1)C_2^{CO_2} - (1-I_2)((k_1 - Q_1 - Q_2)C_3^{CO_2} + Q_2 C_2^{CO_2})$$

$$V_3 \frac{dC_3^{CO_2}}{dt} = I_2(k_1 - Q_1 - Q_2)C_2^{CO_2} + (1-I_2)((k_1 - Q_1 - Q_2)C_3^{CO_2}$$
$$+f_3 k_3 C_2^{CO_2} - (k_1 + f_3 k_3)C_3^{CO_2}$$
$$f_3 = e^{-0.02 t_0}$$

For CO, the equations follow the same mass balance as the CO_2 equations.

$$V_1 \frac{dC_1^{co}}{dt} = S^{CO}(C_3^{CO_2}) + k_1 C_3^{CO} + k_2\left(C_2^{CO} - C_1^{CO}\right) - I_1 k_1 C_1^{CO} - (1-I_1)((k_1 - Q_1)C_2^{CO} + Q_1 C_1^{CO})$$
$$V_2 \frac{dC_2^{CO}}{dt} = I_1(K_1 - Q_1)C_1^{CO} + (1-I_1)(K_1 - Q_1)C_2^{CO} + k_2 C_1^{CO} + f_3 k_3 C_3^{CO}$$
$$-(k_2 + f_3 k_3)C_2^{CO} - I_2(k_1 - Q_1)C_2^{CO} - (1-I_2)((k_1 - Q_1 - Q_2)C_3^{CO} + Q_2 C_2^{CO})$$
$$V_3 \frac{dC_3^{CO}}{dt} = I_2(k_1 - Q_1 - Q_2)C_2^{CO} + (1-I_2)((k_1 - Q_1 - Q_2)C_3^{CO}$$
$$+f_3 k_3 C_2^{CO} - (k_1 + f_3 k_3)C_3^{CO}$$
$$S^{CO}([CO_2]) = S_0^{CO} e^{3([CO_2]\% - \tau\%)^2}$$

The parameters that appear in the model equations are

S^{CO_2}: the production of CO_2 (mg/min);

S^{CO}: the production of CO (mg/min);

τ: the CO_2 concentration where S^{CO}=$S_0{}^{CO}$

k_1: airflow through the burner (cm^3/min), determined by its kilowattage

k_2: exchange rate between compartment 1 and 2 (cm^3/min)

k_3: exchange rate between compartment 2 and 3 (cm^3/min)

Q_1: ventilation rate of compartment 1 (cm^3/min)

Q_2: ventilation rate of compartment 2 (cm^3/min)

Q_3: ventilation rate of compartment 3 (cm^3/min)

V_1: volume of compartment 1 (cm^3)

V_2: volume of compartment 2 (cm^3)

V_3: volume of compartment 3 (cm^3)

CONSEXPO asks for the following parameters to quantify the model. These define all model parameters as defined in the above.

CO_2 production rate, The production of CO_2 in mass per time by the burner. Default: 18000 mg/minute, based on a 10 kW burner.

CO production rate. The production of CO at the CO_2 concentration given as "CO production offset" (see next parameter).

CO production offset. Parameter in a quadratic exponential function relating CO_2 concentration in air with the CO production rate. The function is $k = e^{([CO_2]-\tau)^2}$, as suggested by data of Dijkhof (pers. comm.) and which is 1 at the offset τ, lower below and larger above it. The CO production rate is then calculated as kS_{co}.

Room volume. Volume of the room where exposure takes place, including all layers of the above mentioned

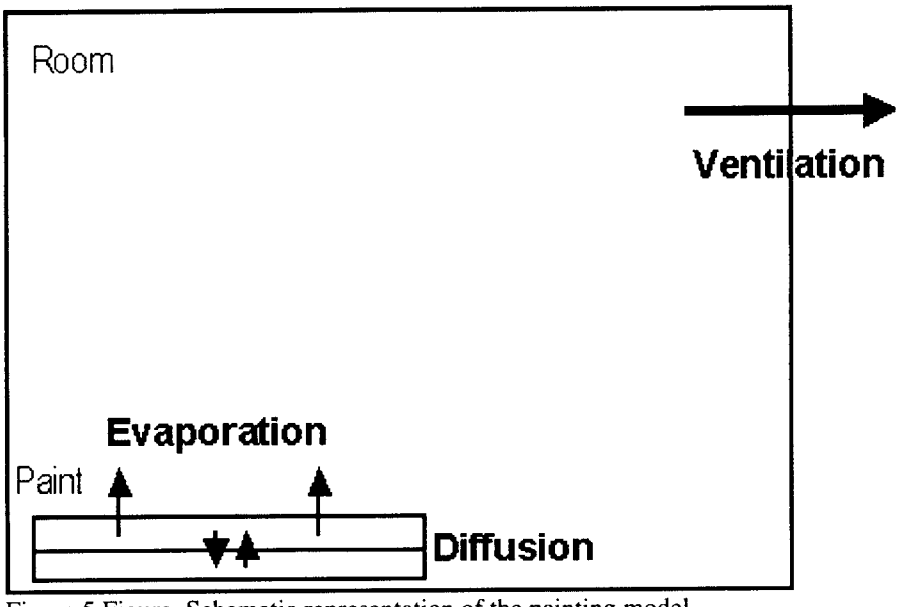

Figure 5.Figure. Schematic representation of the painting model

Room surface. Surface of the room. Room volume and room surface together determine the room height.

Outlet height. The height of the outlet of the burner, where exhaust gas enters the room air.

Mixing rate upper layers. A mixing factor which determines how well both upper layers are mixed by exchange of air.

Mixing upper/lower layer. A mixing factor which determines how well the upper and lower layer mix by exchange of air. The mixing factor as given here is the base factor at a zero temperature gradient. The model assumes an exponential decrease of mixing by an increasing temperature gradient, with a half life of 30 minutes, as observed in experiments (Dijkhof, pers. comm. 1997).

kW Burner. The kilowattage of the burner. Default 10 kW, relating to a geyser.

Exhaust ventilation. The outward directed ventilation in the air layer just above the burner.

Upper ventilation. The outward directed ventilation in the upper air layer next to the burner.

Painting. The scenario predicts the exposure to compounds evaporating from paint applied to some surface.The model is schematically represented in figure 4 and described in full by Van Veen et al (in prep.). In principle, a surface is painted in a single room. The painted surface is subdivided in two layers, the upper one exchanges the compound with air, the lower one acts as a store. The "Painting" scenario models a finite amount of compound in the paint, in contrast to the "Evaporation from Mixture" scenario. In the "Painting" scenario, evaporation stops when the compound has disappeared from the paint.
The model has been validated by Van Veen et al. (in prep.) using organic solvent paint and monitoring n-alkanes in the range n-octane to n-undecane. In summary, the model predicts peak concentrations and half life of n-alkanes in the room the well, but it has difficulties to predict the exact timing of the peak concentration.
The "Painting" scenario uses a Runge-Kutta fourth order numerical algorithm to solve the underlying differential equations. The algorithm is expected to converge for many parameter settings, but it may fail. The user is urged to check if the calculated time course does not contain any anomalies, before using summary measures.

The parameters used in the model are the following.

Release area. The painted area from which compounds may evaporate.

Product amount. Amount of product used to paint.

Weight fraction. Weight fraction of the compound of interest in the paint.

Density product. Density of the paint. Default 1, the density of water.

Layer exchange rate. Exchange rate between the lower, reservoir layer and the upper layer of paint.

Fraction to upper layer. Fraction of paint applied to the upper layer during painting.

Room volume. Volume of the room. Default 25 m3.

Effective ventilation. Ventilation rate of the room.

Temperature. Room temperature. The paint is assumed to have the same temperature as the room. Default, the temperature is 293 Kelvin, about 20 degrees Celsius.

Molecular weight solvent. Mean molecular weight of the "other" compounds in the paint.

4.3.3. Inhalatory uptake

To calculate the uptake of a compound in the lung, three models are available, 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). For particulate material, the nose and larynx act as filter (Freijer et al., 1997). Material deposited in this region is generally swallowed and enters the gastro-intestinal tract.

Fraction Model. The fraction model calculates the uptake rate as

$$U(t) = F\, Q_l R E(t).$$

The primary factor that expresses uptake in the foregoing equation is F the fraction taken up. It is multiplied with Q_l, the inhalation rate, R, the respirable fraction and $E(t)$, the exposure. To calculate the total amount taken up, the integral over the duration of exposure T is taken

$$U_c = \int_T U(t)dt$$

The scenario contains the following parameters:
Contact duration (defined in the contact menu)

Inhalation rate. The volume of air that passes the lungs in a certain amount of time. The default value is based on the body weight that is defined in the `Contact->Human` 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)

$$Q_l = 460 W^{0.7579} \ (\mathrm{cm}^3 / \mathrm{min})$$

where W is body weight in kg.

Absorbed fraction. Default value: 1. Status of default: worst case situation, where there is total uptake.

Respirable fraction. The 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.

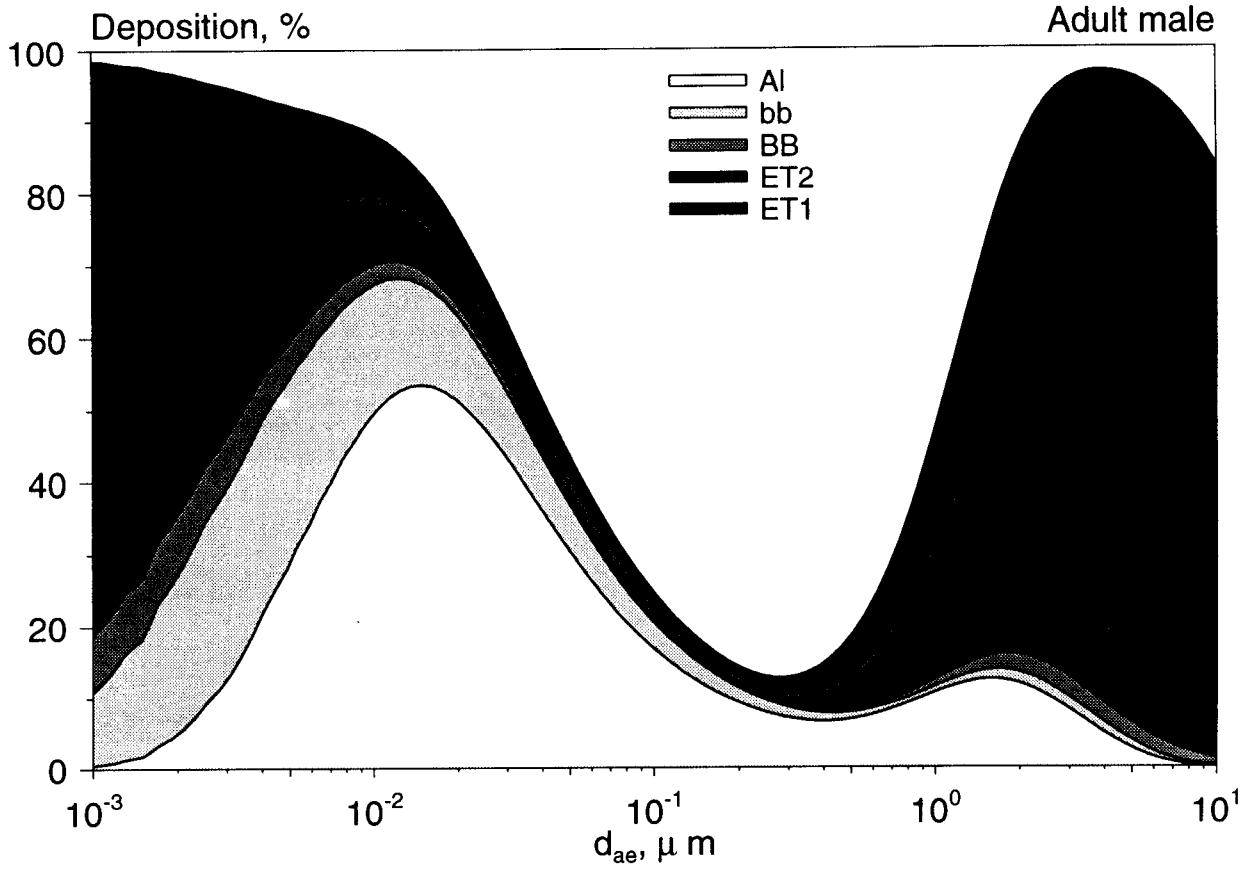

Figure 6. Deposition of aerosols in the lung tract (Freijer et al., 1997). The fraction that is not deposited in the extrathoracical airways, ET1 and ET2 in the figure, is considered to be the respirable fraction. Al-alveoli, bb=bronchioles, BB=bronchia, ET1=extrathoracical region 1, ET2=extrathoracical region 2.

Exposure. Exposure is 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, 1996). Essentially, the uptake rate is defined as:

$$U(t) = A_{lung} P_{lung} (C_{lung}(t) - K_{ab} C_{blood}(t)),$$

where U is the uptake rate, A_{lung} is the area of the lung wall, P_{lung} is the permeability of the lung wall, C_{lung} is the compound concentration in lung air, K_{ab} is the air/blood partition coefficient, and C_{blood} is the compound concentration in lung blood. The uptake rate $U(t)$ is a function of time because both the lung air concentration C_{lung} and blood concentration B_{blood} vary in time. The underlying model is explained in detail by Van Veen (1996). It is assumed that there is no body burden of the compound, resulting in clean venous blood with a zero compound concentration.

The program calculates the amount of compound taken up from a single breath, and sums all breaths during the period of exposure. 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 initial concentration in lung air, $C_{lung}(0)$, 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:

$$C_{lung}(0) = \frac{V_e + (1-F)V_r}{V_e + V_r} C_{ambient}$$

where $C_{ambient}$ 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 $V_e = 0.25V_{lung}$, where the volume of the lung $V_{lung} = V_e + V_r$.

The diffusion uptake model is based on the following parameters:

Air/Blood Partition Coefficient. The ratio between the equilibrium concentration of the compound in air and in blood. Default value: none.

Blood Flow. The flow of blood through the lungs. Default value: 6000 cm3/min. Status of default: it is the cardiac output of an adult.

Blood Volume. The volume of blood that is present in the lungs. Default value: 750 cm3. Status of default: guess.

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.

Lung Area: Area of the contact surface between lung air and blood. Default value: 600000 cm2 = 60 m2. Status of default: literature value for adult.

Lung Volume: total volume of the lung. Default: 2500 cm3 = 2.5 liter. Status of default: approximated from Silbernagl and Despopoulos (1993).

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

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), explained in the "Fraction model" section.

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.

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_{lung} 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:

$$F = \frac{K_{ab}}{K_{ab} + Q_{lung}/Q_{blood}}$$

where the variables are already defined in the "Diffusion model" section. The parameters of the model are a subset of the parameters used in the diffusion model. Therefore, no separate input dialogue 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 blood. Default value: none.

Blood Flow:The flow of blood through the lungs. Default value: 6000 cm3/min. Status of default: the cardiac output of an adult.

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).

Respirable Fraction. The fraction of the compound that enters the lung and is not deposited in the throat. A 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 dropletsize.

4.4. 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.
In comparison to CONSEXPO 1, the migration screening model and the SKINPERM uptake models are added.

4.4.1. Dermal contact

The contact with a compound is defined using the `define` subentry of the `contact` menu entry, see section 4.2.

4.4.2. Dermal exposure

There are three exposure scenarios defined, and one scenario to model dermal exposure to airborne compounds. The "Fixed Volume" scenario assumes that the product is well mixed, and no diffusion gradients occur in the product. 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. The third scenario, "Migration", models dermal exposure as a result of migration of product to the skin. 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:

$$E = \frac{w_f A}{V_{product} D}$$

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

The parameters to describe this model are:

Amount of Product. the weight of the undiluted product that contacts the skin. Default value: none.

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

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

Dilution. the dilution factor after the weight fraction of the chemical in the product has been established. Values below 1 imply concentration of the product, values above 1 dilution. If the weight fraction is the weight fraction in the diluted product, 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

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:

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

where D is the diffusion coefficient of the compound inside the product and $E(x,t)$ is the ompound concentration in the product at depth x and time t. At the border between product and skin, $x = 0$. At the product/air border at $x=H$, the loss of material from the product is proportional to the concentration difference between the surface of the product and air

$$\phi_{air} = K_l\left(E(H,t) - C_a(t)\right)$$

where ϕ_{air} is the evaporation rate to air, K_l is the exchange coefficient, $E(H,t)$ 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

$$\phi_{skin} = P_d\left(E(0,t) - K_{pb}C_{blood}(t)\right)$$

where ϕ_{skin} is the dermal uptake rate, P_d is the dermal permeability, $E(0,t)$ is the concentration in product at the skin border, K_{pb} is the product/skin partition coefficient, and $C_{blood}(t)$ 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 5 segments will do in most circumstances. By modelling the diffusion gradient inside the product explicitly, while modelling 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.

The parameters in the scenario are:
Concentration compound. The concentration of the chemical compound in the product. Default: none.

Diffusion product. The diffusion rate of the chemical compound in the product. Default: none.

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.

Thickness product. The thickness of the layer of product, measured perpendicular to the skin. Default: none.

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: 5. Status of default: allows for quick calculations, which are not too inaccurate.

Migration. Calculate dermal exposure by migration of a compound from a product onto the skin. The model calculates the amount that has migrated as

$$E = CRt$$

where C is the concentration in the product, R is a transfer rate constant, and t is the duration of exposure. The product volume is used to set the maximum amount of the compound present in the product, limiting the maximum amount that can be transferred onto the skin.

The parameters of the model are
Concentration. The concentration in the product.

Product volume. The volume of the product.

Rate constant. The rate is interpreted as i) the volume of product cleared from the compound per unit of time, ii) the volume of product migrating to the skin per time.

4.4.3. Dermal uptake

Three 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 (Van Veen, 1996). The SKINPERM model is taken from the work of Ten Berge and Wilschut (1995). In the latter two models, 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. Six 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), Robinson (pers. comm.), Wilschut et al. (1996), and Bogen (1995). The equations for the dermal permeability P_d are derived from the octanol/water partition coefficient K_{ow} and the molecular weight MW:

1. Fiserova-Bergerova (1990):
$$P_d = \frac{1}{15}(0.038 + 0.153K_{ow})e^{-0.016MW} \text{ cm / hr}$$
2. Guy and Potts (1992)
$$P_d = 0.0018K_{ow}^{0.71}e^{-0.014MW} \text{ cm / hr}$$
3. McKone and Howd (1992)
$$P_d = MW^{-0.6}\left(0.33 + \frac{h}{0.0000024 + 0.00003K_{ow}^{0.8}}\right)^{-1} \text{ cm / hr}$$
where h is the thickness of the skin, taken as 0.0025 cm.
4. Robinson (Wilschut et al., 1996).
$$P_d = \frac{1}{1/(P_{sc} + P_{pol}) + 1/P_{aq} + 1/P_{cap}} \text{ cm / hr}$$
$$P_{pol} = 10^{-6}\frac{300}{\sqrt{MW}}$$
$$\log P_{sc} = -2.74 + 0.62\log K_{ow} - 0.0054MW$$
$$P_{aq} = 0.15\frac{300}{\sqrt{MW}}$$
$$P_{cap} = 0.93(1 - e^{-P_{cw}A/F}) \approx 0.93,$$
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.
5. Ten Berge, as defined in Wilschut et al. (1996)

$$P_d = \frac{1}{\frac{1}{P_{psc} + P_{pol}} + \frac{1}{P_{aq}}} \text{ cm / hr}$$

$$\log P_{psc} = -1.326 + 0.6097 \log(K_{ow}) - 0.1786 MW^{0.5}$$

$$P_{pol} = \frac{0.0001519}{\sqrt{MW}}$$

$$P_{aq} = \frac{2.5}{\sqrt{MW}}$$

6. Bogen (1995).

$$\log P_d = -0.812 - 0.0104 MW + 0.616 \log K_{ow}$$

Wilschut et al. (1996) evaluated most empirical equations, except number 4 and 6, 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

$$U_c = VEF(t)$$

to calculate the total amount U_c taken up.

The definition of the parameters is:
V: *volume of product*. Defined in one of the exposure scenarios.
E: *exposure*. Defined with the dermal exposure menu entry.
F(t): *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.

Diffusion Model. The diffusion model is based on the concentration difference between the product and skin blood (Van Veen,1996). The uptake rate is defined as

$$U(t) = A_d P_d (E(t) - K_{pb} C_{blood})$$

where *U(t)* is the uptake rate, A_d is the area of dermal contact, P_d the dermal permeability, K_{pb} is the product/blood partition coefficient, *E(t)* is the compound concentration in the product and generally a complex function of time and C_{blood} is the compound concentration in blood. The two compartment model behind the uptake rate equation is described in detail in Van Veen (1996). Essentially, the concentration in the product and the concentration in the blood compartment underneath the skin form the compartments, and the uptake rate is the amount transferred from product to blood per unit of time. The concentration in the product decreases because of uptake, while the blood is continuously diluted by inflow of clean blood.
In case of exposure to airborne compounds, the uptake rate 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

$$U = A_d P_d E(t).$$

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

Exposed Area. The skin area exposed to the product. Default value: 4340 cm2, unless the exposure parameter "product volume" has been defined. Status of default: 4340 cm3 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.

Blood Volume at Exposed 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 area*0.1.

Skin Blood Flowat Exposed Area. 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 * area / 19400, where 19400 cm2 is the total body surface and 2500 cm3/min is the total adult blood flow through the skin.

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.

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 dialogue 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 can be estimated from one of the QSARs.

SKINPERM model. The SKINPERM model is described in detail in Wilschut (1995) and most of the underlying theory in Wilschut et al. (1995). SKINPERM is a diffusion model, but is simplifies the blood concentration to zero. Therefore, parameters relating to body blood are not relevant and the SKINPERM model only uses the area of contact and the permeability to calculate uptake. The uptake equations as given in the diffusion model simplifies to

$$U(t) = A_d P_d E(t),$$

where all parameter have been defined in the above.
The CONSEXPO 2 program only contains the base version of SKINPERM. For the full program, refer to the program of Ten Berge.

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

Exposed Area. The skin area exposed to the product. Default value: 4340 cm2, unless the exposure parameter "product volume" has been defined. Status of default: 4340 cm3 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.

Permeability Skin. A rate parameter which defines how fast the skin is passed. It can be measured or estimated from the molecular weight and the octanol/water partition coefficient, both to be set in the Compound menu entry. The dermal uptake dialogue 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 can be estimated from one of the QSARs.

4.5. 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; Heisterkamp en Olling, 1996, for an overview of food exposure estimation) nor to estimate the acute, local effects of corrosive or reactive products.
In comparison to CONSEXPO 1, the daily intake scenario disappeared. It differed from the single ingestion scenario by the possibility to use measured values. Because each parameter can be defined by measured values, the difference between the scenarios disappeared. The hand-mouth, direct migration and product leaching scenarios have been added.

4.5.1. Oral contact

The contact with a compound is defined using the `define` subentry of the `contact` menu entry, see section 4.2.

4.5.2. Oral 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:

$$E = \frac{w_f q}{D V_{product}}$$

where q is the amount of product, w_f is the weight fraction, D is the dilution and $V_{product}$ is the product volume.

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.

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.

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.

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.

Hand-mouth contact. The scenario is used to quantify oral exposure originating from dermal exposure on the hands and subsequent hand-mouth contact. It is automatically selected when a dermal exposure is present.The scenario asks for the exposure concentration, and calculates intake from concentration times medium intake rate times use duration.

The parameters of the model are
Concentration. The concentration, mass per volume, in the product on the hands. Default: none.

Ingestion rate. The ingestion rate, volume per time, of the product. Default: none.

Leaching from product. Calculate oral exposure by leaching of a compound from a product into the mouth. The scenario is, for example, applicable to teethers. The model calculates the concentration in the product as

$$E(t) = E_0 e^{-\frac{RA}{E_0 V}t}$$

E_0 = initial concentration in product (mg/cm3)
R = initial leaching rate (mg/cm2/minute)
A = area of contact (cm2)
V = volume of product (cm3)
t = contact duration (minute)
The ingested amount of the compound upto time t is calculated from the difference between the initial concentration and the concentration at time t as:

$$I = V(E(0) - E(t))$$

The parameters in the model are
Concentration. The concentration in the product.

Product volume. The volume of the product.

Rate constant. The rate constant set the initial leach rate from the product, as measured for example in laboratory conditions. It is measured in amount leach per time per surface area.

Area. The area in contact with the mouth.

Migration from product to food. The scenario has been set up to screen the migration of a compound from packaging material to food. The model follows the EU Technical Guidance Document, where the amount available for migration is calculated by the concentration of the compound in the product times contact surface times the thickness of the productlayer from which migration may occur. The actual migration is determined by a migrated fraction, calculated from the migration rate times the exposure duration.

The parameters in the scenario are

Article concentration. The concentration of the compound in the article (packaging material) in contact with the product. Default: none.

Wall thickness. The amount of article material in contact with the product, measured by the depth of the article from which the compound may leak into the product. Default: none.

Wall area. Area of the article in contact with the product. Default: none.

Product volume. Volume of product present in the article. Default: none.

Migration rate. Migration rate of the product, given as a rate constant per time. The migration rate times the exposure duration will define the fraction of compound that has migrated into the product. Default: none.

Ingested product volume. The amount of product actually ingested. May be equal to the product volume, but is may be less. Default: none.

4.5.3. Oral 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. The 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 dialogue.

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

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.

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 overal 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:

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

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.

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.

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 travelled in 4 hours.

Intestinal Blood Flow:The flow rate of blood in the wall of the intestine. Default: 1500 cm3/min. Status of default: a value frequently encountered in pharmacokinetic literature.

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.

Intestine Radius:Radius of the small intestine. Default value: 2 cm. Status of default: guess.Range: 0 - 1.

5. DATABASE

CONSEXPO uses a database to retrieve default models and parameter values for product categories. The database can either be local or on a local area network. The local database is a Paradox 5 database, which is a part of the CONSEXPO program. The database is under development, and presently CONSEXPO is distributed with an empty database, containing only a test item. In the future, we will distribute and update the defaults database separately from CONSEXPO. A description of the conceptual and physical model of the database is underway.
The local area network database may be any database able to use SQL statements. The database is identified in the IDAPI interface to the Borland Database Engine. Users interested in setting up a defaults database on an SQL server should contact the author for instructions. We are not able to test all database environments. The database interface is provided as is, without implying that it will work on your system.

5.1. Disabled database

The database may be unavailable when

- the Borland database engine is not installed
- the database files are not present in the database path;
- the database is incomplete;
- the database engine can not be initialised;

In this case, the database entries in CONSEXPO are grey and disabled.
If errors occur during database queries, the program will inform you with a message. Most messages speak for themselves. If an unspecified error occurs, most likely the database can not be reached (path ? files present ?).

6. STOCHASTIC PARAMETERS

6.1. 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 variability and uncertainty of parameters. Therefore, it convolutes variability and uncertainty into one distribution. There are three distributions available at the moment, the normal, lognormal and uniform distribution. In addition, measured data can be used to establish an empirical 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.

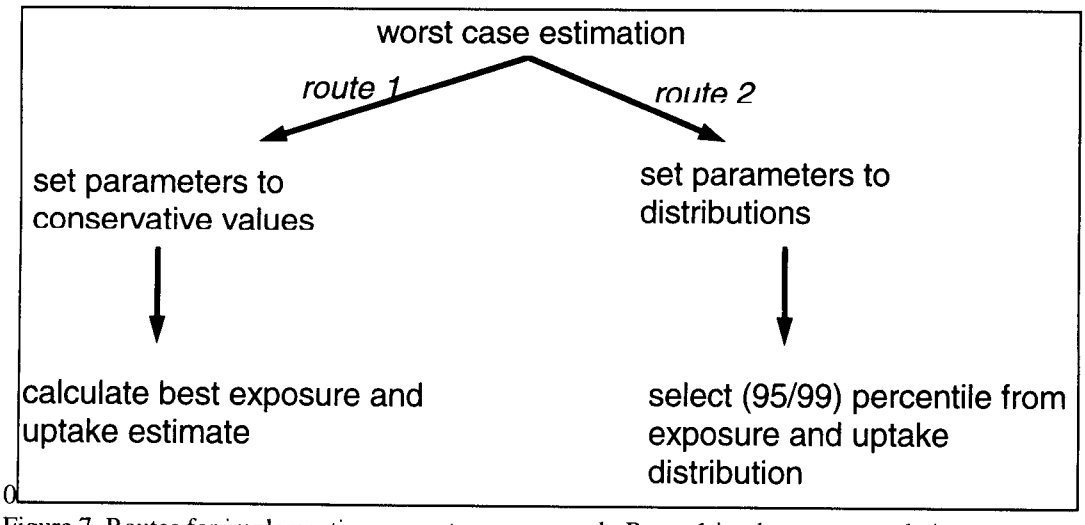

Figure 7. Routes for implementing a worst case approach. Route 1 implements cumulative worst case, while route 2 implements worst case stochastically.

6.2. 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 values (Fig. 6, route 1). In CONSEXPO 2 this route can be chosen by selecting the worst case option in the exposure definition dialogues, 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 nicknamed "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. 6, 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, 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. The exposure and uptake distributions are then calculated directly from the parameter distribution, without numerical calculations (see Van Veen (1995) for details). Calculations are relatively simple for a single parameter distribution. When multiple parameters attain a distribution, calculations quickly become tedious. The CONSEXPO program therefore applies this technique only when a single parameter attains a distribution.
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 that attain a distribution achieve a value randomly taken from their distribution. Then, exposure and uptake are calculated, using those parameter values. This process is repeated, typically in the order of 5000-10000 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.

6.3. Distributions

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

6.3.1. 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.

6.3.2. 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 the 50 percentile, the value that is exactly in the middle of the distribution. The coefficient of variation is the mean divided by the standard deviation.

6.3.3. 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.

6.3.4. Empirical distribution

The empirical distribution is based on data. The program constructs a cumulative distribution from the data and samples from this distribution. The sampling will therefore only return one of the data points. Data are contained in a data file. The data file contains measured concentrations, the dimension of the concentrations and optionally comments. Each line of the file may contain either of the following:

- A dimension specifier, in the form of:

  ```
  dim:xx
  ```

  where xx is a valid dimension, i.e. one of the dimensions in the dimension box in the parameter dialogue. Please adhere literally to these dimensions. A dimension specifier is obligatory.
- A concentration, which has to be a number starting on the beginning of the line.
- A multiple of concentrations, to specify a concentration that occurs more then once. Its specification is:

```
yy*zz
```

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

- 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
```

6.4. 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 uptake 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. 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. 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 `System` dialogue in the `Options` menu.

6.5. Sensitivity analysis

The uniform parameter distribution and the procedures to display exposure and uptake distributions allow 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 may differ from the earlier estimates. A global sensitivity analysis, on the other hand, would determine the sensitivity of a model for parameters regardless of the value of others. This is not possible with the present program.

7. TUTORIAL

The use of CONSEXPO 2 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 due to evaporation from the can and how much of that is taken up in the person cleaning the bike ?

7.1. Step 1.

Start the CONSEXPO 2.0 program from the program or the file manager. The program will created an consumer exposure group if that is not present. The program opens with the model overview window, which shows that no exposures have been defined.

Now you are ready to use the program.

7.2. Step 2.

Choose the "Product" entry from the menu bar. A submenu will pop up with the entries "Select category", and "Select compound". Choose the "Select compound" 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 need, click on the arrow in the dimension box, and choose the appropriate dimension. Now, Choose "Ok" to accept the compound parameters.

The Retrieve button is only available when you are connected to the CONSEXPO database.

Now, the compound is defined.

7.3. 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 dialogue 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.

7.4. 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 dialogue 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. Eeeh ?? 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 dialogue 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^3/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^2. First, set the right dimension, dm^2, in the dimension box. Then, click on the parameter name. A dialogue 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 dialogue. 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 dialogue 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.

7.5. Step 5.

Last but not least: uptake. The uptake model and parameters can be reached via the Uptake menu entry (surprise!). 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 dialogue is displayed. This dialogue 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), the lung blood flow to 5000 cm^3/minute and accept the default for ventilation rate and respirable fraction. We don't need the permeability. Choose Ok. And once again Ok to leave the uptake definition.

That's it for uptake.

7.6. Step 6.

What about the results ?
If we choose from the Report menu the Point entry once again, the report dialogue 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 dialogue ("Ok") and choose "Options" and "Graph display". Alternatively, click on the second button from the right in the button bar, the white button with the graph. Now, select "Time course" from the "Report" menu. From the dialogue, 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 report dialogue.
What about the effect of variation in the release area in the open can scenario ? In step 4, an 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 0.0002 mg/cm3 (=200 mg/m3).

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