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Aggregating human exposure to chemicals

An overview of tools and methodologies

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Abstract

Aggregating human exposure to chemicals – An overview of tools and methodologies

Available computer models for estimating the exposure to substances from multiple consumer products are not suited for this task. Consumers are daily exposed to chemical substances from consumer products. The level of this exposure has to be assessed to evaluate the consequences of exposure to a substance for public health. Considering that a substance may be contained in several consumer products (for instance, aromatic substances, flame retardants and softeners), the contribution of these products to the total exposure will have to be added up to determine the aggregate exposure. Aggregate consumer (non-food) exposure is not routinely evaluated in European assessment frameworks. This report examines to what extent available computer models are suited for evaluating aggregate exposure to consumer products. A method for performing aggregate exposure assessment is also described.

Key words: consumer, exposure, aggregate, risk, substances

Rapport in het kort

Blootstelling aan chemische stoffen vanuit verschillende consumentenproducten

Dagelijks staat de consument bloot aan chemische stoffen die zijn verwerkt in verschillende (non-food) producten. Om de gevolgen voor de volksgezondheid te kunnen beoordelen moet in de eerste plaats de blootstelling bepaald worden. De optelsom van de totale (geaggregeerde) blootstelling aan een stof uit verschillende consumentenproducten (denk bijvoorbeeld aan geurstoffen, vlamvertragers, weekmakers) moet kunnen worden vastgesteld.
Dit rapport kijkt in welke mate bestaande computermodellen geschikt zijn om geaggregeerde blootstelling aan chemische stoffen uit consumentenproducten te bepalen. Op dit moment berekenen de Europese beoordelingskaders deze geaggregeerde consumentenblootstelling (non-food) nog niet routinematig. Als eerste aanzet tot het opvullen van dit hiaat beschrijft dit rapport een methode waarmee een dergelijke geaggregeerde blootstellingsbepaling kan worden uitgevoerd.

Trefwoorden: chemische stoffen, geaggregeerde blootstelling, consumentenproducten

Glossary

The main part of this glossary is adopted from the IPCS Risk Assessment Terminology[1]

absorption factor

Percentage or fraction of an external exposing mass that is taken up systemically (uptake).

acute exposure

A contact between an agent and a target occurring over a short time, generally less than a day. (Other terms, such as 'short-term exposure" and "single dose,' are also used.)

aggregate exposure

The total exposure that arises from multiple sources via different pathways and routes.

chronic exposure

Multiple exposures occurring over an extended period of time or over a significant fraction of a human's lifetime.

cumulative exposure

The total exposure to multiple chemicals that have a common mechanism of action.

dose

The amount of agent that enters a target after crossing an exposure surface. If the exposure surface is an absorption barrier, the dose is an absorbed dose/uptake dose (see uptake); otherwise, it is an intake dose (see intake).

deterministic model

A mathematical representation of a system in which the input data needed to evaluate a particular state of the system, are represented by single (point) values.

exposure factor

Value for a parameter that determines the level of exposure, such as food intake rate, consumer product use characteristics, anthropometric data.

exposure pathway

The course an agent takes from the source to the target.

exposure route

The way in which an agent enters a target after contact (e.g., by ingestion, inhalation, or dermal absorption).

exposure scenario

A combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur. These may include the source, the ex-

posed population, the time frame of exposure, microenvironment(s), and activities. Scenarios are often created to aid exposure assessors in estimating exposure.

hazard index

Risk ratio of the dose from exposure to the reference dose.

intake

The process by which an agent crosses an outer exposure surface of a target without passing an absorption barrier, i.e., through ingestion or inhalation

Margin of exposure (MOE)

The ratio of the no-observed adverse-effect-level to the estimated exposure dose.

probabilistic model

A mathematical representation of a system in which the input data needed to evaluate a particular state of the system, are represented by distributions of values.

reference dose

A numerical estimate of a daily oral exposure to the human population, including sensitive subgroups such as children, that is not likely to cause harmful effects during a lifetime. RfDs are generally used for health effects that are thought to have a threshold or low dose limit for producing effects.

risk index (RI)

The quotient of the margin of exposure (MOE) and the acceptable margin of exposure (the margin of exposure incorporating the uncertainty factors).

source

The origin of an agent for the purposes of an exposure assessment.

subchronic exposure

Multiple or continuous exposures lasting for approximately ten percent of an experimental species lifetime, usually over a three-month period.

toxicity equivalent (TEQ)

Contribution of a specified component (or components) to the toxicity of a mixture of related substances.

time profile

A continuous record of instantaneous values over a time period (e.g., exposure, dose, medium intake rate).

uncertainty factor

Uncertainty factors are intended to account for (1) the variation in sensitivity among humans; (2) the uncertainty in extrapolating animal data to humans; (3) the uncertainty in extrapolating data obtained in a study that covers less than the full life of the exposed animal or human; and (4) the uncertainty in using LOAEL data rather than NOAEL data.

uptake (absorption)

The process by which an agent crosses an absorption barrier.

use pattern

Specification of the use of a consumer product in terms of use frequency, amount of product used etc.

Contents

Summary

In this report an inventory was made of techniques and tools that are available to aggregate the human exposure to chemicals from different sources and along different pathways and routes. In the first chapter a brief summary of the considerations that apply to aggregation was given. In the second chapter an overview of existing software tools that assess the human exposure from different sources and along different pathways, is presented. It is pointed out that the level of detail, with which aggregation is done, should be dictated by the scope and purpose of the assessment. Demands for a first tier, screening type of assessment on the required level of detail are much lower than those of an assessment that has to give a realistic quantification of the variation of the exposure in a population. Whatever the scope the assessment, however, the aggregation should be based on a person oriented approach: exposure profiles should be constructed for a single person, (may he represent the entire population or be a realistic model of a person in the population) as this is the only way to ensure the consistency of exposure profile in the sense that no unrealistic or unrepresentative combinations of exposure are added in the aggregation.

In spite of the fact that the need for doing aggregate exposure assessments is increasingly acknowledged, the only area in which aggregation techniques are fully implemented and made use of, is the field of exposure assessment to pesticides in the USA. This on the mandate of the US Food Quality Protection Act. The Calendex, CARES and LifeLine 2.0 software programs, described in detail in section 2.2, enable the assessor to estimate exposures arising from different sources, such as tap water, food residues and household products to be aggregated in a consistent manner. Tools developed in other fields, in particular the assessment of human exposure to chemicals released as waste into the environment, generally do consider different pathways of exposure and sometimes allow for the aggregation (addition) of the exposures along these pathways, but do so in a crude manner, not enforcing the consistency and representativeness of the constructed exposure profiles. The results obtained by these methods should as a rule only be used as screening of upper boundaries or average values of the population exposure (depending on the choices of input parameters, e.g. probable or conservative values).

Section three focuses on the more specific area of the assessment of human exposure to chemicals in consumer products. Exposure to chemicals may arise from different products at different occasions. To account for all these contributions, similar methods as described for the general aggregation of exposure may be used.

There is a number of specialized software tools available for the assessment of consumer exposures, but none of these implements or facilitates doing aggregate assessment.

The general procedure for aggregation of exposures given in chapter 1 was adapted to the

case of consumer product exposure. Again, the detail with which such a scheme should be implemented depends on the scope and purpose of the assessment. Approaches at increasing level of detail were sketched and illustrated with a simple example. The gained insight in the exposure in proceeding to higher tiers comes at the cost of rapidly increasing data demands and complexity of the assessment.

Introduction

Humans may be exposed to chemicals at different occasions and in a number of ways. Chemicals may be released into the environment during production or due to the disposal of products. After release these chemicals may disperse into residential air, tap water and food stuff and may be contacted by people via inhalation and ingestion. Alternatively, the chemical may be contained in materials and consumer products, and users of these materials and products may be exposed to the chemical by inhalation, dermal contact and ingestion. To assess the total exposure to chemicals all the emission sources of the chemical and all the ways in which a human can be exposed have to be taken into account.
To assess the total human exposure to a chemical, all the contributing sources, pathways and routes should be taken into account; that is, the assessment should aggregate all these contributions.
In this report, aggregation of the exposure is defined as the addition of the contributions of all the sources, pathways and routes (oral, dermal and inhalation) from and via which the exposure to a single chemical takes place.
Aggregate exposure is to be distinguished from cumulative exposure, which is, in this document, understood as the exposure to substances with the same mechanism of action.
Aggregation of the exposure in risk assessments is not common practice.The risks from chemical exposure are often assessed for different sources and exposure pathways separately. In such a procedure, there is always a possibility that the risk of chemical exposure is underestimated.
The need to consider aggregate exposure in assessments is increasingly acknowledged. The US Food Quality Protection Act[2] mandates the evaluation of both aggregate and cumulative risks associated with pesticide use, therefore a lot of experience is already gained in the USA.
Special attention is paid in this report to the aggregate exposure of chemicals from multiple consumer products. Consumer products constitute a potentially important pathway for a variety of chemicals such as flame retardants, phthalates, pesticides and VOCs[3,4,5] . Exposure assessments for chemicals released from consumer products are regularly done for the authorization of substances or the evaluation of product safety. Mostly these assessments are performed on a per product basis and the exposures arising from other products containing the same substance are neglected. Obviously, this approach may yield an underestimation of the risks involved. To account for the exposures from several products containing the same substance of concern, similar techniques as for determining aggregate exposure can be employed.

In this report an inventory of tools and methodologies for aggregating exposure, is made. Basic principals and considerations of aggregation in exposure and risk assessments are briefly discussed in chapter 1. Subsequently, in chapter 2, an overview and a discussion of computer exposure estimation tools that, in one way or another, implement aggregation is given. The applicability of the various tools to determine aggregate exposure of consumer to chemicals in consumer products is discussed, when appropriate.
In chapter 3 the discussion is focused on the human exposure to chemicals in consumer products. Specific considerations that pertain to aggregate exposure assessments for a chemical contained in multiple consumer products are given in section 3.1. In section 3.2 specialized computer tools modeling the human exposure to chemicals in consumer products are briefly reviewed and their applicability in aggregate exposure assessments is discussed.
In section 3.3 we sketch in some detail how an aggregation of the exposures from different products may be performed for different required levels of detail. This framework is illustrated in section 3.4 with an example, in which the aggregate exposure is estimated for a combination of cleaning products containing the same (hypothetical) substance.
In the discussion of different exposure (software) tools that are available, focus will be on the way they deal with the aggregation of the exposure. More general comparison studies of these tools have been presented elsewhere[6,7,8]. It is not the intention of this study to duplicate that work.

1. Introduction

1.1. Aggregate exposure assessment

Assessments of human exposure to chemicals may be conducted for different reasons and with different objectives. The purpose of an assessment may be to get a rough, order-of-magnitude estimate of the maximal level to which a population is exposed to a chemical, or it may be to obtain a detailed insight into the distribution of exposure over and within different subpopulations in order to quantify the effects of the exposure and to analyse the relative contributions of different sources, pathways and routes to the expected health effects in the population.

Usually, different levels of detail and sophistication of assessment are combined in a tiered approach (see for example[9,10]). In such an approach, the first step often consists in a very crude, quasi-quantitative estimate (often referred to as a tier 0 estimate) in which a number of worst case assumptions is made regarding the exposure of a population (e.g. the fraction of the total production tonnage of a chemical that ends up in the population is conservatively assumed to be very large). If a level of concern is exceeded, stepwise more realistic and detailed approaches will be used, requiring real data or more refined assumptions, until a final conclusion can be drawn.

The required level of detail of the assessment determines how the exposure will be assessed and, in particular, how the aggregation has to be performed.

Irrespective of the required level of detail of the assessment, however, the aggregation should adhere to a person-oriented approach to maintain consistency. In an assessment, the exposure for a hypothetical individual is estimated. If exposure potentially occurs via different pathways, the combination of the pathways considered in the assessment should represent a realistic situation for the individual considered. Pathways that in reality would never co-occur, should not be combined (for example: the occupational exposure of an industrial worker should not be combined with the hand-mouth contact exposure of a toddler). Unrealistic combinations of exposure pathways are avoided by starting an assessment with the selection of an exposed individual and constructing a realistic exposure profile for this person.

Acknowledging the fact that aggregating the exposure should be person-oriented, there still remains the question what this person represents.

It may be that this person is entirely hypothetical and stands model for a high-exposed, sensitive subpopulation (e.g. industrial workers or children). Or it can be that this person is intended to be a realistic model of a real person in the population under consideration. The first case is habitually employed in lower tier assessments. The assessment boils down to a deterministic (point) calculation using conservative input values for all expo-

sure parameters. The outcome of the assessment will be an estimate of the exposure that is very likely to be an upper bound of the exposures that occur in reality. This high bound exposure may be compared to some acceptable level to judge whether there is any reason for concern associated with the exposures to this substance. If there is reason for concern (or at least adverse health effects can not be excluded in this first step), the assessment will have to be refined by additional data collection or more detailed and advanced modeling.
The second approach is usually encountered in detailed, probabilistic population exposure assessments. The assessment is repeated for a large number of similarly modeled individuals that together represent the population of interest. Usually the modeled individuals are randomly constructed from elaborate (distributional) data on the population such as anthropometric, social status and time activity data. The integration of the individual aggregate exposures to population exposures is done, in most cases, by Monte Carlo simulation.

Another important consideration when aggregating exposure is the toxicity of the substance under study. The timescale on which the exposure is assessed should be consistent with the exposure durations for which health effects are observed. If acute toxicity is a critical endpoint, the assessment should estimate exposures on acute timescales (e.g. of one day). If, on the other hand, only chronic exposures have to be considered, the assessment may estimate one year average doses, or a similar long period average.
In the case of acute exposures, details of the temporal and spatial correlations of the exposure events become important, since, for instance, the simultaneous occurrence of two or more exposures along different pathways may in combination lead to peak exposures exceeding some tolerable level, although each exposure event individually may remain below this level (see Figure 1). If, on the other hand, longer (chronic or sub-chronic) timescales are considered, adding the average exposures of the different pathways without explicit reference to the temporal correlations between the exposure events, may be acceptable.
In determining longer time averages from detailed exposure profiles (such as weekly or yearly averaged profiles from daily profiles) it should be noted that the time averaging of a highly variable profile may depend not only on the length of the averaging interval but also on the begin and end time of the averaging interval. The value of a weekly averaged exposure may be dependent on whether the averaging interval ranges from Monday to Monday or from Sunday to Sunday, for example.

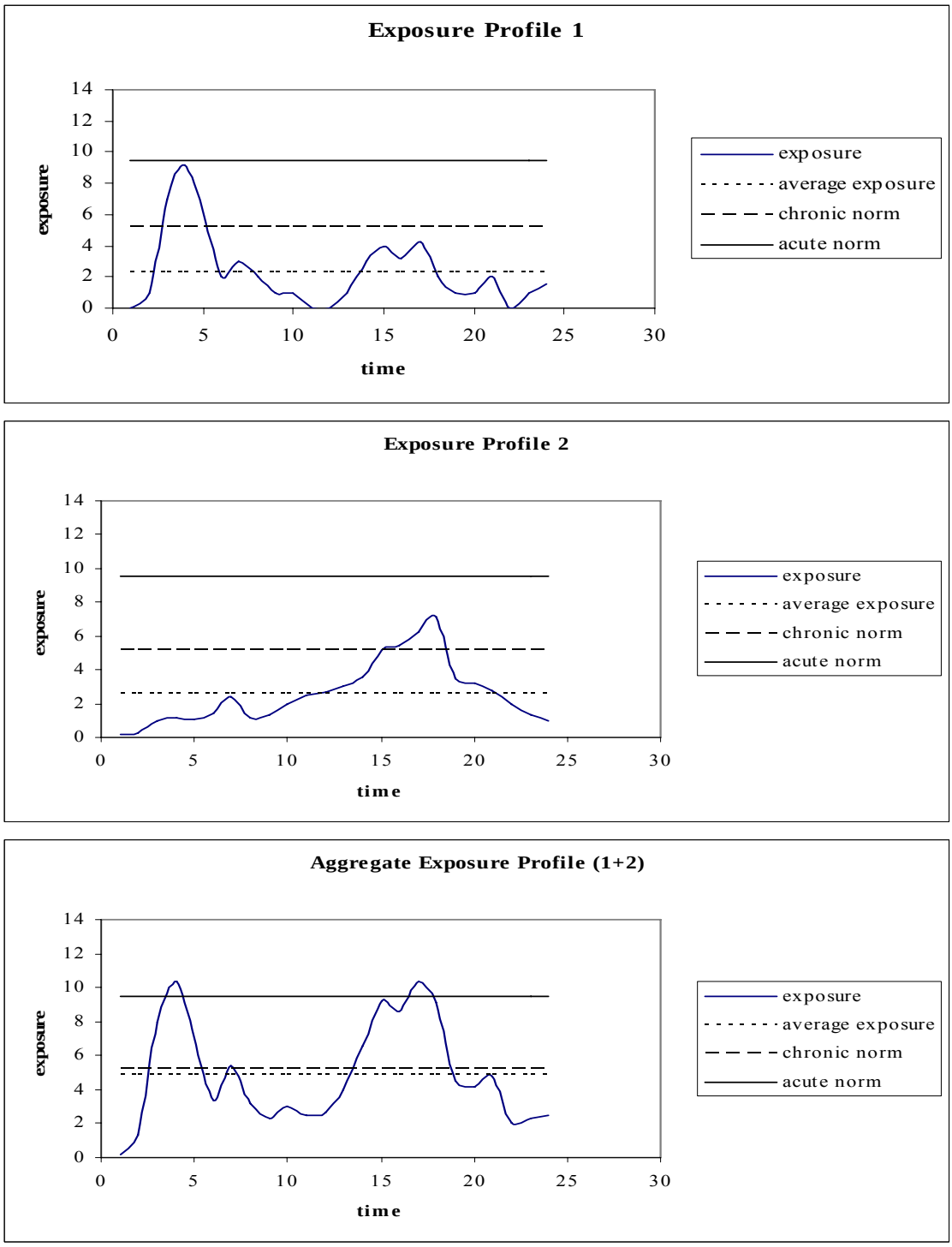


Figure 1 Combining exposure profiles that are correlated in time. The aggregate exposure of events 1 and 2 may lead to exceeding of a norm for acute toxicity whereas the exposure profiles separately remain both below this level and the long time average of the aggregate exposure remains below the level of concern of the chronic exposure.

Besides the timescale on which the exposure assessment should be based, also the route of exposure (e.g. inhalation, dermal or oral exposure) is determined by the toxicological profile of the substance under consideration. If adverse health effects are observed for a specific route (e.g. dermal specific toxicity such as eczema), the exposure should be assessed for this route separately from other routes, and the risk would be assessed for the route of concern explicitly.
More generally, health effects may differ among routes of exposure. In this case, aggregation should be performed first for each individual route and, after this per-route evaluation, the aggregate exposures per route should be integrated to a total aggregate exposure. In the summation of the exposure over different routes, the usual considerations for integration over different routes apply. The exposures should be expressed in a metric that is common for the different routes and subsequently be added.
The US EPA Office for Pesticide Programs suggests the use of two risk metrics the 'total margin of exposure' (MOE_{tot}), and the 'aggregate risk index' (ARI)[11].

The MOE is calculated by dividing the No-Observed-Adverse-Effect Level (NOAEL) by the estimated exposure for the considered route.
The MOE for each route is compared with an UF (typically a factor of 100) which serves as a standard when ascertaining whether a given exposure is acceptable. To combine different MOEs into one, one uses the following equation:

$$MOE_{tot} = \frac{1}{\frac{1}{MOE_1} + \frac{1}{MOE_2} + \ldots + \frac{1}{MOE_n}}$$

where MOE_1, MOE_2, ….MOE_n represent route specific (e.g. oral, dermal, inhalation), MOEs.
This approach is only valid when the uncertainty factor for each of the different routes is the same, so the MOE_{tot} can be assessed by comparing it to this uncertainty factor.

If this is not the case, the constituting MOEs should be normalized into a ARI first by dividing each MOE by its corresponding UF:

$$ARI \equiv \frac{MOE}{UF}$$

now, the total ARI is obtained by:

$$ARI_{tot} = \frac{1}{\frac{1}{ARI_1} + \frac{1}{ARI_2} + \ldots + \frac{1}{ARI_n}}$$

Both approaches are equivalent if the UFs are the same for all routes.
Other methods to combine exposures via different routes make use of Toxicity Equivalency Factors (TEFs)[12](used for cumulative exposure assessment) or the Hazard Index (HI)[13]

Aggregation of the chemical exposure from different sources is routinely done in dietary intake studies, where a chemical may be contained in widely different food products and commodities and the total exposure is from the intake of a daily varying selection of these products and ingredients. A procedure commonly applied in these cases, is the construction of daily consumption patterns for a population of potentially exposed individuals combining data on food consumption surveys and measurements of chemical levels in foodstuff. From daily consumption patterns in a population, the total daily intake of a chemical follows from the addition of the intake over all consumed food products. From the individual daily intakes, long term averages and distributions of the exposure within the population follow.

Aggregating the chemical exposure from multiple sources could follow a similar procedure. A typical aggregate exposure assessment could take the following steps:

1. identify the sources and pathways of exposure.
2. identify and define the populations of concern.
3. construct the exposure profiles for individuals taken from these populations
4. aggregate the exposure per route for each individual from his exposure profile, on the timescales that are required for the assessment as dictated by the toxicological end points of the substance under consideration (e.g. daily intakes per route).
5. construct appropriate time averages and population exposure measures from the individual exposure profiles. In this step, for instance, specific percentiles of the exposure within a population are determined, or sub-chronic or chronic exposures are derived from daily exposure values.
6. integrate the exposures over the different routes, using an appropriate dose metric.

2. Human Exposure Assessment Computer Tools

A number of the models and approaches used in various fields of chemical exposure assessment have been implemented in computer programs that are publicly available. In this section we will give an overview and a brief description of some commonly used tools and discuss to what extent aggregation has been implemented. For non-European tools, the applicability of the tool to the European situation is discussed.
We included the following programs in this review:

- CalTOX
- CSOIL
- E-FAST
- EUSES
- Calendex
- CARES
- LifeLine

The only criteria for inclusion in this list were that the tools aid in the estimation of human exposure to chemicals and that they in one way or the other include multiple sources and pathways of exposure. As already remarked, the area of application and the level of sophistication vary widely among the tools. A detailed comparison between the different tools was therefore not deemed useful.
Several reports exist on the comparison and description of computer tools that can be used to perform exposure assessment[5,6,7]. We do not aim at repeating the work done in these reports. We will only briefly describe each of the computer tools and discuss how they implement aggregation of the exposure. In addition, we will indicate, if appropriate, to what extent the tools are capable of dealing with human exposure to chemicals in consumer products.
The modeling tools can be divided into two distinct groups.
The first group of tools (CalTOX, CSOIL, E-FAST, EUSES, SHEDS) model the exposure of humans to chemical emissions into the environment by industrial waste or disposal of chemicals and subsequent dispersion into contact media and, finally into the personal environment. These tools will be described in section 2.1.
The second group (CALENDEX, CARES, LifeLine) is a number of tools that are used exclusively for the evaluation of pesticides that are used both in agriculture and in residences. Tools in this group differ in the level of complexity and the number of pathways examined.
This group of tools will be described in section 2.2.

2.1 Programs modeling human aggregate exposure to chemicals from environment

2.1.1 CALTOX

General description

CalTOX is a risk evaluation model that has been developed at the Berkeley National Laboratory with the support of the US EPA National Exposure Research Laboratory. It is designed to assist in the assessment of human exposures and risks from continuous releases of hazardous wastes into multiple environmental media, i.e. air, soil and water. Soil is assumed to be the primary environmental medium contaminated. From the contaminated soil, multiple pathways of human exposure are considered, such as exposure via contaminated tap water, soil, outdoor air, indoor air and food.
CalTOX calculates chronic daily intakes (route specific and integrated). These chemical exposure doses can be used to quantify health risks[14].
The models have been implemented in Microsoft Excel and therefore need this program to run.

Exposure calculations

CalTOX has two main modeling components:

- a multimedia transport and transformation module to estimate the time-varying distribution of contaminants among different environmental compartments, using fugacity and fugacity capacity data for the modeled chemicals.
- a multiple pathway exposure model, which calculates how much of a chemical reaches the body using environmental concentration and contact factors (e.g. breathing rate).

The primary emission is assumed to be into the soil. From the soil concentration human exposure may arise along a number of pathways such as:

- inhalation exposures indoors
- inhalation in shower/bath
- inhalation outdoors
- inhalation particles indoors
- transfer of soil dust to indoor air
- use of ground water as tap water
- ingestion of tap water
- ingestion of crop
- ingestion of homegrown meat
- ingestion of locally caught fish

- direct soil ingestion
- breast milk ingestion by infants

For each of these pathways, daily intake rates of the contacting medium (air, tap water, crop, meat etc.) that characterize the exposed person must be specified. The user can customize the exposure profile of the exposed person by in- or excluding pathways.
A total daily intake for the exposed person is obtained by aggregation over the different exposure pathways. The model outputs are averaged daily (chronic) doses.
CalTOX does not include exposures from chemicals in consumer products.

Data needs

The user has to specify a number of different sets of data. These are:

- chemical data (basic physical chemical data, partition coefficients to different environmental compartments, biotransformation data, half life times in various compartments)
- landscape properties (boundary layers, water and air content in soil, porosity sediment, and more)
- human exposure factors (intake rates of various contacting media, body weight etc.)

For all of these, CalTOX provides default databases within the Excel sheet, but the data may be manually overwritten. Properties of a number of chemicals are given, as well as landscape data for US states and US average data. Default human exposure factors for different groups in the population are given.

Aggregation

CalTOX aggregates the exposure over different pathways. The aggregation is done by constructing an exposure profile (customizable by the user) for the modeled person by specifying the routes and pathways via which the person is exposed. Variations within the population and uncertainty about the exact value of the input parameters can be accounted for by supplying distributions as input. Variations within the population in exposure profile (i.e. different persons may be exposed via different pathways) can not be assessed within a single simulation. As a consequence, aggregation is performed only for distinct groups (with specific, fixed exposure profiles) in a single assessment. Thus it is not possible, for example, in the program to accommodate in one simulation the exposure of children through the intake of breast milk and the exposure of an adult population via fish and meat intake. These two populations have to be simulated in separate model runs. Another limitation of the aggregation in the CalTOX program is the fact that the program does not aggregate over multiple releases into the environment. Only the exposure arising from one source at a time can be assessed.

Daily intake data are given as year averaged values. Temporal variations in intake rates (for instance, day to day or seasonal variation in meat or fish intake rates) can not be accounted for, limiting the timescale of the CalTOX assessments to chronic (that is, one year (or longer) average) exposures.

Applicability to European situation

The CalTOX tool is fully customizable. The sets with default input data on landscapes and human exposure factors are only valid for the US, but may be overwritten with data adapted to a (non-US) region of application.

2.1.2 CSOIL

General description

CSOIL is an aggregate model that estimates the total human uptake of a soil contaminant. The conceptual model (that is, the set of equations) has been developed at the Dutch National Institute for Public Health and the Environment (RIVM) and it has been implemented in the commercially available RISC-HUMAN tool (http://www.risc-site.nl). The tool allows only for deterministic calculations[15].

Exposure calculations

From the user-specified soil concentration of a chemical the model calculates human exposure in a number of steps. First, the distribution of the chemical over different phases in soil (solid, liquid and gas) is determined. Next, the concentrations in contact media are estimated (air flux into indoor and outdoor air, accumulation in crops, permeation into tap water and the concentration in bathroom air). And finally, human exposure is assessed. Pathways include:

- ingestion of dust and soil
- dermal contact with dust and soil
- inhalation of soil particles
- ingestion of contaminated crop
- intake of tap water
- vapour inhalation during showering
- dermal contact during bathing and showering

Data needs

CSOIL needs a set of basic physical chemical properties of the substance of concern such as molecular weight, water solubility, K_{ow}, vapour pressure, bioconcentration factor. In addition to these data, toxicological information has to be provided. For a number of parameters such as soil properties, and anthropometric data, defaults are suggested.

Aggregation

The total uptake of the chemical in the body is determined by summation of the contributions of the different pathways and routes using (default) intake rates and absorption factors for each route and contact medium. From this total intake an average lifelong daily (aggregate) intake is determined. Distributional calculations are not supported although the model distinguishes between two different subpopulations: adults and children for which assessments are performed separately.

2.1.3 E-FAST

General description

E-fast is an acronym for 'Exposure and Fate Assessment Screening Tool'. It is a screening level computer tool that allows the user to generate estimates of chemical concentrations in water to which aquatic life may be exposed and estimates of human inhalation and ingestion exposures resulting from chemical releases to air, water and land. E-FAST can also be used to assess inhalation and dermal exposures to chemicals that may result from use of certain types of consumer products. The program was developed by Versar Inc., to support the US Environmental Protection Agency (EPA) assessments of potential exposures to new chemicals which are submitted to EPA under the Toxic Substances Control Act.

The program does not allow for probabilistic exposure evaluations, but considers different age groups within the population[16].

Exposure calculations

1. Indirect human exposure via the environment

In assessing the indirect human exposure via the environment E-FAST considers as exposure pathways the inhalation of air, the ingestion of drinking water and fish consumption. To arrive from surface and ground water concentrations to concentrations in tap water the effects of purification are estimated. Intake of the chemical is determined by combining this concentration with drinking water intake rates.

The estimate of human exposure to the chemical by intake of fish combines estimates of the surface water and ground water concentrations with the estimation of the bioaccumulation of the chemical in fish and assumptions on the fish consumption.

For inhalation exposures, E-FAST uses simple, conservative methods to estimate ambient air concentrations that may result from industrial air emissions. Using this estimate of the ambient air concentrations, an average inhalation intake (either over 30 (ADDpot) or 75 years (LADDpot)) is determined.

2. Exposure to consumer products

E-FAST estimates potential inhalation exposure and potential and absorbed dermal exposure to chemicals in certain types of consumer products. E-FAST implements the same calculations as the MCCEM, SCIES and DERMAL tools.
Consumer exposure scenarios include:

- general purpose cleaner
- interior latex paint
- fabric protector
- aerosol paint
- liquid laundry detergent
- solid air freshener
- bar soap
- used motor oil
- user defined scenarios

Data needs

The user has to provide data on:

- Releases to air, water and land
- Frequencies and durations of release events
- Removal in wastewater treatment
- Removal in drinking water treatment
- Fractions of the chemical that will sorb to sludge
- Bio concentration factor
- Potential for migration to ground water from land disposal
- Removal by air pollution control devices or by incineration
- Weight fraction in consumer products
- Physico-chemical parameters
- Anthropometric data (body weight, inhalation rate). The program provides defaults for different age categories that can be overwritten.

E-FAST includes a database of stream flow values obtained from the ‘Gage File’ in the EPA's STORET (STOrage and RETrieval) system. Necessary stream flows are retrieved from this database, on basis of explicit facility name or on Standard Industrial Classification (SIC) code. In addition the program contains facility information for over 27.000 direct discharging facilities in the US.
For many of the input parameters, the program suggests default values.

Aggregation
E-FAST considers the ingestion and inhalation routes of exposure and a number of exposure pathways but the exposures are only reported per pathway and not summed. Hence, the model does not aggregate the exposure in the sense defined in this document.

Applicability to European situation
The tool is especially designed for exposure estimations in the US. The methods can be applied to regions outside the US, but the included databases on stream flows and discharging facilities may not be usable or representative.

2.1.4 EUSES

General description
Full program name: European Union System for the Evaluation of Substances 2 (EUSES 2). The development of EUSES was commissioned by the European Commission to the National Institute of Public Health and the Environment (RIVM) of The Netherlands. The work was supervised by an EU working group comprised of representatives of the JRC-European Chemicals Bureau, EU Member States and the European chemical industry. TSA Group Delft BV was responsible for programming the system.

The PC program EUSES is designed as a decision-support system for the evaluation of the risks of substances to man and the environment. The system is fully described in the EUSES documentation and is based on the EU Technical Guidance Documents (TGDs; EC-TGD, 2003) for risk assessment of new and existing substances and biocides.
EUSES allows for a number of different human risk assessments including the assessment of human exposure to chemicals via the environment, humans exposed to chemicals via consumer products and humans exposed at the workplace.
The inhalation, dermal and oral routes of exposure are considered. The tool allows only for deterministic calculations. Quantitative evaluations of the uncertainty of and the variability in the assessments can therefore not be made[17,18,19].

Exposure calculations
EUSES comprises several exposure modules:

1. Exposure of man via the environment

With EUSES, first releases to environmental compartments (air, surface water, marine water, sediment, soil and groundwater) or the indoor environment are predicted based on the volume of the chemical produced, imported or used, the use pattern, and physico-chemical properties of the chemical. Next, estimates are made of the human intake of the chemical via drinking water and food products (root crops, leaf crops, meat, milk and fish) and of the exposure via indoor air. The intake rates of the different media are assessed on

basis of a standard consumption pattern that represents the total population and these intakes via the different pathways are added. Exposures can be estimated both on regional and local scales.

2. Consumer Exposure

To assess the human exposure to chemicals in consumer products, EUSES offers different consumer exposure scenarios. One inhalation, two dermal and two oral scenarios:

- Inhalation: a substance that is released as a gas, vapour or airborne particulate into a room (e.g. a component of an aerosol insecticide, a carrier/solvent in a cosmetic formulation, a powder detergent). Release may be the result of direct release as a gas, vapour or particulate, or by evaporation from liquid or solid matrices. In the latter case, the equation represents a worst-case situation by assuming that the substance is directly available as a gas or vapour.
- Dermal a: a substance contained in a medium. This dermal scenario also applies to i) a non-volatile substance in a medium used without further dilution and ii) a non-volatile substance in a volatile medium.
- Dermal b: a non-volatile substance migrating from an article (e.g. dyed clothing, residual fabric conditioner, dyestuff/newsprint from paper).
- Oral a: a substance in a product unintentionally swallowed during normal use (e.g. toothpaste).
- Oral b: a substance migrating from food contact materials (e.g. plastic film, plastic-coated cups/plates).

The EUSES scenarios for consumer exposure are based on crude assumptions. Use patterns are limited to the amount of chemical that is used or released during use, and the frequency of exposure events (i.e. the number of exposure events per year). Details of the release and of transport of the chemical are not taken into account. The EUSES scenarios are meant to be generic and applicable for a wide range of consumer products rather than to give a detailed description of the exposure for a specific consumer product. The risk evaluation for more than one consumer product is possible. However, risks are evaluated for each product separately, and exposures for different products are not added in the program.

3. Worker Exposure

(Sub)chronic exposure of workers in EUSES is estimated by means of the model EASE, implemented in EUSES. In addition acute exposure values can be entered by the user. Different scenarios can be assessed for the inhalation and dermal route and for each scenario a total exposure is calculated. EASE is a decision tree type of system. The user needs to provide answers on the questions presented by the model. Based on the answers,

exposure ranges are assigned, derived from experimental measurements from workplace environments. The model accounts for inhalation exposure to vapours, fibres and dust, and for dermal exposure.

Data needs

The program first needs the physical and chemical properties of the substance considered, to be provided by the user.
Second, the different environmental compartments, transport and fate parameters, such as partition coefficients, bio concentration factors, degradation and transformation have to be specified. For most of these, default data based either on expert judgement or on extrapolation methods are provided. Most of these defaults can be overwritten by the user, if better data are available.
Third, emission rates must be given, the program gives default data based on expert judgement for most of these. Finally, in order to evaluate the risks from the exposure to the chemical, the user must specify various effects data such as NOAELs and LOAELs for different toxic endpoints.

Aggregation

EUSES considers a number of different exposure pathways and routes, but nevertheless, complete aggregation is not implemented in the program.
The contributions from different pathways of indirect human exposure via the environment are added by assuming a standard consumption pattern. This consumption pattern can be adapted by the assessor to represent other individuals or groups in the population, but (inter- and intra individual) variations in consumption patterns (i.e. consumption patterns of children, vegetarians) can not be handled within a single assessment.
Contributions to the total exposure from consumer products are not added to the human exposure via the environment in the program. In addition, the contributions of the exposure from different products are not added. Chemical intakes are evaluated per product. Risks are evaluated for each consumer product separately, disregarding the exposures from other products and environmental sources or exposures at the workplace.
Similarly, the exposure at the workplace is treated separately from the other pathways and the results are not added to those of the other pathways. And risks are evaluated in isolation from any exposures that may occur from other sources, via other pathways.
We conclude that aggregation in EUSES is implemented in a very limited way, in spite of the fact that exposure via different routes and a large number of pathways is considered. The program does not integrate all these sources and pathways. The program does not deal with variations in exposure profiles. This limits the use of EUSES in aggregate exposure assessments to screening level assessments.

2.2 Programs modeling human aggregate exposure to pesticides

This section discusses a number of US pesticide exposure assessment tools. The US Food Quality Protection Act (FQPA) mandates that the US Environmental Protection Agency evaluate both aggregate and cumulative risks associated with pesticide use. EPA's Office of Pesticide Programs (OPP), which is responsible for regulating pesticide residues in food, has developed guidance on aggregate exposure assessments for pesticides[11].
The assessment tools described below implement, in varying extent, the requirements posed by the OPP guidance document.
Aggregate should, according to the OPP guidelines, be performed on an individual basis and should maintain the linkages and associations between consumption data and demographic data.
The OPP identifies three pathways of exposure of the human population to pesticides:

- pesticide residues in tap water
- pesticide residues in food
- residential exposure resulting from pesticide applications made in and around the home and in public places

Food
Pesticides are used on crops as protection from various pests. Residues of these pesticides will end up in raw food commodities and in prepared food. The residue level in the food as it is eaten will depend on the composition of the food (which crops are consumed, whether tap water with residue levels was used) and the way the food was prepared (cooking the commodities and pealing treated fruits and vegetables may reduce residue levels).
A standard method to evaluate dietary intake exposure to residues is to combine known levels of pesticide residues in either raw commodities or complete foodstuff with dietary studies, constructing daily menus for individuals in a population and estimating population exposure using Monte Carlo techniques. Details of the method, specific to each of the modeling tools are discussed in the section on the tool concerned.
In the OPP guidelines it is suggested that the development of aggregate exposure scenarios starts with the food exposure pathway. By using the extensive demographic data in the US Census Continuing Survey of Food Intake by Individuals[20] (CSFII), the assessor constructs a hypothetical population, representative of the food intake of the US population.

Tap water

Residues in wells, ground water and surface water are due to pesticide run-off from agricultural application. From these sources, residues will end up in tap water. Exposure will arise due to consumption of tap water and dermal and inhalation exposures during showering. Exposures to pesticide concentrations in drinking water are usually a local or regional phenomenon and will depend on the time of year. The OPP guidance requires that these spatial and temporal variations be accounted for in the aggregate exposure assessment.

Residential exposure

The OPP guidelines prescribe that exposure assessments for residential and other non-occupational sources should focus on the US EPA Draft Residential Standard Operating Procedures (SOPs)[21,22]. These consist of a number of fixed use scenarios:

- lawn care
- vegetable garden care
- ornamental plant care
- tree care
- pick own fruits/vegetables
- crack & crevice treatment
- termite control
- rodent control
- pet care
- outdoor fogger use
- indoor fogger use
- indoor treatment
- paint/wood treatment
- impregnated materials
- detergent/hand soap use
- swimming pool use

These crude, general scenarios specify an amount of product used in the task, and use generic exposure units such as UnitDose or UnitConcentration, which are units of exposure per amount of product used (i.e. dose per kg product used), to estimate total exposure. Many of the post-application exposure scenarios defined in the SOPs make assumptions regarding the amount of dislodgeable pesticide residues. Dislodgeable residues are those residues that may be transferred to the skin as a result of contact and are available for dermal absorption or ingestion. Assumptions regarding transfer of dislodgeable residues are generally based on the experience and professional judgment of OPP staff from the review of monitoring studies. Many of the handler SOPs use unit exposure values from

the Pesticide Handlers Exposure Database (PHED) as inputs into the exposure assessment algorithms. PHED is a database containing surrogate handler data collected from field exposure studies.
The pesticide exposure of residents will depend on the use pattern, whether a professional applicator was hired or not, on the season, and on social status of the resident. The OPP suggests that these factors should be accounted for in the aggregate assessments if data are available.

The OPP guidelines recommend the use of a number of databases:

- **NHAPS (National Human Activity Pattern Survey) survey on activity patterns**[23,24]**.** Data from a study conducted for the US EPA in 1992-1994. A large amount of data was collected on activity patterns for 9,386 subjects from regions all over the US over a 24-hour day. Data include information on race, gender, social status, activities subjects were engaged in and for how long, and residence times in various microenvironments.
- **NHGPUS (National Home and Garden Pesticide Use Survey) database on pesticide use**.
- **AHS (American Housing) database**[25,26]. The American Housing Survey (AHS) collects data on the US housing, including apartments, single-family homes, mobile homes, vacant housing units, household characteristics, income, housing and neighborhood quality, housing costs, equipment and fuels, size of housing unit, and recent movers. The national sample covers an average 55,000 housing units. Each metropolitan area sample covers 4,100 or more housing units.
- **CSFII dietary surveys (Continuing Survey of Food Intake by Individuals, 1994-1998)**[27,28]**.** Data on food consumption habits of US population. It is a 24 hour dietary recall study for 2 or 3 days.
- **PHED database on pesticide handling**[29,30]**.**
  A database containing voluntarily submitted empirical exposure data for workers involved in the handling or application of pesticides in the field; it currently contains data for over 2000 monitored exposure events. The system assumes that exposure to pesticide handlers can be calculated generically, based on the available empirical data for chemicals, as worker exposure is primarily a function of the formulation type and the handling activities (e.g., packaging type, mixing/loading/application method, and clothing scenario), rather than chemical-specific properties31.

2.3. Program by program review

2.3.1 Calendex – Calendar-based dietary and non-dietary aggregate and cumulative exposure software system

Calendex has been developed by Durango Software and distributed by Exponent, inc., USA. It was designed specifically to conduct aggregate and cumulative human exposure assessments from pesticides, as required by the Food Quality Protection Act (FQPA) of 1996[32].

General description

The Calendex aggregate exposure model estimates human exposure to chemical residues in foods and home-based chemical treatments, such as pest control and turf treatments. The model assesses acute, short-term, intermediate, or chronic time periods for a large, representative sample of the US population and for a wide range of sub populations. The model simultaneously accounts for the temporal, spatial, and demographic variation in chemical use and chemical users.

Exposure calculations

1. Dietary exposure

Calendex uses the database of population demographics and dietary intake data from USDA's CSFII for 1994-96, 1998 to provide a representative sample of the U.S. population and user-specified sub populations. Individual intake of specific agricultural commodities (e.g. wheat, corn, tomatoes) is derived from the foods-as-eaten intake amounts in the CSFII using 'recipe' translation factors from the joint USDA/EPA Food Commodity Intake Database (FCID). CSFII statistical weighting factors for the individuals in that survey assure that the exposure distributions are representative of the entire US population and related subpopulations.

2. Residential exposure

The residential pesticide exposure calculations are based on the US EPA SOPs for Residential Exposure assessments, but the user may develop and use his own models. Scenarios include application and post-application exposures and both professional and amateur uses. Dermal, inhalation and ingestion routes of exposure are considered.

3. Water exposure

Pesticide intake are estimated from the daily water intake (from the CSFII survey) and the residue values of the pesticide.

Data needs

Calendex includes a large number of databases such as the USDA's CSFII and the USDA/EPA Food Commodity Intake Database (FCID). The user has to provide data on the residential use of pesticide products, exposure factors and environmental pesticide concentrations. In addition, the user has to specify chemical residue values for the agricultural commodities.

Aggregation framework

Calende*x* aggregates using a 'Calendar Model' which sets up a schedule of dietary intake events and pesticide applications and human contact events in the residential environment over a calendar year for a designated individual using Monte Carlo analysis methods. It then allows the user to assess the probable aggregate and cumulative exposure for that individual on a daily, weekly, multiple-week, or annual basis. These exposure amounts are calculated for many thousands of individuals in a user-specified subpopulation (e.g., 1-2 year olds in the Northeast), and distributions of exposure amounts for that subpopulation are generated and compared to benchmark risk measures (e.g., RfD or NOEL). In addition, a critical exposure contribution report is generated for any given segment of this distribution (e.g. 99-100th percentile of exposure), showing the relative contribution of each pesticide use by exposure route (dietary, inhalation, dermal, and incidental ingestion).

Applicability to European situation

The use of the Calendex software is data intensive. Much of the available data is specific for the US-population. Not all of these databases can be adjusted to fit the European situation, which severely limits the applicability of the tool outside the USA.

2.3.2 CARES- Cumulative Aggregate Risk Evaluation System

General description

CARES is designed to conduct complex exposure and risk assessments for pesticides, such as the assessments required under the 1996 Food Quality Protection Act (FQPA). CARES was originally developed under the auspices of CropLife America in collaboration with consulting companies, the USEPA and US Department of Agriculture (ASDA). It has been transferred to the ILSI Research Foundation, where the CARES program and source code will continue to be publicly available at no charge.

CARES evaluates aggregate and cumulative human exposures to pesticides for multiple route-specific pathways (drinking water, food, residential). Doses are compared with toxicity data to quantify human health risks. Timescales of the risk assessment range from a single day (acute) to year averaged (chronic). Assessments are population based. The user can specify sub populations or make an assessment for the entire US population[33,34].

Exposure calculations

1. Dietary exposure

The user makes a selection which part of the reference population is to be included and which foods will be considered in the assessment. By matching the selected individuals to data in the CSFII database, food consumption data for each of the 365 days are obtained. Using the FCID (Food Commodity Intake Database, USDA/ARS and EPA/HED), the daily eating event data are converted to 24-hour summaries of raw agricultural commodity intakes (limiting risk assessments to periods for one day or more), both in amounts and preparation of the commodity (raw, peeled, cooked, juiced, etc).
Data on pesticide residues in the raw agricultural commodities (RACs) must be provided by user. These may be single values such as tolerance data, small groups of field trial data, or large monitoring databases.
Residue data are matched to the food intakes using additional (user supplied) information such as percentage of the crop treated, surrogate values for similar commodities, number of residue zeroes to be used, modification factors for prepared commodities. Actual exposure is calculated by assigning residues from a distribution to all the foods consumed by a person on every day of the year and integrating this procedure over the selected population. CARES produces three summary values for a simulated individual: maximum daily value, average daily exposure and the total exposure value for the 365-day period.

2. Residential exposure

CARES uses exposure scenario definitions as defined in the US EPA SOPs. For the residential exposure estimation the program needs relations between:

- ingredients and products
- products and efficacy periods
- products and exposure scenarios (from the SOPs), including user/non-user and professional vs. consumer use
- scenario and seasonal use
- scenario and day of the week use
- products and re-entry periods
- scenarios and co-occurrences of use
- scenarios and annual numbers of use

Furthermore, market share data of the product are needed.
Based on the provided relations exposure events are allocated for a simulated person for the entire range of 365 days. This is done in steps:

- the number of scenario events is randomly generated
- these events are distributed randomly over the year
- the number of products used per event is randomly generated
- a product that is used is randomly picked per event

The distribution of exposure is obtained by repeating the procedure for all individuals in the selection of the population.
The program needs user input data (depending on the scenario) on available residues, degradation of the residue, dermal contact areas, use durations, flux rates, areas treated and transferable residues.
The actual exposure estimation relies on the route specific unit exposures (such as milligrams exposure per amount active ingredient used) as derived in the PHED database.
Parameters such as exposure probabilities are derived by CARES from the individual characteristics.

3. Water exposure

CARES evaluates tap water exposure by combining 365 daily water consumption values with daily water residue values provided by the user. The profile of residue data has to be spatially and temporally specific. Each individual in the CARES reference population is linked to a water consumption pattern based on individual characteristics such as age, gender, state of residence.
CARES offers 4 options to characterize the water consumption of the people in the reference population:

- water consumption based on USDA/CSFII-data
- a default of 2 liters per 70 kg body weight
- EPA/WHO constants for water consumption
- Age adjusted constant water consumption

CARES does not include tap water exposure due to bathing and showering.

Data needs

CARES utilizes a large number of databases and default data, such as the CSFII database on dietary consumption, the Novigen Sciences Food Commodity Intake database, the 1990 U.S. Census (PUMS dataset) and the PHED database.
The user has to provide data on pesticide residues in food, transfer coefficients and active ingredient amounts for residential exposures, residues in ground or surface water, physical and chemical properties of the active ingredient and toxicity information.

Aggregation framework

CARES calculates aggregate and cumulative exposures for pesticides using a calendar-based approach: aggregate doses are evaluated for an individual for each day in a year (extending from 1 January to 31 December). The program evaluates potential risks from dietary, drinking water and residential sources from oral, dermal and inhalation routes of exposure. Risks can be calculated deterministically or probabilistically using Monte Carlo techniques. CARES calculates doses and risks from acute (1-day), short term (2-30 days), intermediate term (1-3 months) and chronic (1 year) exposures, allowing for the calculation of moving averages.
Exposure pathways include dietary exposure, exposure to pesticide residues in tap water, and residential exposure due to pesticide use in the home.
Risks are expressed as percentile distributions of toxicologically equivalent doses, margins of exposures, or hazard indices (the ratio between actual dose and RfD).
Doses are calculated route and source specifically for one individual on one day and combined to obtain an aggregate dose for the individual. A population distribution of the dose is constructed from the aggregate doses of a group of individuals in a specified population.
Aggregate risk is characterized by the distribution in the population of a risk measure such as the MOE.
For assessing the cumulative risk the joint probability of exposure to two or more chemicals is determined.
The resulting exposure is presented as a combined distribution of toxicologically equivalent doses, hazard indices or margins of exposures.

CARES constructs a reference population of 100.000 persons combining data of the 1990

US census (PUMS database) with the CSFII/FCID food intake databases and NHAPS/REJV databases on activity patterns by matching records with the same or similar attributes such as age, gender and ethnicity.
For each modeled individual in this reference population (or a sub selection thereof) a 365-day exposure profile is created, consisting of daily doses from exposure aggregated across all routes and pathways.

Applicability to European situation

CARES has intensive data requirements. The databases provided with the program are US specific databases. Many of these data may not represent situations at other geographical locations than the US very well. For any specific assessment at a non- US (e.g. European) location, it may be necessary to obtain similar data for the geographical region of interest.

2.3.3 LifeLine 2.0

General description

The tool was developed by the LifeLine Group, Inc.
LifeLine 2.0 implements an aggregate framework to assess the total human exposure to pesticides that are either released by agricultural or residential use. The program distinguishes three pathways: dietary intake of pesticide residues in food, exposure to pesticide residues in tap water via ingestion and bathing, and exposure due to residential use of pesticide products. It facilitates both deterministic screening level calculations and more detailed, probabilistic assessments. Exposure levels, carcinogenic and non-carcinogenic risks are assessed either for the total US population or for specified subpopulations. Health risks are reported as Margin of Exposure, Reference Dose or Fraction of Reference Dose. The program can also estimate cumulative exposures[35].

Exposure calculations

1. Dietary exposure

Dietary intake is estimated from pesticide residue data in the food stuff by selecting food consumption records from CSFII dietary surveys. Dietary records can be matched to demographic characteristics of the simulated individual such as age, sex, region or socio-economic status. Residue data must be specified at commodity (raw ingredient) or food form levels.

2. Residential exposure

Residential exposures arise from the use of pesticides in and around the house. LifeLine determines pest pressures for the residence of the modeled individual using NHGPUS

data on (geographical related) pesticide use and additional residential factors (presence of lawn/fruit trees etc.). From pest pressures and labeling instructions, daily probabilities of home pesticide application are inferred. LifeLine 2 follows the residential pesticide exposure scenarios as described in the EPA SOPs. The program distinguishes between handler (application) exposure and post-application exposure to residues.
For the user exposure the program offers two approaches: 1) unit dermal and inhalation exposures are obtained from the PHED database as surrogate values, or 2) the user must specify exposure as percentages of the active ingredient that is applied. Using these unit exposure data, exposures are modeled using the dimensions of the modeled residence and application rates.
The post-application exposure is determined from residues left behind in different media after application. These residues are estimated for different product types using the amount of active ingredient used and crude assumption with regard to the emission. The residue level is modeled as declining in the course of time based on a user specified decline rate. Exposure is determined by deriving contact data with the contaminated medium from time activity data (NHAPS survey).

3. Tap water exposure

Pesticide residues from agricultural runoff may disperse into surface and ground water, from where these residues may end up in drinking water sources and may lead to exposures of persons drinking the water or bathing in it.
The user of the program has to provide residue data for different types of drinking water sources. Dependency on census region, water source, season of the year and others can be included, if the data are available.
Residue data are matched to residences based on census region, season, urban or rural setting, and the type of water supply, using the AHS database.
In determining the inhalation dose of a person taking a shower in the bathroom, the air concentration in the bathroom is estimated based on the (seasonal) water concentration, the water throughput, the Henry-coefficient of the active ingredient, and the bathroom volume of the residence of the modeled person.
The dermal dose due to contact with shower water is estimated from the estimated exposed surface area of the skin, the estimated K_p of the skin, the concentration of active ingredient in tap water and the exposure duration.
Oral exposure is calculated as the concentration of active ingredient in tap water times the amount of tap water consumed.

Data needs

LifeLine utilizes a number of US databases, such as the National Centre for Health Statistics data on population characteristics (Natality database and National Health and Nutrition Examination Survey), CSFII database on dietary consumption, NHAPS, NHGPUS

and AHS.
The user has to provide data on pesticide residues in crops, agricultural commodities or food, drinking water supplies, physical and chemical properties of the active ingredient and toxicity information.

Aggregating exposure

In LifeLine, the exposure of a person is simulated for every day of his life, resulting in a day-by-day exposure profile for the modeled person. All the above mentioned pathways will contribute to this profile. The day-by-day exposures are evaluated and stored both per route and integrated over the routes. A population distribution of these profiles is generated by repeating the procedure for a reference population by performing Monte Carlo analysis.
Within this modeling procedure the program:

- assigns appropriate age dependent attributes to the modeled person at various life stages.
- maintains autocorrelations (over time) between exposure factors such as body-weight at different ages.
- maintains correlations between various factors such as pesticide use with season, region of country, type of home, frequency of use and last time of use.
- registers exposures arising from pesticide applications in the past.

After the construction of the exposure profiles specific evaluations can be made such as:

- exposure of subpopulations
- the impact of frequency and duration of exposures, by calculating running averages over various time periods, ranging from days to years
- the relative contributions of the different routes of exposure

Applicability to European situation

Assessments with the LifeLine software require a large amount of data. The databases provided with the program are US specific databases. Many of these data may not represent situations at other geographical locations than the US very well. For any specific assessment at a non- US (e.g. European) location, it may be necessary to obtain similar data for the geographical region of interest.

3. Aggregate exposure to chemicals from consumer products

One potentially important pathway of exposure of humans to chemicals is the exposure to chemicals released from consumer products. As a chemical may be contained in widely different types of products, it may not be appropriate to evaluate risks for each product containing the chemical separately. Rather, the total of the exposure arising from all the different products has to be determined.
In this section we discuss how a determination of the exposure from different consumer products might be done. We will refer to this summation as aggregation, understanding that this is a narrower definition of the term than the one used in earlier sections of this report, since not all, but only a part of all possible pathways of exposure and sources is considered. Many of the considerations and methods discussed in chapter 1 apply here as well.
In section 3.1 a conceptual procedure for the aggregation of consumer product exposures is given. In the field of consumer exposure assessment, monitoring data and other direct measurements of the exposure are rare. In practice, the assessor often has to revert to the use of modeling. In section 3.2 a list of available consumer exposure modeling tools is presented with a short description of their characteristics. Their possible utility in the aggregate assessment of the exposure from consumer products is briefly discussed.
Finally, in section 3.3 possible implementations of the conceptual procedure defined in section 3.1, for different applications in a risk assessment, are sketched and illustrated with a detailed example.

3.1. Assessing aggregate exposure to consumer products

In the assessment of the impact on the human health due to chemicals in consumer products, it is customary to take following steps:

- determination of the scope and purpose of the assessment
- establishment of the exposure scenario
- assessment of the exposure based on the scenario
- characterization of the expected health impacts

When presenting the results of a risk assessment to the public or other stakeholders, the assessor will in addition have to discuss the accuracy and reliability of his assessment.

Uncertainty pertains to all the different parts and steps of an assessment[36,37,38]. A systematic treatment of uncertainty is to be an integrated part of any risk assessment. To limit the scope of this report we do not consider these aspects here, however.

Scope and purpose of the assessment

Exposure assessments are usually performed to protect public health, i.e. to protect a population of potentially exposed persons. The approach to estimate the exposure of this population may vary from one occasion to another.

The scope and purpose of the assessment dictates what level of detail is required to meet the demands of the posed risk question. If an order-of-magnitude estimate is asked for (for example: an initial screening of the exposure of a population for potential risks or prioritizing of assessments for different chemicals), the population is often represented by a single, hypothetical, high-exposed person for which a deterministic exposure assessment is done, using conservative values for exposure factors. It is assumed that the exposure of this person represents a higher bound to the actual exposure in a population, so that, if for this hypothetical individual the exposure is below a certain safe level, there is no reason for concern relating to the exposure to this chemical. If, however the estimated exposure level lies above a level of concern, an additional, more sophisticated assessment of the exposure may be required.

If on the other hand, a detailed assessment of the distribution of exposure in a population has to be established (for instance to identify the highest exposed subpopulation, or to quantify the distribution of expected effects within the population), different groups or individuals have to be identified in the population, for which exposure estimates have to be determined separately. This approach requires more detailed data on various parameters (distributions of exposure parameters within a population, data distinguishing different groups or individuals in the population such as age, sex, social status, region).

The exposure is, as a rule, determined using probabilistic techniques, such as Monte Carlo simulation.

These different levels of complexity are often combined in a tiered approach. The relatively simple screening evaluations are performed first to assess whether a more detailed approach is needed, and if so, whether specific pathways or sub populations can be neglected in a more elaborate assessment.

If the screening level assessment is not conclusive, progressively more detailed and sophisticated evaluations have to be performed.

Exposure scenario

The actual assessment always starts with some sort of scenario definition: a conceptual description of the processes, assumptions and parameters that are thought to represent the exposure situation in so much detail as is adequate to answer questions posed by the risk assessment requirements. This scenario will direct how the evaluation will be performed

and what monitoring, data collection or modeling strategies will be used. The scenario description addresses questions regarding the required detail of the assessment. For instance, the timescales of the exposure assessment should correspond to the toxicological endpoints that are of interest. The timescales on which the exposure is to be determined, on the other hand, determine the level of aggregation of a population or dis-aggregation into sub-populations, and the detail with which individual exposure events should be described.
The scenario will identify which pathways and routes of exposure are to be regarded and what the endpoints of the exposure assessment should be.
For the case of the assessment of aggregate exposure to substances in consumer products, the scenario description will include a list of consumer products that contain the chemical(s) of interest. In addition, it will have to describe how exposure to each of these products may take place, that is, it will include sub-scenarios for the different products.
In the construction of these sub scenarios it should be acknowledged that the exposure from a single product can occur in different ways and at different occasions. The exposure may arise when a person uses the product himself, or it may occur when someone else is using the product and a person is just standing-by. Still differently, it may be that a person is exposed after the product has been used upon entry of the room where the product was used. All of the relevant exposure events have to be identified and described. In addition, a strategy to add the exposures from these different events has to be adopted. As described in chapter 1, this addition should be done using a person oriented approach. Depending on the time resolution, this profile could consist for instance in a day-by-day listing of the exposure events that are likely to take place for the modeled person, or it could be a year averaged profile, consisting of summation of all the averaged doses for the different exposure events. The approach to follow in this aggregation step again is dictated by the demands posed by the scope and purpose of the risk assessment question.
Exposure events from different products may overlap when products are used simultaneously or when the exposure to one product extends for some time its use, and may coincide with the exposure to another product or a repeated use of the same product. The exposures may in combination lead to an excess of a tolerable level, although the exposures from each product separately are below this level. So, in addition to exposure factors relating to single product exposures, data on the temporal correlations and the autocorrelations will have to be known (i.e. the probabilities that products will be used simultaneously, the average time between repeated uses of the product, etc).

Assessment of the exposure

The exposure scenario and its sub scenarios that describe the exposure profile, point out how the evaluation of the exposure should be done. This evaluation consists in the translation of the functional relationships determined in the scenario into mathematical equations, the selection or formulation of models describing the different exposure events, the

collection and description of data on the included products, relevant exposure factors, anthropometrics and other population characteristics, the design and implementation of monitoring studies etc.
The collected data, models and directly measured exposure data are used to evaluate the different sub-scenarios that describe individual exposure events. These are subsequently integrated in a way that corresponds to the risk question. For instance, the day-by-day exposures in a population per route, or integrated across all routes, the distribution of the year averaged exposure over the population, or just the conservatively estimated higher bound of the exposure within the population etc.

Risk evaluation
Finally, the results of the exposure assessment are used to quantify the health impacts within the population. This can be as simple as a statement regarding the probability that a certain level of concern is exceeded in the population, but could also be a detailed quantification of the number of people for whom the exposure exceeds this level of concern and the extent to which it does. Also various questions with regard to the distribution of exposures and risks within the population should be answered in this phase. Such as the identification of dominant routes of exposure, the determination of the products that drive the exposure to the chemical, the evaluation of possible risk reduction measures.

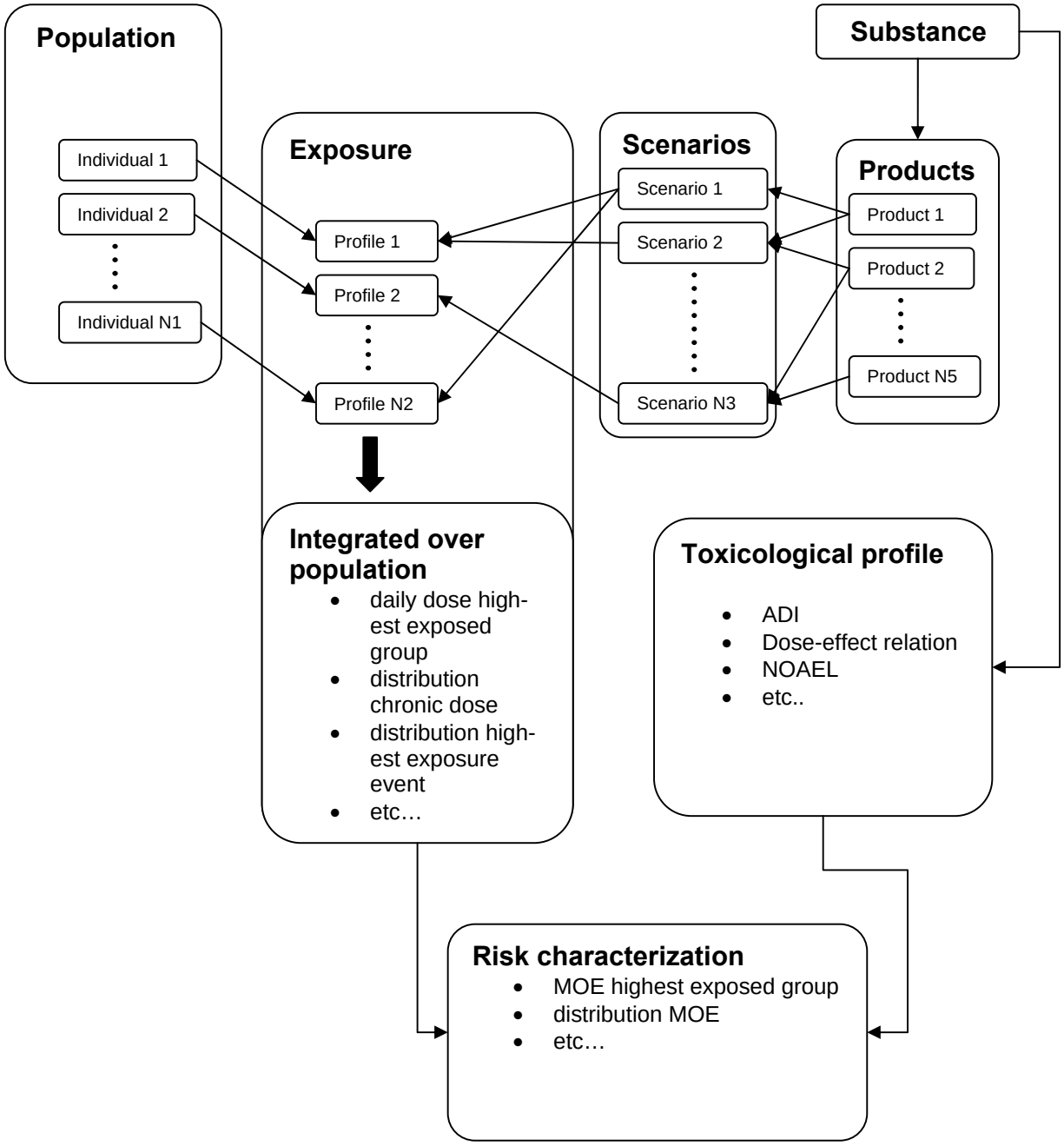


Figure 2 Conceptual model of the aggregation of the risk assessment of chemicals from multiple consumer products. Exposure profiles are constructed for individuals or groups of individuals in a population. These consist of the combination of exposure scenarios describing different ways in which a person may be exposed to chemicals in consumer products. These individual exposure profiles are integrated over the entire population to obtain measures of the exposure of this population. These exposure measures may subsequently be used to characterize the risk or health effects in the population.

3.2 Consumer exposure modeling tools

There is a number of more specialized computer tools that implement models to estimate the exposure of humans to chemicals in consumer products. The level of complexity and the area of applicability vary among the tools. Some of these programs only cover a limited group of products or a limited number of exposure routes.
Below, a short description of the capabilities of the different programs is given. It is discussed to what extend, if at all, each of the tools could be used in aggregate exposure assessments.
The computer tools discussed in this section are:

- ConsExpo
- MCCEM
- PROMISE

ConsExpo
ConsExpo has been developed at the Dutch National Institute for Public Health and the Environment (RIVM)[39,40]. The program implements a suite of consumer exposure models. The complexity of these models ranges from screening level to more advanced, detailed mechanistic models. The tool covers the oral, inhalation and dermal routes of exposure. Using simple absorption models the exposures can be integrated across the different routes to yield total internal doses.
Typical pathways of exposure which can be studied with the models include:

- aerosol exposure due to the use of spray cans for user and bystander
- exposure to vapours from products (i.e. paints, cleaning products) both during application and post-application.
- dermal exposure due to transfer from contaminated surfaces to the skin (i.e. pesticides, cleaning products)
- migration of chemical substances from clothing to the skin (i.e. dyes from clothing)
- diffusion of a chemical from a product to the skin (i.e. cosmetic cream)
- ingestion of substances migrating from a mouthed object to the saliva (i.e. teething rings)

Chronic (yearly averaged dose per day) and acute (total dose per event or per day of exposure) exposures are evaluated. Risk evaluation is not a part of the program.
The program includes a database with default data and recommended exposure scenarios for different consumer product groups. At present data on cosmetics, pest control products, cleaning products and disinfectants are included.

Aggregation

Evaluations in ConsExpo are done for one product and one chemical at a time.
In ConsExpo exposure events are treated separately. The exposure is calculated for a single exposure event. Inference of chronic doses is done by multiplication with the exposure frequency data. Temporal overlap between exposure events is not considered.
The program includes limited tools for performing distributional calculations. Only simple, one-dimensional Monte Carlo analyses are supported and correlations between model parameters are not regarded. This makes the feature more suitable for sensitivity calculations than for population assessments.
Hence the model as such does not facilitate aggregate exposure assessments.

Multi-Chamber Concentration and Exposure Model (MCCEM)

The program is developed by Versar Inc. on behalf of the US EPA/OPPT to aid in the evaluation of new and existing chemicals[41]. The tool considers inhalation exposure only. It models time varying indoor air concentrations and inhalation exposures in different chambers of a residence, including the effects of emission sources, sinks, air exchange between different chambers (zones) in the residence.
The possible sources of exposure include consumer products, building materials and indoor furnishings. These sources must be characterized by the user as time-dependent emission rates (as constant, single exponential incremental and data entry).
Up to four different zones within a residence can be simulated. The software maintains a library of residences in different US geographical areas with data on zone volumes and interzonal flows and whole house exchange rates[42]. The user can use this library or specify his own values.
The time scales considered range from acute (peak concentrations and single day doses) to chronic (lifetime average daily doses).
The program offers a limited possibility to do distributional calculations: only for a number of parameters such as infiltration rates, emission rates, and sink rates.

Aggregation

The usability of the program for doing aggregate exposure estimates seems limited. In the first place, it considers only inhalation exposure, which restricts the applicability to sources and products for which this route of exposure is the dominant one. Secondly, the program combines the exposure of different sources in one event, but has no option to integrate over multiple exposure events. Such an integration (which is essential in an aggregate assessment where exposure could arise from different sources at different points in time) should be done outside the program by the user. Furthermore, the program does not support population based assessments. Its applicability is therefore restrained to the screening type of assessments.

PROMISE©

PROMISE© is a software tool developed by Silken, Inc. for the Solvents Council of the American Chemistry Council to assist in the exposure assessment of industrial chemicals[43]. PROMISE© is primarily designed for estimating single exposure events in occupational settings and in certain consumer-type applications. The program is best adapted to chemicals that have some volatility and exist either in the pure form or in a formulation. Multiple routes of exposure (inhalation, ingestion, and skin absorption) may be assessed. With the program, event exposures are estimated for a scenario. It is assumed that the exposure is the same for all the exposure events that may occur in the course of time. Year averaged daily doses are derived by multiplication with the use frequency (per day).

PROMISE© has a probabilistic 'front-end' that allows the use of input variable ranges and distributions rather than single value point estimates in the calculation of dose. The user has a choice of up to 15 different types of distributions. PROMISE© allows the distribution of dose (milligrams of chemical per kilogram of body weight per day) from the defined scenario to be evaluated, visualized, analyzed, documented, saved and compared to alternative scenarios, alternative exposure and uptake models, and different similar scenarios using alternative input values.

Aggregation

PROMISE© was not designed for use in cumulative or aggregate exposure assessments. Variation of the exposure between exposure events can not be modeled. Also, exposures from different sources can not be combined within the program.

Conclusion

As can be concluded from the reviews above, none of the programs developed for the assessment of consumer exposure supports aggregation of the exposure from different consumer products. The ConsExpo and PROMISE programs (or more likely, the exposure algorithms they implement) can however be used in a higher level aggregation framework to evaluate the separate exposure scenarios. Proper addition of these scenarios, however would have to be done in a separate routine, to be implemented in the embedding framework. As the MCCEM model only considers inhalation exposures its applicability in a general aggregation framework seems limited.

3.3 Possible implementation of aggregate human exposure assessment to chemicals in consumer products

As described in section 3.1, the manner in which aggregate exposure is assessed depends on the scope and the purpose of the assessment as defined by the risk management question. In this section we propose in some detail approaches for three different types of risk assessments:

- a screening level assessment (tier 1)
- a more detailed population assessment in which only chronic exposure (year averaged) endpoints are to be considered (tier 2)
- a detailed assessment of the population exposure on a day-by-day basis, to assess, among other things, the acute (daily averaged) exposures (tier 3)

These three types of assessments typically constitute different steps in a tiered assessment, where a non-conclusive outcome of a lower tier assessment calls for a more refined estimation of the exposure[*].
For each approach data requirements are specified and an outline of a general framework that could be used in the evaluation is sketched. As direct measurement of exposure data for chemicals from consumer products is rare and costly, the assessment of the event exposures is assumed to be done by modeling.

All the approaches described below share a number of common steps. First of all, in the specification of the scenario the products that contain the chemical of interest will have to be listed, together with, at a minimum, data on the amount of chemical that these products contain, a basic description of the use pattern of the products such as its use frequency and the amount of product used per event. Based on the expected use of these products, pathways of exposure have to be determined and in relation to these, the subpopulations that will be exposed via these pathways. From these, exposure profiles will be constructed, combining the exposures from different exposure events for the different products. In assessing the actual exposure for the different events, these different exposure events could, in principle, be determined by direct measurements, but in the absence

[*] The assessment type that is defined here as the first tier, is in practice sometimes preceded by a yet cruder estimation, which could be referred to as a zeroth tier: an order-of-magnitude estimation based on an estimate of the total volume of the chemical available for potential exposure (derived from estimates of the number of products on the market and the amount of chemical each product contains) and the size of the exposed population. In this approach, no specific exposure scenario is assumed, only the potential uptake of the chemical in the population. Such an approach is principally used to prioritize between risk assessments of different substances.

of representative monitoring data these exposures may be modeled (or the computer tools described in section 3.2 could be used). Depending on the specifics of the approach, these event exposures have to be summed into an aggregate assessment.
Summarizing, the basic data needs for all three approaches are:

- listing of the products containing the chemical
- the amount of the chemical that is contained in the product
- use data on the product: a use description, amounts to be used, use frequencies
- basic population data: body weight

Tier 1
The exposure for a subject is estimated using conservative assumptions on the different exposure factors. The assumption is that when the exposure for this person is below a certain level of concern, this is a reasonable guarantee that the exposure levels for most of the population are below this level and hence, there is no reason for concern regarding the exposure from this substance. This is a cheap and quick approach that is mostly taken as a first tier in a more complete risk assessment, screening whether a more elaborate approach should be enforced or whether this is not necessary.
In using this approach for the aggregate exposure estimation to chemicals in consumer products there is a number of specific considerations that apply. Although the approach permits and demands the use of conservative assumptions, consistency of the exposure profile should be maintained. This means that not all possible exposure events will apply to the person that is to represent our (sub) population. As a consequence it may be necessary in this type of assessment to repeat the procedure for different persons, representing different groups in the population. It may, for example, be necessary to estimate the exposure for users of different (mutually exclusive) products and for children that are indirectly exposed, but possibly more sensitive to the effects of the substance.
This type of screening assessment needs to construct a representative person for each group within the population. A conservative estimate of the exposure will be made for each group, assuming high exposure values for the different exposure factors (high percentiles of distributions if these are available). For each of the exposure pathways, a single exposure event is calculated (variation in the exposure between different events is not included). The group for which the impact of the exposure is expected to be highest determines the conclusions regarding the safety of the exposure. Using this approach, there is no information on the variation of the exposure within the population, nor is there any indication of how conservative the estimate is. It may be far beyond any level of exposure actually encountered in the population, or it may be just at a high percentile of the ‘true’ distribution of the exposure in the population, not protecting a group of highly exposed individuals.

Tier 2

A more detailed population assessment in which only chronic exposure (year averaged) endpoints are to be considered.

In this case, sub populations would not be represented by a single, hypothetical individual, but one rather aims at characterizing the entire population, specifying distributions of exposure determinants within the population, and then modeling individuals in the population from realistic population data and constructing exposure profiles for these persons. This procedure is repeated for a large number of similarly modeled persons, so that a representative modeled population is obtained. Since one is regarding long time averages here, details of the temporal correlations between exposure events are neglected, exposures can be determined using estimates of the separate exposure events multiplied by the exposure frequencies and add the average exposures from the different products.

Additional data that are needed to follow such a scheme include:

- distributional information on product use:
    - variation within the population of the amounts used per event
    - variation within the population of the number of products used
    - variation within the population in use frequencies
    - (anti-)correlations between the use of different products (i.e. some products are more often used together or their uses are mutually exclusive)
- distributional information on anthropometric data
- distributional information on exposure factors

This approach yields a distribution of the year average exposure to the combined exposures of several products. With this type of assessment one obtains an insight in the variation of the exposure within the population making it possible to identify high exposed sub-populations and quantifying the number of people that experience exposure levels higher than an acceptable level and the amount by which their exposure exceeds this level.

In this approach there still remain different options as to what level of detail one wants to describe the exposures, and hence, what data to include and for which of these data one wants to determine the distributions within the population and for which one would use average estimates or other suitable point values. The choice between these different levels is on one hand dictated by the risk question and on the other hand by a limitation of resources. Useful data on exposure factors is sparse in the field of consumer exposure estimation. Filling these data gaps for a specific assessment will be costly and time consuming. Including more detail into an assessment will as a rule require more input data. In the absence of these, the introduction of more detail into the assessment comes at the cost of a higher degree of uncertainty in the outcome.

In this approach a variation in the exposure arising in the different exposure events should be included. This variation will be the consequence of the variation in the various exposure factors. To keep the assessment as simple as possible, a good starting point

seems to be the minimal data set specified earlier. The only variations in exposure taken into account would then be due to the variations in use frequency, used amounts and number of products used. Each exposure event could be characterized by an exposure per unit of product used (i.e. an exposure per kg product or per liter product). Unit exposures could be estimated using models (such as, for instance but not necessarily, implemented by computer tools). The exposure profile is constructed on a person-to-person basis from the product use data. The exposure events can in this (long term average) case be evaluated as an average per event per route (lifelong or yearly, or whatever the required timescale is). This is, as was explained in chapter 1, because only chronic exposures are determined and whenever the averaging time is much longer than the typical exposure times, the co-variances between the different events averages out and averaging can be done per pathway irrespective of the other pathways. In the calculation of the average exposure per event, the information of the use frequencies should be used. From the different (time averaged) exposure profiles, aggregation is done, first per route (yielding a total average exposure per route) and is subsequently integrated over the different routes to obtain a total average systemic or potential exposure.

Tier 3

In the last and most detailed tier, also acute toxicity endpoints are considered in addition to the chronic toxicity. The timescale on which exposure assessment will have to be performed should correspond to that on which acute effects are expected. If this timescale is one day, for instance, exposure profiles have to be constructed on a day-to-day basis. In this case, additional data is required on temporal correlations between different exposure events. In the construction of daily exposure profiles, the probabilities of simultaneous exposure to two or more products on the same day should be accounted for. Also, it may be necessary to consider the fact that exposure after use of a product may last for longer than a day. So the history of exposure events should be explicitly regarded.

The sort of data that would be needed (additionally) to complete an assessment in this tier would include:

- the probabilities that products will be used simultaneously
- the time profile of the individual exposure events

For the entire exposure duration (which may vary from case to case and could be one year or a lifetime, for example) daily (or another acute timescale) exposure profiles must be constructed, again on a person-to-person basis. From the resulting exposure diary, longer time averages as well as maximal acute exposures (e.g. highest days of exposure) could be derived for the population under study. Aggregation is essentially done in the same way as in the second tier. First, the daily exposures are summed per route for one individual, and subsequently integrated over the different routes (using an appropriate risk metric) and, if necessary, averaged over longer exposure durations.

3.3.1 Example: exposure to a substance contained in multiple cleaning products

As an example of the techniques described above we show in this section how the aggregate exposure to a hypothetical substance in multiple cleaning products could be assessed. We implement the three different procedures proposed and illustrate how the data demands increase as the required level of detail increases.

We base the discussion on a research by Weegels[44], which provides preliminary data on the use of different cleaning products. In this study, data were collected on the contact of consumers with different consumer products (in particular household products). These data included use durations, frequencies and amounts used. It is shown how these data could be used in a progressively more detailed exposure assessment.

The substance of concern is supposed to be contained in a dishwasher product, an all-purpose cleaner and a toilet cleaner. The nature and function of the substance are not specified here, but it could for example be a surfactant, a perfume or a dye.

Scenario and exposure event models

To begin the specification of the exposure scenario, the products that contain the chemical have to be characterized in terms of the amount of the substance they contain (i.e. as a concentration or fraction of the weight).

Next, the pathways and routes of exposure should be identified. In this case we assume the following sub scenarios:

For the (liquid) dish washer, exposure takes place:

1. when preparing the suds (dermal exposure due to spillage)
2. when washing the dish (dermal and inhalation exposure)
3. due to residues of the substance on the dish (oral exposure via food intake from the dinnerware)

The scenarios 1 and 2 apply only to the people using the product. Scenario 3) applies also to non-users. Scenario 1) and the dermal contact of scenario 2) apply to users of the product only. Inhalation exposure during scenario 2) also applies to non-users of the product who are in the same room where the product is used.

For the all-purpose cleaner we assume exposure:

4. when preparing the suds (dermal exposure due to spillage)
5. during cleaning (inhalation exposure due to evaporation, dermal exposure due to rinsing of cloth in the suds and wiping with a cloth)

Finally, we assume the exposure to the toilet cleaner to take place during the use of the product (cleaning) only. Exposure is via inhalation of evaporating substance as well as by dermal contact.

For the sub scenarios described above, the exposures during a single event must be assessed as a function of exposure factors that may vary within a population (such as the

amounts used, for example). To evaluate these sub scenarios different options are available. Exposures could be estimated from monitored concentrations or can be modeled using tools such as ConsExpo or Promise. In this case we choose to describe the event exposures using a set of simple model equations. These equations and tables, with the input data used, are described in Appendix A.

Exposure evaluation

Tier 1

Data on exposure factors are collected from different sources. Data on the use patterns of the above products are derived from the study by Weegels on the contact of consumers with household products. This study was performed in small populations (the number of persons is ranging from 9 to 45) which limits the representativeness for larger populations. The values for the different exposure factors should therefore mostly be regarded as illustrative for the procedure.
Anthropometric data such as body weights and surface areas of body parts are derived from the RIVM ConsExpo general fact sheet[45].

In the first tier we make an-order-of-magnitude estimate of the exposure of the highest exposed group within the population. We identify two possible groups of exposed persons: 1) the (adult) users the product and 2) children that are indirectly exposed. The absolute amount of chemical to which group 1) is exposed will be much higher than that of the second group, in terms of the systemic dose, which is expressed as an uptake per unit of body weight, the second group may prove to be the most important.
For each group we choose representative, but conservative point values for the different exposure factors. What we are aiming at is an estimate of a realistic upper bound of the exposure in the population. This means that we will chose values for all parameters that are in the high-exposure range, but preferably not beyond the realistic boundaries of the parameter. When detailed data are present, such as for body weights, conservative, but not overly conservative values are adopted. In the case of more limited datasets such as the consumer contact data from the Weegels study, the most unfavorable values are chosen (maximum values encountered in the experiments).

Using the values given in Appendix A, the total exposures for the two different groups are calculated as:

adult user (chronic exposures mg/kg/day)

	dish washer	all-purpose cleaner	toilet cleaner	summed over products
inhalation	3.6	0.3	0.5	4.4
dermal	16.3	0	0	16.3
oral	1.1E-7	0	0	1.1 E-7
summed over routes	20	0.3	0.5	21

indirectly exposed child (chronic exposures mg/kg/day)

inhalation	0	5.75E-02	0	5.75E-02
dermal	n/a	n/a	n/a	n/a
oral	6.18E-7	0	0	6.18E-7
total	6.18E-7	5.75E-02	0	5.75E-02

This first tier estimate serves different purposes. First of all, it gives some crude upper bound of the exposures to be expected from the chemical. Second, if the MOE or other risk measure that is calculated from these exposures is not acceptable and a more detailed assessment is appropriate, the screening of the exposures for different sources, via the different routes and pathways indicates which of the sources, routes or pathways can possibly be ignored in the more detailed assessment to save resources, as their contribution to the overall exposure is expected to be negligible. In this case, when advancing to a higher tier assessment, we might choose to neglect the contributions of the oral route. Similarly, it is seen from this crude estimate that the dish washer is the most important source of the chemical exposure of adult users. Refinement of the assessment in a more advanced tier for this source should be a priority.
For the sake of the example however, we include all the sources and routes in the elaboration of the second tier assessment below.

Tier 2

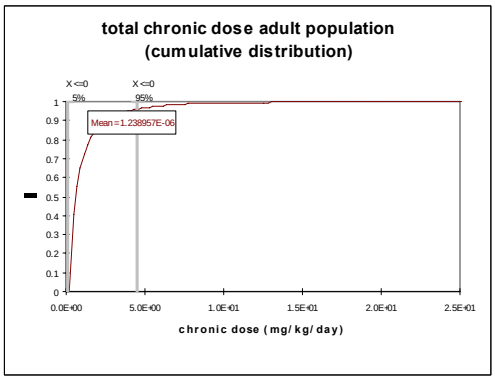
In the next step, we refine the procedure above by including information on the variation in the values for the different exposure factors. Using distributions of values we calculate the distribution of exposure within the population. To properly aggregate the exposure arising from different products, we should pay attention to the following points:

- personal consistency should be maintained in the aggregation. This means that for every simulated use of the product by a person, all the different sub scenarios describing the exposure from this product should be evaluated together for this per-

son (i.e. in their evaluation the same data describing the person should be used). This is effectively achieved, by first assigning a use frequency and body weight to a person and using the numerical values of these parameters in the evaluation of all the sub scenarios.

- correlations between data describing the exposed person and the exposure scenarios that apply to this person should be taken into account. We choose in the scenario description to distinguish between two groups in the population with entirely different exposure profiles: adult users and children that are exposed indirectly. There is obviously a strong correlation between data such as body weight and the exposure scenarios that apply to the simulated individual. This correlation was addressed by splitting distribution describing the body weight into two classes: body weights < 40 and body weights > 40. The first class is supposed to describe the children, the second group is the group of adult users. Note that this is a somewhat crude solution to the problem. A more refined procedure could also include exposure profiles of adults who are indirectly exposed during some events and exposed while using the product in other instances.

Possible correlations between the different exposure factors (such as use frequency and amount used) are neglected in this assessment. Whenever such information is available, it should be included, however.
Using this approach, insight is gained in the distribution of exposure within the population. Rather than being able to identify only the highest exposed group and obtaining a reasonable higher bound of the exposure of this group, this procedure could estimate for instance the number of people within a population with exposures exceeding an established safe level and the amount by which they do.
This approach can however not give estimates of the acute exposures. The exposures are averaged over the time span of one year, and data on more detailed timescales can only be obtained when more detailed data on the temporal correlations of the different exposure events is known.



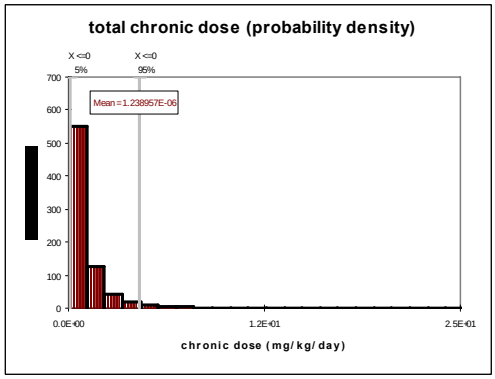
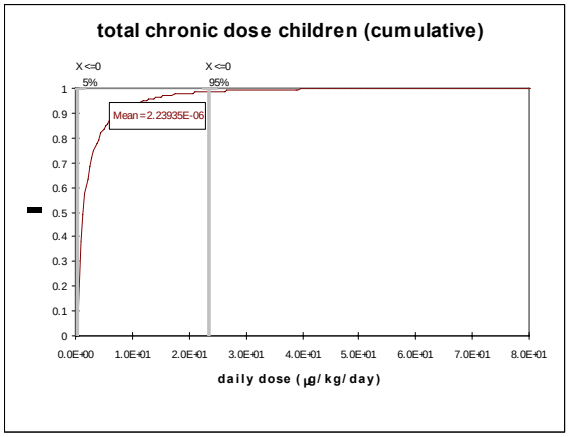


Figure 3 Estimated total chronic dose of the exposed adult population



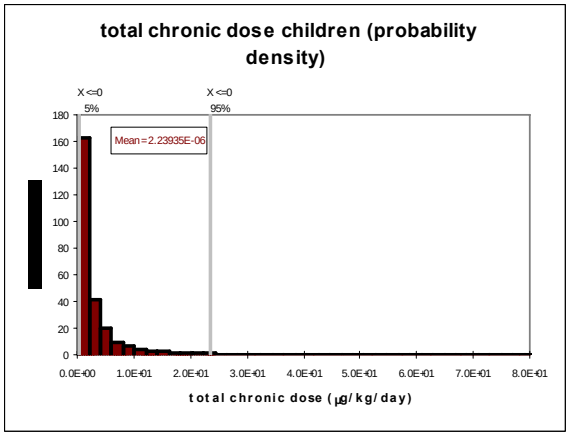


Figure 4 Estimated total chronic dose of the exposed population of children

(note: exposures in µg/kg/day)

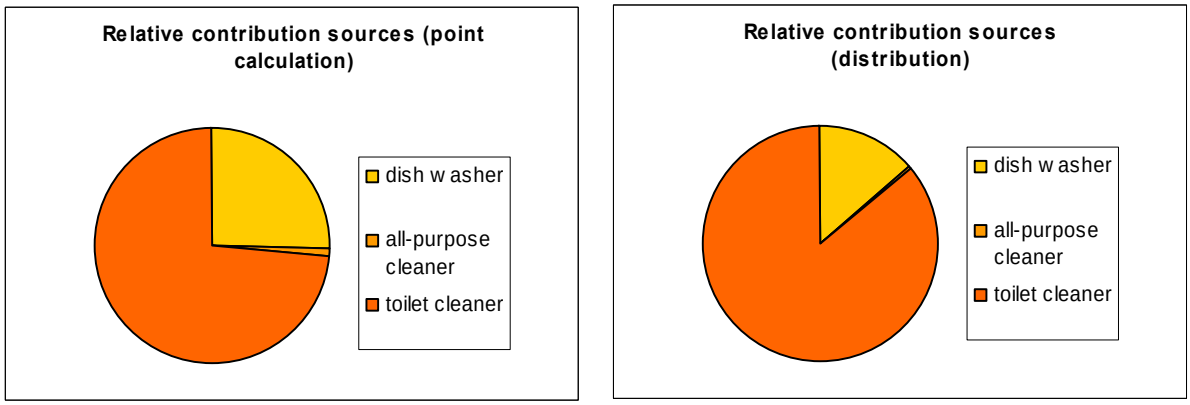


Figure 5 Relative contributions to the total exposure of the different products in the point calculation vs. probabilistic calculation (adult population)

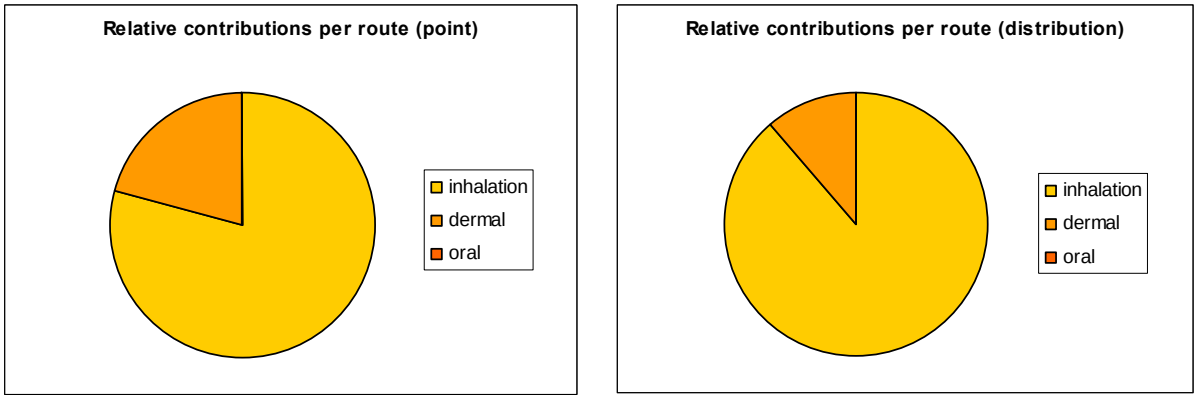


Figure 6 Relative contributions to the total exposure of the different exposure routes in the point calculation vs. probabilitstic calculation (adult population)

In increasing the level of detail of the assessment one acquires a more refined insight in the exposure of the population. In particular, an estimate of the distribution of the exposure in the population under study is made. Comparing this with the deterministic calculations of tier 1, it is observed that the latter largely over-predict the exposure levels in the population as assessed in tier 2. As for the estimation of the relative importance of the different routes and pathways: these numbers change somewhat in going from the first to the second tier, but remain in the same order of magnitude.

To conclude this example, we describe the procedure that could be followed to arrive at an estimate on a more detailed timescale.

Tier 3

For this detailed approach, most of the relevant data is missing. It should be collected if such an assessment were needed. In the absence of these data and in view of the somewhat advanced complexity of the calculations, these are not performed here and only an outline of the procedure that could be followed is given.

The customary approach is to construct an exposure profile with a time resolution of the required timescales. That is, if the required time resolution is one day, a daily exposure profile is to be constructed. For every day of the total exposure duration of a person (which could be a year, or a lifelong exposure depending on the circumstances) one has to determine which exposure events are likely to occur. This is normally done probabilistically: based on data on the use frequency of the product and the history of the exposure (the number of exposures that has already occurred) a probability that exposure to this product will take place on the considered day is determined. Using this probability, one decides at random whether the exposure event will take place this day or not. This procedure is repeated for all the products for the considered day. Subsequently, this procedure is repeated for the next day and the days thereafter, until the temporal exposure profile for the whole exposure period is determined. Then, the next person from the population is taken and the exposure profile for this person is determined in the same fashion. Finally, one arrives at a population of simulated individuals for which day-by-day exposure profiles are determined.

In the construction of the daily exposure profiles data on (auto-) correlations between exposure events should be considered if available. If, for instance a product is used only once a week, the probability of reuse of this product on the day after a day the product has been used should be set to zero. On the other hand, if the exposure to the substance stretches over a period for longer than a day (for instance due to the fact that the substance may still be evaporating into the air on the next days), this should be accounted for in the exposure profile on the day after the product was used. Similarly, if two different products have an increased or decreased probability to be used on the same day, this should be accounted for in the construction of the daily exposure profile.

In our example, we would start with selecting a person from our defined population. As we distinguish in our exposure sub scenarios between children and adults, who are fundamentally differently exposed, we should first decide to which group our selected individual belongs. This could be based on age or body weight for instance (note that a finer distinction could be made at this point, if desired. One could, for example, differentiate based on gender, social status, geographical location if such a distinction is expected to be relevant and this type of data on the population is available). Next, suppose we assess the yearly exposure to the substance. We would construct a profile consisting of

365 days. Starting at day 1 (1st of January), we would determine the probability of an exposure to dish washer based on the use frequency of dish washer for this person, than determine at random whether exposure to the dish washer takes place or not, and similarly for the all-purpose cleaner and the toilet cleaner. Next, we would move on to the second day (2nd of January) and repeat the procedure. In this fashion we arrive at a day by day exposure profile for a year for this person. From this profile, the daily exposure can be assessed in the same fashion described earlier, using values for the exposure factors that are drawn at random from the distributions of these parameters (amount of product used, exposure duration etc). This results in a day by day exposure estimation for this person. Repeating this for a large number of individuals results in a distribution of day by day exposure estimations. From this, not only distributions of year averaged exposures follow (which should match the results of the second tier approach), but also estimates of the distribution of the exposure on a single day (acute exposures) within a population.

4 Conclusions

In this report we explored various tools and methods that can be used to assess the aggregate human exposure to chemicals. Several existing computer tools that in one way or another consider exposure from different sources and along different pathways were described. Especially their applicability to assess the aggregate exposure from chemicals in multiple consumer products was discussed. From the discussions in this report we draw the following conclusions:

- The level of detail, with which aggregation is done, should be dictated by the scope and purpose of the assessment. Demands for a first tier, screening type of assessment on the required level of detail are much lower than those of an assessment that has to give a realistic quantification of the variation of the exposure in a population.
- Whatever the scope the assessment, the aggregation should be based on a person oriented approach: exposure profiles should be constructed for a single person, (may this person represent the entire population or be a realistic model of a person in the population) as this is the only way to ensure the consistency of exposure profile in the sense that no unrealistic or unrepresentative combinations of exposure are added in the aggregation.
- The only area in which aggregation techniques are fully implemented and made use of, is the field of exposure assessment to pesticides. The Calendex, CARES and LifeLine software programs enable the assessor to estimate exposures arising from different sources, such as tap water, food residues and household products to be aggregated in a consistent manner. Tools developed in other fields, in particular the assessment of human exposure to chemicals released as waste into the environment, generally do consider different pathways of exposure and sometimes allow for the aggregation (addition) of the exposures along these pathways, but do so in a crude manner, not enforcing the consistency and representativeness of the constructed exposure profiles. The results obtained by these methods should as a rule only be used as screening of upper boundaries or average values of the population exposure (depending on the choices of input parameters, e.g. probable or conservative values).
- There is a number of specialized software tools available for the assessment of consumer exposures, but none of these implements or facilitates doing aggregate assessment.
- A lot of chemicals are present in a wide variety of consumer products At present risk assessment generally is performed on a product basis. Aggregate exposure to

chemicals in multiple consumer products is currently hardly considered but should be taken into account to get insight whether actual risk is .A tool to perform aggregate exposure to consumer products needs to be developed.

- The present report provides a basis for the development of such a tool.

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APPENDIX A. Aggregate Exposure to Household Products: Model Equations And Input Data

In the equations below the following list of symbols is used:

$A_{applied}$	amount of product applied
A_{spill}	amount of product spilled on hands
A_{suds}	amount of product contained in suds
C_{air}	air concentration of the chemical
C_{suds}	concentration of the chemical in the suds
D	(absorbed) dose of the chemical
D_{inh}	inhaled dose of the chemical
d_{layer}	thickness of the layer of spilled product on the skin
f_{abs}	fraction of the substance absorbed
K_H	Henry's coefficient
K_{ow}	octanol-water partition coefficient
K_p	skin permeability
M_w	molecular weight of the chemical
Q_{inh}	inhalation rate
$S_{contact}$	surface area of dinnerware that comes in contact with foodstuff
S_{hands}	surface area of the hands that is in contact with the chemical
t	exposure duration
V_{suds}	volume of the suds
W_{body}	body weight
w_f	weight fraction of the chemical in the product
$\sigma_{residue}$	surface density of the chemical residue on dinnerware

The input data are derived from ref. 45,45

Dish washer

For the evaluation of the aggregate exposure to chemicals in household products we assumed the following exposure (sub) scenarios:

1. exposure during the preparation of suds (dermal exposure due to spillage)
2. exposure during washing the dish (dermal and inhalation exposure)

3. exposure due to residues of the substance on the dish (oral exposure via food intake from the dinnerware)

The scenarios 1 and 2 apply only to the people using the product. Scenario 3) applies also to non-users. Scenario 1) and the dermal contact of scenario 2) apply to users of the product only. Inhalation exposure during scenario 2) also applies to non-users of the product who are in the same room where the product is used.
The following simple model equations were used to estimate the exposures:

1. The amount of undiluted product spilled on hands during preparation is described in the TNsG[45] on biocides to be 0 to 3.2 mg per event.
   A fraction w_f of this amount is the amount of chemical, of which a fraction of f_{abs} is absorbed. Hence, from this the systemic dose per event is calculated as:

$$D = \frac{A_{spill} \times w_f \times f_{abs}}{W_{body}}$$

2. The air concentration resulting from the evaporating of the substance from the suds is approximated by the equilibrium air concentration as predicted by Henry's law:

$$C_{air} = K_H \times C_{suds}$$

   from this, the inhaled dose is estimated as:

$$D_{inh} = \frac{C_{air} \times Q_{inh} \times t}{W_{body}} = A_{applied} \times w_f \times \frac{K_H \times Q_{inh} \times t}{V_{suds} \times W_{body}}$$

   in which it is implicitly assumed that the absorption in the respiratory tract is 100%.
   The dermal exposure arises from the diffusion of the substance from the solution through the skin. The permeability of the skin for a substance can be estimated using experimental QSARs such as the one by Potts and Guy:

$$\log(Kp) = -2.7 + 0.71 \times \log(K_{ow}) - 0.0061 \times M_w$$

   Using this value for the permeability, the dermal absorbed dose is given by:

$$A_{suds} \times w_f \times \frac{(1 - e^{-K_p \times t})}{W_{body} \times V_{suds}}$$

3. The surface density of residues left on dinnerware after washing are estimated by HERA[45] as 5.5 x 10^{-5} ml/ cm^2 and the value for the area of dishes in daily contact with food as 5400 cm^2. All of the residue that is in contact with the foodstuff is supposed to be taken up systemically. Thus:

$$D = A_{suds} \times w_f \times \frac{S_{contact} \times \sigma_{residue}}{W_{body} \times V_{suds}}$$

All-purpose cleaner

For the all-purpose cleaner we assume exposure:

1. when preparing the suds (dermal exposure due to spillage)
2. during cleaning (inhalation exposure due to evaporation, dermal exposure due to rinsing of cloth in the suds and wiping with a cloth)

As the model equations describing these scenarios we choose:

1. The exposure during preparation is estimated similarly to scenario 1. for the exposure to dish washer.
2. During use, that is the cleaning of surfaces, the diluted product is applied in a thin layer. This situation (large surface in relation to the volume) highly favours the evaporation of the substance. It is therefore assumed that all of the applied chemical (w_f x $A_{applied}$) evaporates into the air. The air concentration is thus calculated as:

   $$C_{air} = \frac{A_{applied} \times w_f}{V_{room}}$$

   and the inhalation dose as:

   $$D_{inh} = \frac{C_{air} \times Q_{inh} \times t}{W_{body}} = A_{applied} \times w_f \times \frac{Q_{inh} \times t}{V_{room} \times W_{body}}$$

   To assess the dermal exposure we follow the assumptions made in the TGD, which suggest a default value for the thickness of a product layer left on the skin of 0.01 cm. For dermal exposure to the dilution, the amount can be calculated by multiplying the exposed area (cm^2) with the thickness of the layer d_{layer}. The exposure follows:

   $$D = A_{spill} \times w_f \times \frac{d_{layer} \times S_{hands} \times f_{abs}}{V_{suds} \times W_{body}}$$

Toilet cleaner

Finally, we assume the exposure to the toilet cleaner to take place during the use of the product (cleaning) only. Exposure is via inhalation of evaporating substance as well as by dermal contact.

1. the inhalation exposure is due to the evaporation of the substance from the toilet where it is supposed to be diluted with water. We describe the resulting air concentration and exposure again by the equation used in sub scenario 2 for the dish washer (Henry's Law).
2. The dermal exposure is due to accidental spilling. For this exposure we follow the TGD default approach, used also in scenario 2. for the all purpose cleaner (dermal exposure).

Exposure factors

For the sub scenarios described above, we used the following values for the exposure factors to evaluate the exposure:

parameter	Adult user point estimate	distribution : mean (s.d.)
body weight (kg)	65	75 (13)
inhalation rate (m^3/hr)	1.44	-
uptake fraction inhalation (%)	100	-
uptake fraction oral (%)	100	-
uptake fraction dermal (%)	10	-
Henry's coefficient	0.01	
dish washing		
weight fraction	0.01	
use frequency (times a year)	426	230 (288)
amount spilled during preparation (g)	2	0-32
volume of suds (liter)	5	-
exposure duration (hour)	1	
amount used (g)	70	LogNorm (30, 50)
exposed area dish (cm^2)	5400	-
residue on dish (ml/cm^2)	5.5e-5	-
all-purpose cleaner		
weight fraction	0.01	
use frequency (times a year)	104	128, 255
amount spilled during preparation (mg)	2	-
volume suds (liter)	5	-
amount applied during use (g)	74	27, 30
exposure duration (hr)	1	0.3, 0.4
volume room (m^3)	20	20
thickness layer suds residue on skin (mm)	0.01	-
surface area hands (cm^2)	860	-
toilet cleaner		
weight fraction	0.01	
use frequency (times per year)	260	102, 206
volume suds (liter)	5	-
amount applied (g)	55	40, 22
exposure duration (min)	2	1.2, 0.7

thickness layer suds residue on skin (mm)	0.01	-
surface area hands (cm^2)	860	-

Indirectly exposed child

parameter	**point estimate**	**distribution : mean (s.d.)**
body weight (kg)	11	11.1, 1.9
inhalation rate (m^3/hr)	0.06	-
uptake fraction inhalation (%)	100	-
uptake fraction oral (%)	100	-
uptake fraction dermal (%)	10	-
dish washing		
frequency	426	230 (288)
exposed area dish (cm^2)	5400	-
residue on dish (ml/cm^2)	5.5e-5	-
all-purpose cleaner		
use frequency (times a year)	204	128, 255
volume suds (liter)	5	-
amount applied during use (g)	74	27, 30
exposure duration (hour)	1	0.3, 0.4
volume room (m^3)	20	-