FINAL REPORT

CEFIC-LRI project ETHZ-B7

Estimation of realistic consumer exposure to substances from multiple sources and approaches to validation of exposure models

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Executive Summary

The project CEFIC-LRI-B7 aimed at deriving a tiered approach to aggregate exposure modelling for consumer products. A guidance for exposure modelling was developed and tested in two case studies for decamethylcyclopentasiloxane (D5) and triclosan (TCS). D5 is mainly used in cosmetics and personal care products (C&PCP) and triclosan is used in many different consumer applications such as C&PCPs and household cleaning products. A laboratory study with two cyclic siloxanes (D4 and D5) as pure substances and as ingredients of two personal care products (cream and deodorant) was performed to primarily study dermal uptake and secondly uptake by inhalation in human volunteers. A second guidance was prepared for human biological monitoring of consumer exposure. During the project both guidance documents were revised to include the experience obtained during the project.

Modelling

A conventional tiered approach was followed in modelling aggregate consumer exposure. The tier 1 model used literature information on the use of consumer products to determine (reasonable) worst-case point exposure values from single sources. These exposures were added up to yield a worst-case aggregate exposure. For the tier 2 assessment an ad hoc model was developed (PACEM: probabilistic aggregate consumer exposure model) that employs use data from 516 Dutch consumers (age 18-70) who completed an electronically distributed questionnaire. By constructing individual exposure profiles for each of the respondents a database on C&PCP use was constructed and coupled to the probabilistic exposure model. Thus, in combination with respective substance information this model can yield aggregate exposure levels for all substances present in C&PCPs.

In order to investigate the degree of conservativeness of the simple deterministic worst-case approach (tier 1) and the more refined probabilistic exposure assessment (tier 2) the modelling results were compared to the baseline measurements of D5 in end-exhaled air samples obtained in a laboratory study with human volunteers. To this end an existing physiologically based kinetic (PBK) model for D5 was adapted. A similar approach for modelling aggregate consumer exposure was followed for TCS, with the exception of human biomonitoring data being obtained from scientific literature rather than from a volunteer study.

Laboratory study

The experimental work included the assessment of human exposure to D5 and D4 (octamethylcyclotetrasiloxane) by collection of end-exhaled air samples in a group of 15 male and female volunteers. The cyclosiloxanes were collected on solid sorbent tubes and analysed using thermal desorption gas chromatography mass spectrometry (TD-GC-MS). In a first series of laboratory tests baseline exposures to D4 and D5 were determined following normal use of C&PCPs. In a second series of laboratory tests volunteers were asked to refrain from the use of C&PCPs for 24 hours. Next, they received standardized dermal exposure to D4 or D5 (pure substance) or a cream or deodorant or a combination of a cream and deodorant. To prevent inhalation exposure during these experiments, the forearm of the volunteer was placed inside a flow cabinet (exposure period). After removal of the pure substance or formulated product the participant was sitting underneath a fume hood, providing filtered air to prevent uptake by inhalation exposure.

Results and conclusions

The guidance was useful to serve as an organizer for the tiered approach to aggregate exposure modelling. It remains to be tested by other scientists.

Both the tier 1 and tier 2 model for D5 were reasonably conservative if compared to experimentally assessed baseline levels of exposure. For D5 the exposure estimates generated by tier 1 exceed the tier 2 estimates (95th percentiles) by two orders of magnitude, and the tier 2 estimates agree well with the baseline levels (i.e. realistic values). For TCS consumer exposure is overestimated by two orders of magnitude, presumably because the true prevalence of TCS in products is much less than the one assumed in the exposure modelling.

The laboratory study on dermal exposure showed that inhalation is much more important than dermal absorption for explaining the internal exposure of the studied cyclosiloxanes (either pure or as part of a C&PCP). Regarding exposure to self-applied dermal C&PCPs, there may also be a considerable contribution from products used by other persons in the same room or other confined spaces.

List of abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
ARfD	acute reference dose
C&PCPs	cosmetics and personal care products
COLIPA	The European Cosmetics Association (now the Cosmetics Europe)
COPHES	Consortium to Perform Human Biomonitoring on a European Scale
cVMSs	cyclic volatile methylsiloxanes
D4	octamethylcyclotetrasiloxane
D5	decamethylcyclopentasiloxane
GM	geometric mean
GSD	geometric standard deviation
HCPs	household cleaning products
LOAEL	lowest-observed-adverse-effect level
MoE	margin of exposure
NHANES	National Health and Nutrition Examination Survey in US
NOAEL	no-observed-adverse-effect level
PBK	physiologically based kinetic (modelling)
SD	standard deviation
TCS	triclosan, i.e. 5-chloro-2-(2,4-dichlorophenoxy)phenol
TD-GC-MS	thermal desorption gas chromatography mass spectrometry
TDI	tolerable daily intake

Glossary of terms

Aggregate exposure	Exposure to a single substance from all known sources (e.g. hair care products, cosmetics, detergents) via all pathways (e.g. during product use, after ingestion of house dust, due to contact with contaminated indoor surfaces) and routes (e.g. oral, dermal).
Biomarker or biological marker	An indicator (cellular, biochemical, analytical, or molecular) of a recent or previous exposure in a biological system, that should be a measure of body burden related to this exposure. The biomarker may be the chemical itself or a metabolite (adapted from Zartarian et al., 2007).
Biomonitoring	Analytical determination of natural and synthetic chemicals (i.e. biomarkers) in individuals' biological fluids or matrices (e.g. blood, hair, urine, breath) to assess internal exposure to chemicals (adapted from IUPAC, 2007).
Contact profile	A list of contacts (oral, dermal or inhalation) with consumer products for a person in a defined duration.
Consumer exposure	Exposure to a chemical from a non-food source that is caused by pathways not related to professional work and/or the manufacturing process of the respective chemical.
Cumulative exposure	The exposure to multiple chemicals that have a common mechanism of action with regard to the effect for human health.
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	Concentration or amount of a particular chemical that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration (WHO-IPCS, 2004).
Exposure assessment	The process of estimating or measuring the magnitude, frequency and duration of exposure to a chemical, along with the number and characteristics of the population exposed (WHO-IPCS, 2004).

Exposure event A single use of the product (or a specific activity) resulting in exposure.

Exposure factor Parameter that is specific to an individual human being and determines the level of exposure, such as behavioural data (e.g. consumer product use characteristics) and anthropometric data (e.g. bodyweight, age).

Exposure fraction The fraction of the total amount of substance released during the use of a product that an exposed person is actually exposed to. This may, for example be the fraction of an evaporated substance that is being inhaled, or the fraction of a substance applied on the skin that is dermally absorbed.

Exposure medium Material (e.g. air, water, soil, food, consumer products) surrounding or containing a chemical (Zartarian et al., 2007).

Exposure pathway The physical course a chemical takes from the source to the organism exposed (adapted from WHO-IPCS, 2004). An exposure pathway describes a unique mechanism by which an individual or population is exposed to a chemical at, or originating from, a site. Each exposure pathway includes a certain source or release from a source, an exposure point, and an exposure route. If the exposure point differs from the source, a transport/exposure medium (e.g., air) or media (in cases of intermedia transfer) is also included. In other words, it is a time- and space-wise description of the stages a chemical takes from a source to a target. The exposure pathway starts with the release of the respective chemical from the source, and finishes at the point where the chemical reaches the target (e.g. a specific human organ) via any of the three boundaries: skin, gastrointestinal tract or lung.

Exposure profile A list of all exposures (quantitative) for a person in the assessment. Depending on the level of detail of the assessment, an exposure profile may be a specification of acute exposures, or merely a list of long-term average exposures.

Exposure point A location of potential contact between a target and a chemical.

Exposure route	The way, in which a chemical enters a human being/animal after contact (i.e. by ingestion, inhalation, or dermal absorption) (Zartarian et al., 2007).
Exposure scenario	A combination of facts, assumptions, and inferences that define a discrete situation where potential exposure may occur. These may include the source, the exposed population, the time frame of exposure, microenvironment(s), and activities (WHO-IPCS, 2004).
Exposure source	The origin of a chemical for the purposes of an exposure assessment (adapted from Zartarian et al., 2007).
External exposure	The amount of a chemical that is available for inhalation, dermal contact or oral intake.
Internal exposure	The amount of a chemical that has been systemically absorbed e.g. into the blood circulation after inhalation, dermal contact or oral intake.
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.
Worst-case	A semi-quantitative term referring to the maximum possible exposure, dose, or risk that can conceivably occur, regardless of whether this exposure, dose, or risk actually occurs in a specific population.

Introduction to the project

The aim of the project was to develop guidance on when and how to perform an aggregated exposure assessment and to show in two case studies how consumer exposure from different sources can be modelled. We included different tiers of source-to-dose exposure modelling, ranging from deterministic screening methods to the realistic evaluation of the distribution of aggregate exposure within a population. New aspects of the modelling approach involve the individual based modelling on population level for which the **p**robabilistic **a**ggregate **c**onsumer **e**xposure **m**odel PACEM was developed.

Another new aspect relates to the important discussion about model validation. Often exposure models are constructed to represent a worst case, but a comparison with real exposure levels is seldomly performed. Thus, in order to quantify the level of conservativeness of the different tiers and to provide validation for the aggregation of exposure, a laboratory experiment was constructed to quantify the internal exposure after dermal exposure to one substance by different consumer products (single and aggregated). Furthermore, the baseline internal exposure of the volunteers was assessed, which is associated with normal external exposure by all routes. The individual baseline levels were then compared to the respective modelled internal exposure for an individual (obtained by coupling the external exposure with a physiologically based kinetic (PBK) model).

The two substances for the case studies and for model validation have been chosen on the basis of key criteria proposed by our consortium, and after discussion within an expert group. Both substances should be of wide-spread use in consumer products (so that exposure needs to be aggregated) and ideally be present in only one or two product sectors. One of the key criteria for the substance used in the experiment with human volunteers was that the substance is considered not toxic for humans, so that ethical approval is facilitated and that a PBK model already had been established.

This final report is organized into two parts. Part 1 reports the guidance to a tiered approach to aggregate exposure modelling and the case studies that were performed to test the guidance. Part 2 focuses on the experimental biomonitoring study and includes guidance on performing biomonitoring studies. Results and conclusions are given separately for both parts. Conclusions for the whole project and recommendations for future research are given at the end of the report.

Part I: Modelling of aggregate exposure to consumer products

Guidance, exposure factors for personal care products and case studies

I-1. Introduction

The need to develop methodology to perform aggregate exposure assessments for consumer products and articles has been acknowledged for several years. The objective of Part I of the final report to the CEFIC-LRI project B7 was to formulate guidance on *when and how* to aggregate exposure estimates of chemicals for consumer products and articles. Furthermore, a tiered approach to aggregate exposure assessment was established and applied in two case studies. This part of the report was developed in the work packages WP 1 and WP 3 of the project, and is related to the CEFIC-LRI B5 'TAGS' (tiered Aggregate Exposure Assessment) project (duration: 2009-2012). The TAGS project also addressed a tiered approach to aggregate exposure assessment, but had a broader perspective on chemicals relevant for consumer exposure, comprising e.g. pesticides and food contaminants. The focus of the current project is on consumer products (non-food) only, specifically on cosmetics and personal care products (C&PCPs) and household cleaning products.

Within the presented project, aggregate exposure is defined as the combined exposure to one substance from multiple sources, and if applicable, via multiple routes of exposure (such as ingestion, inhalation and dermal uptake). Examples of aggregate exposure are the exposure to limonene (a fragrance) via the use of C&PCPs and household products, the exposure to phthalates (a group of plasticizers) via food and toys, and the exposure to siloxanes from different C&PCPs. Related and sometimes synonymously used denominations for aggregated exposure are total exposure, cumulative exposure and combined exposure. Total exposure is the aggregate exposure to a chemical from all possible media, sources, and pathways, including unknown pathways. Cumulative exposure is defined as exposure to different substances with a common toxicological mode of action. Combined exposure was recently defined as "exposure to multiple chemicals by a single route and exposure to multiple chemicals by multiple routes" (Meek et al., 2011).

Aggregate exposure assessment is taken into account in European legislation and accompanying guidance documents (see Table I: 1-1). In the majority of legislative frameworks, however, only the source under evaluation is taken into account, hence no aggregation is performed. Furthermore, exposure and risk assessments are often performed per product (e.g. in the Biocide Directive 98/8/EC, as of January 1st 2014 the Biocide Products Regulation (EU) 528/2012), and not per substance, even though the substance may be present in more than one product. Also, sometimes the dietary and occupational exposure (mainly dermal and inhalation exposure to the product) are assessed and evaluated separately, although both can occur at the same time (e.g. Pesticides Regulation 1107/2009).

Table I: 1-1. Aggregate exposure in the legislation for exemplary compounds/product groups

Product group (legislation)	**Aggregate exposure**	**remarks**	**In practice**
Plant protection products (EC Regulation 1107/2009)	Not mentioned as such, but account shall be taken of all likely routes of exposure and of cumulative effects	Work in progress on guidance for cumulative risk assessment.	Aggregate exposure assessment performed for the food pathway, other sources not included. Or focus on other sources and food pathway not included
Biocides (EC Regulation 528/2012)	Not mentioned as such, but account shall be taken of all likely routes of exposure and of cumulative effects	In the Technical Notes for Guidance it is recognized that different definitions of aggregate exposure are being used.	Addition of external exposure over routes (dermal, oral, but only non-food) is performed. Assessment is performed per product rather than per substance.
Cosmetics (EC Regulation 1223/2009)	Not mentioned in the regulation	On an ingredient level: for the ingredients present on the different Annexes the safety of an ingredient is assessed (when applicable, e.g. for preservatives, assuming presence in all products at maximum level). On a product level: producers need to demonstrate safe use of their products; aggregate exposure is not accounted for.	Accounted for in several SCCS opinions. Recently also exposure from e.g. food sources are referred to (although not regulated under the Cosmetics Regulation).
Food Contact Materials (EC Regulation 1935/2004)	Not mentioned in the regulation	Assumption that 1 kg food containing the substance at the specified migration limit is consumed.	Aggregate exposure assessment performed for the oral route of exposure, other sources not included.

The aim of this project was to develop guidance on when to perform an aggregated exposure assessment (WP 1) and to illustrate in two case studies how consumer exposure from different sources can be evaluated (WP 3). The guidance, as presented in Chapter I-2, describes the different tiers of exposure assessment and relates each tier to the requirements concerning both available data and methodological approaches. A review of the available data and the results of a panel study on exposure factors for C&PCPs conducted within the project are given in Chapter I-3. In Chapter I-4 detailed case studies are reported that test the guidance for two substances: Decamethylcyclopentasiloxane (D5) and triclosan (TCS). D5 is a substance used almost exclusively in a broad range of C&PCPs, whereas TCS is widely used in a range of products (e.g. textiles, medical devices, plastics, household cleaning products and personal care products). Using the tiered approach, the aggregate exposure of a population to the selected substances was estimated. Chapter 5 contains the conclusions.

An overview how the work packages from the research proposal of the B7 project correspond to the chapters of this report is presented in Table I: 1-2.

Table I: 1-2. Work Packages of the CEFIC-LRI B7 project and the corresponding chapters in this report

Work Package	**Description**	**Chapter/ section**
WP 1.1	Guidance on the tiered assessment of aggregate exposure from household consumer products	2.1, 2.2, 2.3
WP 1.2	Approach to perform realistic aggregate consumer exposure assessments and identification of critical data gaps	2.4
WP 1.3	Panel study on exposure factors and construction of a database	3.2
WP 3.1 and 3.2	Exposure modelling with ConsExpo (tier 1) with D5 Exposure modelling person-oriented for a population (tier 2) with D5	4.1
WP 3.3 and 3.4	Exposure modelling with ConsExpo (tier 1) with TCS Exposure modelling person-oriented for a population (tier 2) with TCS	4.2

I-2. Guidance on aggregate exposure assessment

I-2.1 Tiered approach to aggregate exposure assessment for risk assessment

I-2.1.1 Concept

This section describes a tiered approach for the assessment of aggregate exposure to a substance from several consumer products within the scope of risk assessment. Tiered risk assessment is an iterative process. If, in any tier, negligible or acceptable risk cannot be demonstrated, the assessment moves to a higher tier. The risk assessment is finished if (in any tier of the approach) it has been demonstrated that the risk for the population under consideration is negligible or acceptable, or if in the highest tier the risk is not acceptable and further refinements are not possible. The approach suggested in this section is similar to the approach for a tiered exposure assessment that was recently proposed in the WHO/IPCS framework for risk assessment of combined exposure to multiple chemicals (Meek et al., 2011). This approach is also employed in the TAGS project (TAGS, 2011). Exposure assessments in the lowest tier are supposed to be relatively simple, quick and without heavy demands on input data. Moving to higher tiers leads to more complex, time consuming and data intensive methods.

In general, in a tiered assessment of aggregate exposure, the following actions are performed in the different tiers (definitions according to TAGS et al., 2011):

- Tier 0: Collect preliminary information on the substance and its sources, and interpret this information to decide whether an aggregate exposure assessment is needed.
- Tier 1: Aggregate the worst-case exposures for each source of the substance (i.e. upper boundary estimate). Use the aggregate worst-case to determine whether a risk can be excluded. Note, that the worst-case estimate will rarely be a measure of realistic exposure for the entire population: the most important criterion of the first tier assessment is that the exposure estimate is conservative.
- Refined tier 1: Estimate roughly the realistic exposure in a population. This involves estimating the average exposure as well as lower and upper bounds of exposure in the population.
- Tier 2: Make a detailed estimation of the realistic exposure in the population, including a detailed assessment of the variability of exposure (i.e. of the distribution of exposure within the population).

The tiers suggested here should be considered as a guideline illustrating the way to address an aggregate exposure evaluation for risk assessment purposes. The different tiers will be described in more detail in the next sections. The typical input needed for the different tiers is presented in Table I: 2-1.

Table I: 2-1. Typical input required for the different tiers in aggregate exposure assessment

Tier	Aim	Typical input required
tier 0	To decide if aggregate exposure assessment is needed.	**General**: Basic information on sources (products), product use, relevant population to describe the likelihood of exposure for the scenario. **Source and pathway information:** - List of products or product types containing the substance. - Overview of other sources (e.g. dietary, environmental) and pathways contributing to the exposure. **Toxicological/ kinetic information:** Key toxicological endpoints (plus: whether acute or chronic), reference values (also for higher tiers) for comparison to exposure calculation.
tiers 1&2	Gather 'background' information to compare the exposure with	**Source and pathway information** Expected background levels of other sources. **Toxicological information** Dose-effect studies to derive reference values from, or kinetic information to link external exposure to biomarker data.
tier 1	Aggregate worst case exposure	– General product formulations (higher bound of weight fraction of substance). – Anthropometric data for the different sub-populations identified (e.g. body weight, inhalation rates, surface area of various body parts). – (higher bound of) amount used per product. – (higher bound of) use frequency.
Refined tier 1	Deterministic realistic exposure	– Specific product compositions (range and average value of weight fraction in products) – Amount used per product per event (range) – Use frequency (range) – Information on co-use of products – Varying exposure event modelling factors (e.g. room volume, ventilation rate, exposed dermal surface area, body weight, absorption/uptake fractions), average values and ranges.
tier 2	Distribution of the realistic exposure within a population	– Information on personal use data (used amounts and frequency, use of specific brands), to combine with personal anthropometric data (e.g. body weight) – Distributions of exposure factors needed for exposure event modelling (e.g. room volume, ventilation rate, evaporation rate, spray release rates, exposed dermal surface area, body weight, absorption/uptake fractions).

I-2.1.2 How to perform an aggregate exposure assessment

Aggregate exposure assessments should be done using a person-oriented approach (Price et al. 1996, Zartarian et al., 2000, Arnold et al. 2007). This means that the exposed person in a population is taken as the central entity in the exposure assessment. Departing from this person, the exposure assessment is constructed by considering to which products the person may be exposed. The method of person-orientation ensures logical consistency in the exposure assessment as it excludes unrealistic combinations of product exposures (e.g. the simultaneous exposure to baby care products and hair dye). Any tier of the exposure assessment may be used to model the exposure for several persons, either representing different (sub)populations or various individuals in a real population.

Each tier of the exposure assessment consists of the following steps:

1) A person is defined for whom the exposure is estimated. This person may be a hypothetical person that represents an entire subpopulation (e.g. a heavy user or an average user of a number of products) or a realistic individual in a population in the case of a probabilistic assessment.
2) For each of the products identified in tier 0 and used by the person defined under 1) an exposure scenario is defined. This product specific exposure scenario describes the assumptions on how exposure takes place and identifies the factors that determine the exposure (e.g. used amount of product, frequency of use). Typically, the exposure scenario describes the exposure in a single exposure event (e.g. the exposure that arises during a single use of the product).
3) For the person defined under 1) the products that this person is exposed to are identified. The set of products to which the person is exposed and the assumptions on the time and frequency of exposure are combined in a ‘contact profile’. This contact profile describes to which products the defined person is jointly exposed in the time frame considered. This may, for example be the set of products that a person uses on a specific (moment of the) day, or the set of products and uses of these products in a year.
4) For each contact of the person with the product, the exposure is evaluated. This exposure assessment is performed based on the exposure scenario, using data on exposure factors collected under 2). This yields an exposure profile: a set of product exposures in the considered time frame (e.g. a set of acute or chronic exposures).
5) Addition of the various exposure components in the exposure profile gives the aggregate exposure (e.g. acute or chronic exposure).

The procedure of the aggregate exposure assessment is illustrated in Figure I: 2-1. The procedure will be followed in all tiers beyond tier 0, but the tiers will differ in the detail and sophistication with which the steps are implemented. The details of exposure evaluation in the different tiers are described below.

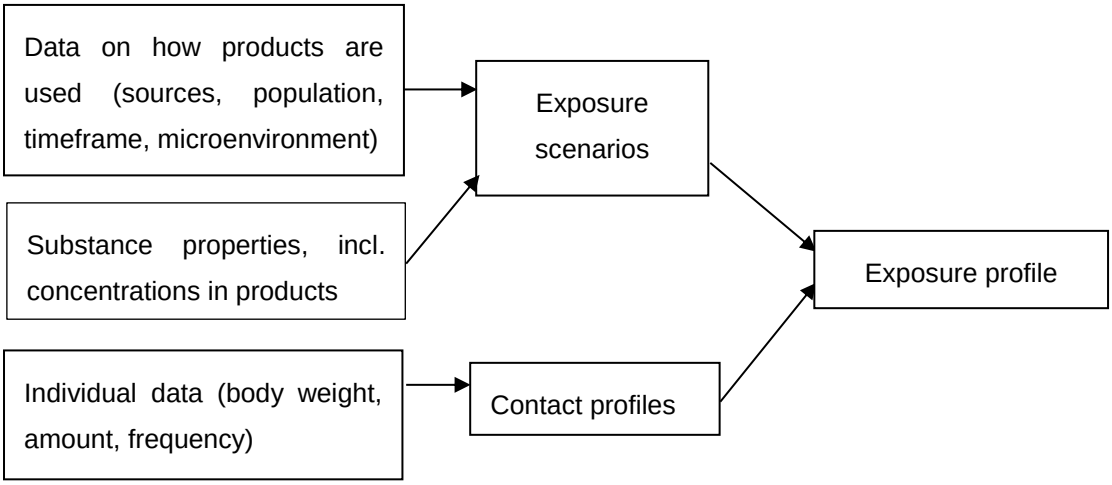


Figure I: 2-1. Schematic representation of the method of calculation of exposure for each contact

I-2.1.3 Uncertainty analysis

In addition to the best estimate of exposure, in each tier of an analysis of the uncertainty in the exposure evaluation should be considered. The purpose of uncertainty analysis is twofold. First, the uncertainty of the exposure (or risk) assessment may provide insight into the robustness of the assessment. When the uncertainty is large, the conclusions on whether there is a risk or not may be more difficult to draw. Second, by identifying the sources highly contributing to the total uncertainty, the data gaps that should be filled in a refined assessment are recognized.

Several methods of uncertainty analysis are described (Morgan, 1990, ECHA, 2008 and WHO, 2008). It is recommended that in tiered approaches such as described in this section, uncertainty analysis in each of the tiers is carried out at a similar level of detail as the exposure assessment itself.

I-2.2 Tier 0 aggregate exposure assessment

In tier 0 the risk assessor defines the scope and purpose of the assessment, the populations and products to be considered and the toxicological endpoint and time frame of the exposure assessment. In subsequent tiers the actual aggregate exposure assessment is carried out. First, a decision is needed whether or not an aggregate exposure assessment is appropriate. Aggregation of exposure should be considered when different products and/or routes are contributing to the total exposure in about the same order of magnitude. Aggregation of exposure is not necessary when one pathway clearly dominates over the others (e.g. results in a 100-fold higher internal exposure). In an explorative phase the scope/purpose of the assessment, general information on the substance (toxicology, properties) and relevant products are evaluated. Based on the gathered information a decision is made whether aggregate exposure assessment is appropriate. Although it is not exactly an assessment tier in the literal sense of the word, in analogy with the terminology of the TAGS project, tier 0 applies for this phase. Note that the information gathered in tier 0 is to be used higher tiers as well.

The following issues should be considered in tier 0:

- Scope and purpose of the assessment (e.g. determination of the average risk, or of a high percentile of the population).
- Toxicological information: To determine the required type of exposure and time frame of the exposure assessment (e.g. internal or external exposure, acute or (semi-) chronic exposure) information on the substance's toxicity is needed.
    - If the substance of concern has more than one relevant toxicological effect or shows differing metabolism following uptake from different routes of exposure, the route-specific exposures cannot be combined.
    - If the substance of concern causes local effects then exposure via various routes *should* not be aggregated to assess the risks of these effects.
    - Effect and exposure should be combined correctly with regard to the duration of the exposure. For example, in the case of acute exposure and a local health effect, exposures can only be added up when they result from simultaneous exposure events via the same route. Note that the decision whether events are "simultaneous" also depends on the elimination half-life of the respective substance in the body. On the other hand, when the critical effect is a systemic, long-term effect, an appropriate duration should be selected in the

exposure assessment. In that case, the duration of the health effect (i.e. reversibility of the effect), information on kinetics, and the possible accumulation of the substance should be taken into account.

- The (type of) consumer products contributing to the exposure.
- The physico-chemical properties of the substance.
- From consideration of the toxicity profile and expected exposure patterns of the substance, distinct target populations may be identified. For example, the toxic effects may be different for adults, children, and pregnant women. Risk should be assessed for each of these populations separately.
- Qualitative estimation of the contribution of the different sources to the aggregate exposure for each relevant population determined by the toxicological profile and expected exposure patterns. Note that the contribution of a single product to the exposure is determined by the size of the population exposed to this product, the intensity of product use (i.e. use frequency and amount) and the weight fraction of the substance in the product.

I-2.3 Tier 1 aggregate exposure assessment

I-2.3.1 Purpose of the first tier exposure assessment

The purpose of the exposure assessment in the first tier is:

1) to screen the aggregate exposure of the population to enable comparison to toxicological thresholds and decide whether further, refined assessment is needed;
2) if refinement of the assessment is needed:
    a. to identify subgroups in the population for which exposure is sufficiently low so that these groups may be excluded from further assessment;
    b. to identify products or exposure scenarios for specific product applications, for which the exposure is sufficiently low so that these may be excluded from further assessment.

I-2.3.2 Assessment of exposure events for tier 1

In tier 1, the assessment of exposure events should be sufficiently conservative. This means that the chosen exposure scenario, the assessment method and parameters for quantification of the exposure scenario (e.g. model input parameters) should be chosen to represent reasonable worst-case (i.e. high exposure) conditions. This can, in principle, be

done on the basis of experiments simulating exposure, direct or indirect monitoring of exposure (e.g. sampling of dermal load by hand wipes, monitoring inhaled air, biomonitoring), modelling, or a combination of these three. When data from monitoring studies or controlled experiments are used in a first tier assessment, special care should be taken to ensure that the data actually represent conservative (i.e. relatively high), rather than typical or average exposure situations. When using exposure modelling for the first tier, simple conservative evaluation methods should be used, assuming direct contact with 100% of the substance that is potentially available for exposure.

Equations for the event exposure calculation for each of the three exposure routes (inhalation, ingestion and dermal uptake) are presented in Appendix 1.

I-2.3.3 Modelling tools

The equations presented in Appendix 1 can be implemented in a modelling platform of choice. A number of special consumer exposure modelling tools are available in which specific exposure equations are included. Examples are ECETOC TRA for Consumers (ECHA, 2010), ConsExpo (Delmaar et al., 2005) and the consumer exposure modules in the EUSES model software (EC, 2008). All of these tools implement very simple equations similar to the ones defined in Appendix 1. ECETOC TRA offers limited flexibility, since for reasons of standardized assessments, many of the parameter values are fixed to default values. Also, these default values are defined only for a limited number of categories of consumer products. For better flexibility and overview, for worst-case exposure calculations such as tier 1 we propose to use the equations presented in Appendix 1, and select input data for these models as appropriate for the specific case under study. Alternatively, the equations from the ECHA Guidance on Consumer Exposure (ECHA, 2010) can be used.

I-2.3.4 Aggregation

In the first tier, aggregation can be done by simple addition of exposures from the different pathways for each subgroup of the population. When the critical health effect and the metabolism of the compound is route specific, summation should be done by route, yielding aggregate inhalation, dermal and oral exposures. If the toxicity and metabolism is not route-specific, total aggregate exposures are obtained by addition of the exposures for all routes. The latter requires information on the absorption of chemical for each route. In the absence of data or a reliable estimation method, the absorption fraction should be set to 1 (100%).

Estimates of chronic aggregate exposures are obtained by calculation of the time-weighted average of the exposure over the appropriate time interval. The size of the time interval depends on the substance and toxicological information. The interval may be for example a year or a lifetime.

Acute aggregate exposure is determined in the first tier by assuming that all exposure events take place simultaneously. This assumption may be overly conservative when exposure events are separated by times that are long in comparison to the substance elimination time from the body: e.g. more than the elimination half-life. If a good case can be made that the assumption of simultaneity is unrealistically conservative, acute exposures can be evaluated for events separately.

I-2.3.5 Interpretation of results

The aggregate exposure in the first tier will be compared to levels of acceptable exposure (e.g. ADI, TDI). If the estimated exposure is close to or above acceptable levels, a higher tier assessment is needed.

The results of first tier assessment can be used to identify subpopulations, products or specific scenario's that are of high importance. This insight can be used to prioritise work and allocate resources more efficiently in the higher tiered assessment.

I-2.3.6 Refined tier 1

If after a tier 1 exposure assessment, risks can not be excluded, the tier 1 assessment can be refined. In contrast to the tier 1 assessment, in the Refined tier 1 the purpose of the assessment is not to estimate the upper level of exposure, but rather the realistic distribution of exposure estimates across the entire population. The steps taken in the refined tier 1 should largely be the same as those described above. In particular, the identified subgroups in the population and their exposure profiles should in principle be the same.

The refinement of the assessment should concern different aspects:

- event exposure evaluation
- assessment of the variability of exposure within the population
- quantitative uncertainty analysis

Event exposure evaluation

To refine the event exposure evaluation, more specific and sophisticated models should be used, rather than the simple models defined under tier 1 combined with conservative input data.. Tools such as ConsExpo contain a number of more specific models and many more, special purpose models exist or may be developed for specific products or emissions. Alternatively, if representative experimental or monitoring data are available, these could be used in this tier. In this case, it should be considered to what extent the monitored and experimental data are indeed representative for the entire population and whether, for example, more extreme exposure situations are sufficiently covered.

Variability of exposure in the population

In tier 1, only an estimate of an upper bound of the exposure is made. In fact, the exposure will vary within a population. By estimating the range of the exposure in a population rather than only an upper bound, more refined conclusions on the risks can be drawn.

The variability of exposure in the population encompasses two different aspects: First, the size of the identified subgroups has to be estimated. Second, in evaluating event exposures, the variability in exposure factors should be accounted for. A rigorous way to include variability analysis is to perform probabilistic evaluations. A simple alternative is to evaluate exposure using different sets of input data representing low, average and high exposure within a (sub)population (e.g. Wormuth, 2006, von Goetz, 2010). While not quantitatively rigorous, this approach gives at least an indication of the range of exposures encountered in a population. Such a variability analysis can in most cases be limited to parameters with the highest impact on the range of exposures evaluated.

It is advised to use this method combined with a sensitivity analysis of the models and analysis of the quality of available data.

Uncertainty analysis

To analyse uncertainty, similar semi-quantitative methods (e.g. using low, average and high values of parameters) can be used as described in the section on variability analysis above. Focusing in this case on scenarios and data with a high uncertainty, ‘likely’, ‘somewhat likely’, and ‘possible but unlikely’ scenarios and data sets can be constructed. In cases where the risk is deemed adequately controlled, analysis of uncertainty may assist in demonstrating the robustness of the assessment: i.e. it may demonstrate that the outcome of the assessment will not likely change in light of the considered uncertainties. However, also in

the case that a higher tier analysis is required, uncertainty analysis is a useful method to provide guidance on refinement of the assessment in the higher tiers, as it will reveal areas in which further improvement of accuracy is most effectively obtained. For example, if in a tier 1 assessment a particular scenario suffers from large uncertainty, the contribution of this scenario to the overall exposure might be overestimated in an effort to be conservative. Reducing the uncertainty of this particular scenario in a subsequent tier of the exposure assessment can therefore have a high impact on the overall estimated level of aggregate exposure.

Interpretation of results

The aggregate exposure for different subgroups in the population should be compared to levels of acceptable exposure. Using estimates on the size of the subpopulation and the variability range of exposure within the group, estimates of the fraction of the population with an exposure higher than the acceptable level should be made. Considering these numbers together with their uncertainties helps to judge whether additional refinement is necessary.

I-2.4 Tier 2 exposure assessment

I-2.4.1 Purpose of a tier 2 exposure assessment

In a tier 2 exposure assessment, the realistic exposure of a population is estimated. This will not only involve a specification of the central tendency of the exposure (e.g. mean or median exposure) but will also quantify in detail the variability of exposure within the (sub)population(s) (e.g. standard deviation, specific percentiles of the exposure distribution). The following sections provide a description of an approach to derive tier 2 aggregate exposure estimates for consumer products.

In WP 3 of the current CEFIC-LRI project a tool was developed based on this approach: the ‘probabilistic aggregate consumer exposure model’ (PACEM). This tool is used to assess exposure in two case studies focusing on substances in consumer products (see Chapter I-4).

The approach used in PACEM can be summarized by the following steps: for each individual in a (sub) population exposure profiles are constructed by the combination of scenarios of use, which specify, for each contact between individual and single product, how exposure will take place. The exposure for each scenario is quantified using modelling or direct measurement and the collective result is called an exposure profile. From the day-to-day

exposure profiles relevant statistics characterizing the exposure of the population can be derived. These descriptive statistics can be used to characterize the associated risk for a population.

The approach is illustrated in Figure I: 2-2 and described in more technical detail in Appendix 2 (also see RIVM-report 'Aggregating human exposure to chemicals' (Delmaar & van Engelen, 2006)).

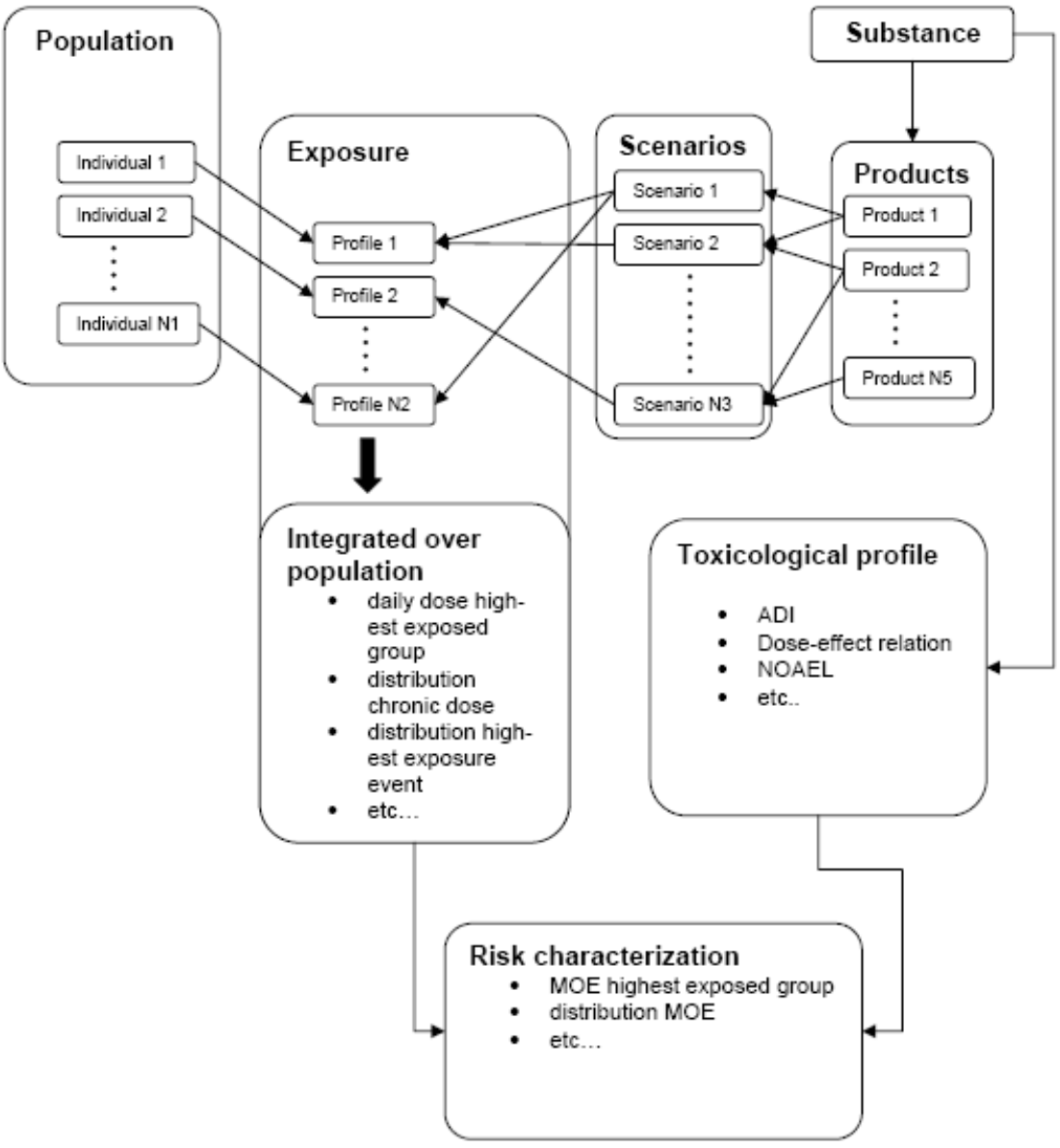


Figure I: 2-2. Schematic representation of an approach to assess aggregate exposure from multiple consumer products in chemical risk assessment.

I-2.4.2 Method

In the tier 2 exposure assessment a realistic estimate is made of the aggregate exposure in the entire population. First, a person, representing a realistic individual in the considered (sub)population is selected. For this person contact profiles are constructed based on realistic product use data (i.e. information on product use frequency and co-use of products). To evaluate the exposure profile for the person, his/her contact profile is combined with individual exposure factors (e.g. the person's body weight, inhalation rate, the amount of product he/she typically uses). Alternatively, exposure in a scenario may be evaluated using measured data, such as monitoring data on the substance concentrations in contact media such as indoor air and dust, or direct personal exposure measurements.

Aggregate exposure for the considered person is obtained by summation over the exposures in the relevant time frame (e.g. on a day, in a year). Repeating these steps for a large number of representative persons, an estimate of the distribution of aggregate exposure in the population is obtained.

The procedure in tier 2 requires first and foremost information on the use of products within a population. Most notably, information on the use frequency and on the amount used per product is crucial. This type of data has been collected for C&PCPs in WP 3 (see Chapter I-3). The data was used to develop PACEM.

I-2.4.3 Probabilistic aggregate consumer exposure model (PACEM)

PACEM implements the procedure outlined in Section I-2.4.2 in a software tool. The tool contains a database with the data on the use of C&PCPs collected in the panel study (WP 3).

Exposure modelling is implemented using the concept of an 'exposure fraction'. The exposure fraction specifies the exposure per unit of product used. To calculate exposure, the exposure fraction is directly combined with the amount of product used, contained in the database on product use. The numerical values of the exposure fraction depend on the product and the substance considered. These have to be calculated outside the model and provided as input.

In PACEM, the database containing product use data and product specific information was built in MS Access. The calculations, combination of data, formatting and analysis of the results are performed in the modelling language R (*http://cran.r-project.org/*). A flow chart detailing the data flow in PACEM is given in Figure I: 2-3. White boxes describe database entities and tables that hold information on independent parts in the tool (e.g. individuals in the population, products that contain the substance *et cetera*). Diamonds describe relations

between the entities (e.g. the relation ‘contacts’ between ‘population’ and ‘product’ describes that an individual comes in contact with a product due to direct use or his presence during use of the product). Red ellipses describe the properties of the entities and typically specify the information on the entities that is stored in the table. Grey entities and relations describe input of the framework that has to be delivered at any application (i.e. for every substance that is considered separately). The blue ellipse finally signifies the calculation of exposure using mathematical equations. Note that some entities appear more than once in the diagram. This is to specify different relations between the entities and does not mean that there are several instances of the same entity included in the tool.

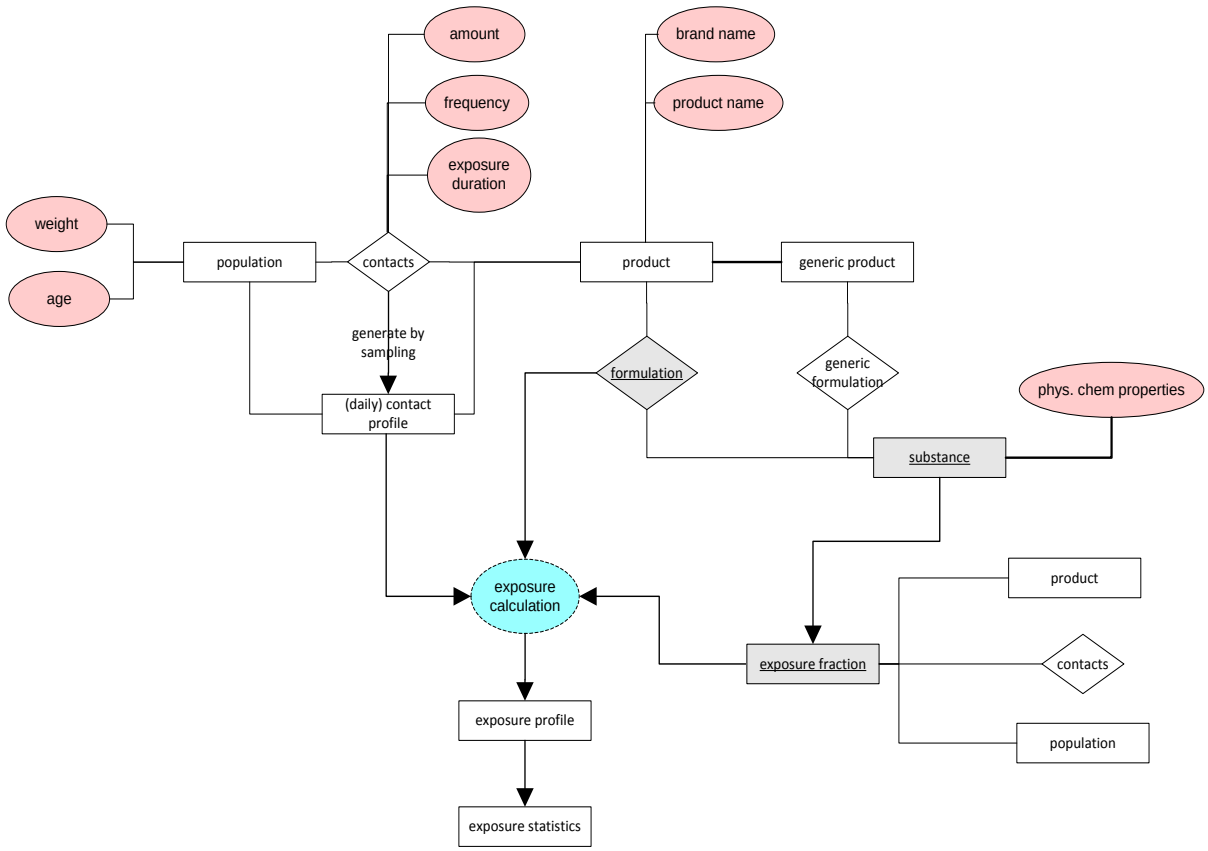


Figure I: 2-3. Entity-relation diagram for the database and data flow in PACEM for aggregate exposure modelling.

I-2.4.4 Timescale, exposure metric and uncertainty analysis

Timescale

The framework should be able to assess both acute and chronic exposures. In general, aggregate acute exposure will be estimated by adding up the maximal number of exposure events that can be considered to occur simultaneously. Aggregate chronic exposure refers to the addition of exposures averaged over a longer time interval (e.g. a year, a life).

Exposure metric

For many contacts with consumer products, the exposure will be via multiple routes. To assess aggregate exposures, contributions via different routes will have to be added. As measures of external exposure are incomparable among different routes, the contribution to the internal dose on systemic or target (organ) level for each of the exposures routes will have to be determined. This requires the specification of absorption, distribution, metabolism and elimination for each route. At the very least the absorption efficiency for each route could be assumed to be complete (i.e. 100%) to assess potential aggregate exposure (rather than actual exposure) assuming that all other kinetics are the same between difference exposure routes. So, the framework should require the input of (product and substance dependent) absorption fractions for all relevant routes.

Uncertainty analysis

Quantitative uncertainty analysis may be applied to study uncertainty due to limited data quality, uncertainty in scenario definition, statistical uncertainty due to limited population size in the product use database, uncertainty in the product formulation etc. Uncertainty analyses as suggested in the refined tier 1 may be of use.

I-3. Data sources

I-3.1 Publicly available data sources

For modelling consumer exposure, data are needed on (1) exposure factors like human body characteristics and product use patterns, stratified by age and gender, and (2) concentrations of the target ingredients in consumer products and market share of different product categories. In the following, data sources for these categories of model parameters are described that can be used for modelling exposure for the European population.

I-3.1.1 Exposure factors

An important compilation of exposure factors for the European population is the expofacts database (*expofacts.jrc.ec.europa.eu*), which is administrated by the EU Joint Research Centre (JRC). This database provides original data summarized in excel-sheets together with citations. It provides a good first overview of available data sources. The data mainly focus on food intake, but the database was recently extended to C&PCP use, e.g. by including amount and frequency of use data for the Dutch population assessed within this study (Biesterbos et al., 2013) and frequency of use data for leave-on cosmetics in the German speaking part of Switzerland (Manova et al., 2013).

For some C&PCPs, the amount of products used per day has been assessed for Europe by the industry association for cosmetics COLIPA (now Cosmetics Europe) (Hall et al., 2007, 2012), but the frequency and consequently the amount used per application event are not reported. European data for the use of household cleaning agents was collected within the Human and Environmental Risk Assessment project (HERA, 2005). Data on body characteristics (e.g. bodyweight) in European countries can be ordered from EuroStat. In general, the product factsheets developed for the ConsExpo exposure model (Weegels and van Veen, 2001; Bremmer and van Veen, 2002; Bremmer et al., 2006a; Bremmer et al., 2006b) are a good source for exposure factors (aimed at the Dutch population, but some may be extrapolated to other populations). Also data for the German population have been collected by a joint effort of agencies and are provided in the XProb database (*http://www.umweltbundesamt.de/en/datenbank-fuer-expositionsfaktoren*) and in the AUH, 1995. For some exposure factors that are not dependent on the cultural background, like e.g.

inhalation rates, it is also possible to use non-European data, like e.g. provided by the exposure factors handbook (EPA, 2011).

Further, national data sources exist, e.g. for Germany a commercial database with use data for many consumer products, including C&PCP, and household cleaning agents (VerbraucherAnalyse [Consumer Analysis], *http://www.verbraucheranalyse.de/inhalte*), providing information on the product types and brands as well as (in some cases) on the frequency of product use within population. Also for use and practices regarding consumer products, the ConsExpo fact sheets provide a lot of data for the Dutch population that to some extent can be extrapolated to other European populations.

I-3.1.2 Concentrations of target ingredients in products

Special sources of information are online database resources offering access to information about ingredients contained in specific C&PCPs. While these resources may contain valuable information, they can also contain conflicting or incomplete information as in some databases data is entered by consumers themselves and no quality check is performed. Examples of databases are detailed below. Some companies also provide ingredients lists online, but these are not always up to date, and may describe phased-out formulations. All online databases provide qualitative information only on ingredients in consumer products.

The Factual Global Products platform (http://www.factual.com/products/cpg) contains over 650,000 consumer goods, which can be tracked by the barcode. The database can be also explored by looking for a specific product category or brand name. The search returns general information of the product (e.g. price, barcode, images, external links, etc.) as well as the ingredients list. The records in Consumer Product Information database (CPID; *http://www.whatsinproducts.com*) are organized in the same manner with the additional advantage of enableing to look for the products that contain a specific ingredient. The GoodGuide database (*http://www.goodguide.com/*) rates the health, environmental, and social performance of products and companies based on the product content.

Codecheck (*www.codecheck.info*) is a Swiss-based online database, also accessible via a mobile phone application, providing C&PCP ingredient information to consumers. The Codecheck database is in German and available free of charge for all users. By either scanning a barcode available on each C&PCP or typing a C&PCP name, consumers can obtain information including C&PCP ingredient lists and human health and environmental relevant ingredient information not available on the C&PCP label. Ingredient information was gathered by experts from the German consumer magazine ÖKO-TEST. Although the website

is currently only available in German, it is designed in a consumer-friendly and an easy-to-understand way and we believe that non-German speakers interested in composition of C&PCPs available on the market in the German-speaking countries would be able to extract the desired ingredient information from the database.

Kosmetikanalyse (Cosmetic Analysis) (*http://www.cosmeticanalysis.com/*) is a powerful bilingual (German-English) Swiss-based online database. C&PCP ingredient lists are available free of charge; however, the ingredients are not ordered by decreasing concentration as on the C&PCP labels. This information is however fee-based. As of January 2014 the six-month membership costs EUR 30 and allows members to analyze products themselves, access all ingredient lists (in decreasing order of concentration as on the C&PCP label), information about properties and judgments of more than 8,500 ingredients and expert and scientific judgments of the ingredients. Kosmetikanalyse is searchable by products, ingredients, and brands.

I-3.2 PCP use in the Netherlands

This paragraph provides a short summary of the panel study. A complete overview of the results can be found in the Appendix 3 (article by Biesterbos et al.: *Usage patterns of personal care products: important factors for exposure assessment.* Food Chem Toxicol, 2013. **55**: p. 8-17.).

I-3.2.1 Introduction

Complete information regarding the use of cosmetics and personal care products (C&PCPs) by consumers is limited, but such information is crucial for realistic consumer exposure assessment. To fill this gap, a database was created with person-oriented information regarding usage patterns and circumstances of use for 32 different C&PCPs.

I-3.2.2 Methods

Out of 2700 invited participants from the Netherlands, 516 men and women completed a digital questionnaire. This questionnaire contained general questions regarding demographics, lifestyle and skin type. The detailed usage patterns of 32 types of C&PCPs were assessed using questions regarding the frequency of use and the amount of product used per application. Photographs were used to visualize the amount of product used in the following product categories: general hygiene (e.g. soap), shaving products, hair care, skin

care and tanning products. Not for all C&PCPs a visual display of amounts was meaningful. Therefore, alternative questions were developed to describe the amounts used such as: “how often did you spray?” (spray products), “where exactly did you apply the product?” (eye shadow, eye pencil and lip pencil), “how many layers did you apply?” (mascara, eyebrow pencil, lip pencil, lipstick, lip balm and nail polish). The questionnaire was tested in a small experimental study. Mean amounts of used products were calculated by weighing before and after application of the product. In addition, the questionnaire contained questions regarding the type and brand of the product, the application area on the body, the time of day a product was used (e.g. morning or evening), the location of use (indoors or outdoors) and the presence of ventilation. Data were analysed using SPSS version 18.0.

I-3.2.3 Results

The prevalence of use varied by gender, age, level of education and skin type. A high frequency of use was observed for some products (e.g. lip care products), while toothpaste, deodorant and day cream were generally used once or twice a day (Figure I: 3-1). The frequency of use for other C&PCPs varied over a wide range. The amounts of use varied largely between and within different product groups. Body lotion, sunscreen and after sun lotion were often applied on adjacent body parts. The majority of C&PCPs were applied in the morning, but some products, such as night cream and after sun, were predominantly applied in the evening or night. As expected, the participants used several C&PCPs simultaneously.

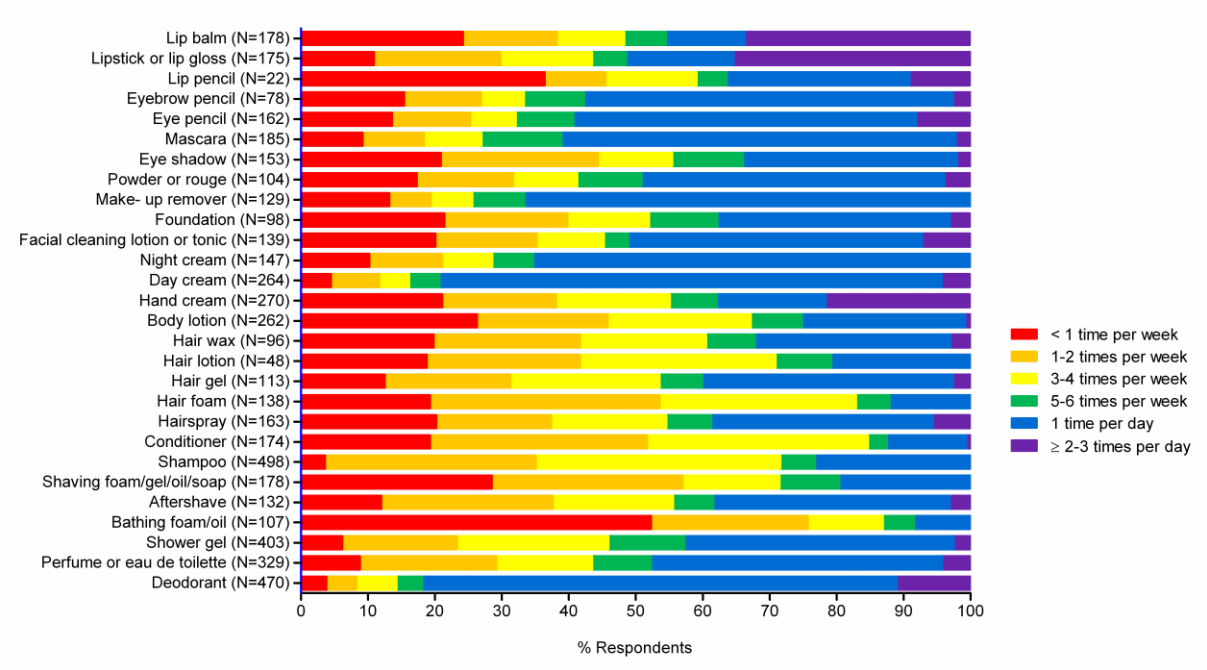


Figure I: 3-1. Frequency of use among respondents (N=516) for the majority of PCPs studied.

I-3.2.4 Conclusion

The database yields important personalized exposure factors, which can be used in the aggregate consumer exposure assessment for substances that are components of C&PCPs.

I-4. Case studies

I-4.1 Introduction

The main objective of the case studies was a methodological evaluation of the tiered approach described in Chapter 2 to modelling aggregate human exposure for substances contained in consumer products. In the succeeding chapters the final results of exposure simulations for two substances – decamethylcyclopentsiloxane (D5) and triclosan (TCS) are presented.

The tiered approach to consumer exposure assessment implies a gradual refinement of exposure estimates, should the calculated values exceed the predefined limits (e.g. TDI, ARfD). However, in this project we did not aim at risk characterization. The comparison of the modelled results with the critical effect levels was provided for reference only. The main objective of the case studies was to quantify the difference in the results for each modelling tier and demonstrate the applicability and robustness of different modelling methods for aggregate consumer exposure assessment. In addition, we attempted to generalize the approach and make it applicable for the exposure assessment of other substances present in various consumer products.

The structure of the case study reports is the following: Each case study consists of two main parts, namely the characterization of the substance and the tiered exposure assessment. In the first part a brief summary of substance's physicochemical properties and toxicokinetic profile is given. The second part contains a detailed description of the input data, explanation of the exposure model and the discussion of the results in each tier of exposure assessment. At the very end of each case study the predicted/modelled exposure is evaluated against human biomonitoring data using the forward dosimetry approach. This validation should demonstrate the applicability and reliability of different models/methodologies to predict population aggregate exposure.

I-4.2 Case study 1: Decamethylcyclopentasiloxane (D5)

I-4.2.1 Substance profile

Physicochemical properties

Decamethylcyclopentasiloxane (D5; CAS 541-02-6) is a low molecular weight cyclic volatile methylsiloxane (cVMS) that consists of five elastic –Si–O– structural units arranged in a ring with two methyl groups attached to each silicon atom (Figure I: 4-1).

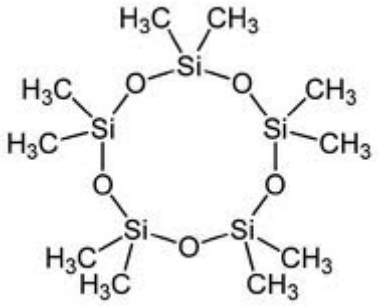


Figure I: 4-1. Chemical structure of D5.

In pure form D5 is a colour- and odourless fluid, which is widely used in cosmetics and personal care products (C&PCPs) due to its distinct physicochemical properties, i.e. high volatility (vapour pressure is 33.2 Pa at 25°C (SEHSC 2005a)) and extreme lipophilicity ($\log K_{ow}$ is 8.0). Extended information on substance properties is presented in Table A4 - 2.1 of Appendix 4.

Kinetics

The kinetics of D5 in the human body after either inhalation or dermal absorption is largely influenced by two specific processes: 1) high lipid partitioning leading to formation of sequestered or unavailable pool of D5 in the blood and 2) fast elimination from blood due to exhalation ($t_{1/2}$ in blood is 4-6 hours). The results of the PBK modelling (Reddy et al., 2008) show that about 90% of the systemically absorbed D5 is exhaled unchanged within 24 hours. It is noteworthy that the inhalation kinetics is much faster, suggesting that the inhalation exposure route will be of major importance.

In addition, D5 is metabolized by hepatic clearance. Hydroxylated D5 (HO-D5) metabolite comprises about 1% of the systemic dose and is excreted with urine and faeces. No metabolization of D5 was discovered in skin or in lung tissue.

A brief summary of the route-specific uptake rates used for the internal dose calculations in the tier 1 assessment is given in Table I: 4-1.

Table I: 4-1. Route-specific uptake rates for neat D5.

Route	Type of study	Subjects	Parameter	Value	Reference
Dermal	In vitro	rat skin	dermal absorption	1.54%	Dow Corning, 1996a
		human skin	dermal absorption	0.04%	Jovanovich et al., 2008
		human skin	steady-state flux into receptor fluid	0.004 $\mu g/cm^2/h$	Jovanovich et al., 2008
	In vivo	rats	dermal absorption	0.80±0.62%	Dow Corning, 1996b
		rats	dermal absorption	0.17%	Jovanovich et al., 2008
		humans	dermal absorption	0.05%	Plotzke et al., 2002; Reddy et al., 2007
Inhalation	6-hour repeated inhalation rat study	rats	retention factor	1-2%	Tobin et al., 2008

Toxicity

In the past the toxicity profile of D5 was thoroughly scrutinized (SCCS, 2010; Johnson et al., 2012). A brief summary is provided below.

The NOAEL for reproductive toxicity of D5 in the 2-generation whole-body vapour inhalation rat study was 160 ppm, i.e. the highest concentration that could be achieved without aerosol formation (Siddiqui et al., 2007). Reproductive parameters in the F0 and F1 generations were not affected by exposure to the test article. In a combined chronic toxicity and carcinogenicity whole-body vapour inhalation toxicity study D5 induced uterine endometrial adenocarcinomas in female rats at 160 ppm (Dow Corning 2005) in addition to other non-neoplastic effects (e.g. liver weight increases) observed at 150 ppm. However, the relevance of this mode of action in humans is unclear at present. Therefore, the lack of genotoxic effects for D5 (based on limited genotoxicity data) suggests that the uterine tumours

observed in the chronic carcinogenicity study could be due to threshold effects. The effects on liver were also observed in subchronic toxicity studies in rats with either whole body vapour inhalation (Burns-Naas et al., 1998a) or oral administration of D5 (Jäger and Hartmann, 1991). The determined oral LOAEL for liver weight increase in rats with oral dosing was 100 mg/kg bw/day. In other subchronic inhalation nose-only studies in rats, liver weight increases were reversible upon cessation of exposure (Burns-Naas et al., 1998b). Dermal application of neat D5 up to 1600 mg D5/kg bw to rats' skin for 28 days did not produce any test material related effects (Dow Corning, 1990). Overall, in the absence of reprotoxicity and carcinogenicity studies with oral dosing, it is not possible to infer whether toxicological endpoints for D5 are independent of the route of exposure. Therefore, aggregation of exposure in this assessment was done by route.

More detailed information on D5 toxicity can be found e.g. in the opinion of the European Scientific Committee on Consumer Safety (SCCS) on cyclomethicone (D4 and D5) present in cosmetics and personal care products (SCCS, 2010). In this document the SSCS does not derive any health based guidance values (e.g. TDI, ARfD), but establishes the following critical effect levels to be used in safety assessments:

- a NOAEL of 150 ppm from chronic inhalation exposure studies in rats (lower dose is chosen with regard to the most critical effects of cyclomethicone in rats, namely reproductive toxicity and potential carcinogenicity of D4), and
- a LOAEL of 100 mg/kg/day from subchronic toxicity rat studies with oral dosing to cover organ weight changes in liver, kidney and thymus.

Based on the screening risk assessment conducted in the SCCS's opinion, D5 is currently considered safe for humans as being used in C&PCPs.

I-4.2.2 Aggregate consumer exposure assessment

I-4.2.2.1 Tier 0 qualitative assessment

General scope and purpose of the assessment

The purpose of the tier 0 exposure assessment is to provide a preliminary overview of all possible exposure sources, pathways and routes for the chemical of interest. In general, based on the results of the tier 0 it can be decided whether an aggregate exposure assessment is needed. The information collected in tier 0 will provide the basis for the subsequent tiers.

Exposure sources

D5 has been recognized as a high production volume (HPV) chemical by the Organization for Economic Cooperation and Development (OECD, 2007). According to the U.S. EPA (2002) its annual import and production in the United States of America increased by ten times in the last 25 years to more than 225,000 tons. In Europe the amount of D5 used annually for personal care applications was estimated by the Environmental Agency of the United Kingdom in its environmental risk assessment reports (UK EA, 2009a, 2009b, 2009c) at 17,300 tons for year 2004.

In cosmetic and personal care products (C&PCPs) D5 is widely used as emollient and carrier solvent for fragrances and essential oils. It is mostly found in deodorants, liquid foundations, hair care and skin care products where its concentration can reach up to 40% w/w (Dudzina et al., 2014). According to the data provided by the Skin Deep Database (EWG), which encompasses more than 74,000 C&PCPs, D5 is currently labelled on the ingredients lists of 4,252 products (EWG, 2013). In addition, D5 may also be present in the form of cyclomethicone, i.e. in a mixture with other cyclic siloxanes (1,148 products). Another cosmetic database lists D5 among the ingredients in 1,275 C&PCPs available on the European market (Cosmetic Analysis, 2013). A search for cyclomethicone returned 610 products. Under current European legislation D5 is required to be labelled on the product package only qualitatively, while for the assessment of consumer exposure quantitative information is needed. The concentrations data can be either sourced from analytical studies in scientific literature or adopted from Cosmetic Frame formulations (Cosmetics Europe, 2013).

Another major application of D5 is dry cleaning. While being used as a safer and eco-friendlier replacement for tetrachloroethylene, D5 carries the detergent to the clothes and rinses away suspended dirt and oils trapped by the detergent. It does not interact with textiles and therefore helps maintain the quality and colour of clothes that are cleaned. This dry cleaning technology is claimed to be a closed-cycle process, which allows recovering and re-using of D5. Therefore, indirect consumer exposure from wearing dry-cleaned textiles is considered to be negligible.

Exposure pathways

Exposure to D5 contained in C&PCPs is supposed to occur mainly via direct dermal application of these products. However, because of its high vapour pressure indirect inhalation exposure to D5 volatilized from skin will also contribute substantially to the total systemic dose. Direct inhalation of D5 occurs from application of spray products. Finally,

ingestion of D5 in lip care products, such as lipsticks, lip balms, etc. must be taken into account when calculating aggregate consumer exposure.

Industrial manufacturing of D5 as well as direct application of D5-containing products by consumers can lead to significant emissions into ambient air or wastewater (Maddalena et al., 2011; Gouin et al., 2012), which results in D5 being found globally in various environmental matrices including outdoor and indoor air (Tuomainen et al., 2002; Norden, 2005; Warner et al., 2010; McLachlan et al., 2010; Genualdi et al., 2011; Buser et al., 2013; Yucuis et al., 2013), dust (Lu et al., 2010), surface and sewage water (NILU, 2007; Sparham et al., 2008; Zhang et al., 2011), biota (Kaj et al., 2005a; Norden, 2005; NILU, 2007), as well as human tissue (US EPA, 1987; Kala et al., 1997; Flassbeck et al., 2001; Kaj et al., 2005b; Hanssen et al., 2013).

At present, the observed environmental concentrations are in the ng/m^3 range, suggesting that the exposure via ambient air, as well as via inadvertent dust ingestion, will be negligible in comparison to the doses received from direct application of C&PCPs (including inhalation of indoor air containing D5 volatilized from skin).

I-4.2.2.2 Tier 1 worst-case scenario assessment

General scope and purpose of the assessment

The aim of the tier 1 assessment is to determine a realistic upper bound of the aggregate consumer exposure to D5 in a population from application of C&PCPs. The results of such reasonable worst-case scenario assessment can be further used in e.g. chemical safety assessment, risk assessment or in delimiting regulatory values. Furthermore, screening assessment can help to identify the exposure sources, routes and/or pathways, for which the refinement in higher tiers should be a priority.

Tier 1 exposure model description

The tier 1 model was constructed upon the original ECETOC-TRA platform (that currently lacks an algorithm for the calculation of exposure to substances from C&PCPs) and incorporated common principles for consumer exposure assessment (ECHA, 2012; SCCS, 2010). In this tier the release and subsequent fate of a substance are governed by the following worst-case assumptions:

1. the release is instantaneous; and
2. there is no removal of the substance.

Exposure calculations were performed for a standard/hypothetical person that can be characterized with the following (default) parameters:

- age – adult
- gender – not defined
- body weight – 60 kg
- whole body surface area – 17,500 cm^2
- inhalation rate – 26 m^3/day

Taking into account the vast variability of C&PCPs available on the European market it was not feasible to perform exposure modelling for each individual product (defined by brand, name, etc.). Instead, groups and corresponding subgroups of generic C&PCPs were considered. Each generic product subgroup is characterized with its unique application scenario (i.e. frequency, the amount used per application, body surface area of application, duration of exposure, etc.). The product classification used in the tier 1 assessment is consistent with that adopted in the questionnaire on C&PCPs use (see Appendix 3). This allowed retaining uniformity and simplicity of exposure calculations throughout modelling tiers.

Aggregate consumer exposure to D5 occurring from the use of C&PCPs only was modelled. The following routes of exposure were accounted for:

- Dermal exposure to D5 from dermally applied C&PCPs;
- Direct inhalation exposure to D5 from spray C&PCPs (e.g. spray deodorants);
- Indirect inhalation exposure to D5 vapour occurring when the substance evaporates from consumers' skin after product application. As a worst-case approximation 20% of the dermally applied amount is assumed to evaporate instantly and become available for inhalation. The arbitrary value of 20% was also taken in risk assessment for D5 conducted by the Environmental Canada (2008);
- Oral exposure from toothpastes, mouthwash and lip care C&PCPs.

General equations that were used to calculate reasonable worst-case consumer exposure via different routes, as well as the default input parameters are presented in Appendix A4-1.

The assessment was undertaken for regular users of C&PCPs. Both acute (i.e. on the day of product application, [mg/kg bw/day]) and chronic (average, [mg/kg bw/day]) aggregate external exposure and the internal doses were calculated.

Aggregation strategy

Aggregation of exposure was performed over all products considered in the assessment. However, to avoid unreasonable overestimation of exposure, amongst product subcategories that have similar application purposes (e.g. deodorant spray and deodorant stick) the one with the highest exposure value was selected.

Since the toxicity profile of D5 cannot be considered independent of the exposure route (see the discussion in Chapter I-4.2.1) aggregation of the internal exposure over all routes was not appropriate. The internal doses received via different routes were calculated by multiplying corresponding external exposures with route-specific uptake rates (see Table I: 4-1).

Input data

Product weight fractions

In the worst-case scenario assessment we assumed that all cosmetics and personal care products that can be used by a hypothetical person would contain D5.

D5 product weight fractions were obtained from the cosmetic frame formulations (Cosmetics Europe, 2013), which list the category or function of ingredients and their maximum concentration in cosmetic products or give relevant quantitative and qualitative information whenever a cosmetic product is not covered by such information. The algorithm for assigning weight fractions to a particular product subcategory was as follows:

- the weight fractions were assigned to each product subcategory as a whole entity regardless of the product brands comprising the subcategory;
- the maximum level (% w/w) of silicone ingredients (if explicitly specified) or emollients in the frame formulations was chosen;
- should a product subcategory not contain any silicone material or emollients according to the frame formulations, a conservative value of 1% w/w was assigned to this product subcategory.

Subcategory specific weight fractions of D5 used in tier 1 assessment are listed in Table A4 – 4.1 of Appendix 4.

Product use amounts and frequencies

The use amounts for each product subcategory were obtained from the following reference materials:

- Cosmetics Europe publications on European consumer exposure to cosmetic products (Hall et al., 2007, 2011);
- SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation (SCCS, 2012); and
- RIVM report 320104001/2006 Cosmetics Fact Sheet (Bremmer et al, 2006).

The values used in the assessment are the 90th percentiles of the product amount distributions. Where applicable, the product use amounts were corrected with the retention factor to account for product dilution in water and/or wash-off.

The use frequencies were taken from either the RIVM Cosmetics Fact Sheet or SCCS's notes of guidance (SCCS, 2012). For the calculation of aggregate acute exposure we assumed that a consumer applies the maximum possible number of C&PCPs considered in the assessment (i.e. 46) on the same day. Yearly averaged use frequencies (e.g. 260 times per year for shampoo) were used for chronic exposure calculations.

Results

Both acute, i.e. on the day of use, and chronic, i.e. yearly average, aggregate consumer exposure were calculated for each route separately. The outputs were either external or internal route-specific doses. The internal doses were calculated by multiplying external exposure with route-specific uptake rates, i.e. 0.17% for dermal route, 2% for inhalation and 100% for oral ingestion. The results of the tier 1 assessment both without and with evaporation scenario included are shown in Tables A4 – 3.1 and A4 – 3.2 of Appendix 4, respectively.

As can be seen from Table I: 4 – 2, in spite of having an uptake rate that is higher by an order of magnitude (i.e. 2% vs. 0.17%) inhalation contributes to the total chronic internal exposure only half of the dermal dose. In addition, inclusion of the evaporation scenario only slightly affects the final results; the total chronic systemic dose is reduced by less than 3%.

Table I: 4-2. Comparison of tier 1 exposure modelling results for D5 obtained with different scenarios.

Scenario	Exposure	Acute exposure, mg/kg bw/day				Chronic exposure, mg/kg bw/day			
		inh	derm	oral	total	inh	derm	oral	total
evaporation of D5 not included	external	38.4	614	4.1	**656.5**	10.8	307	4.1	**321.9**
evaporation of D5 included	external	42.6	491	4.1	**537.7**	12.5	246	4.1	**262.6**
evaporation of D5 not included	internal	0.77	1.04	4.1	**5.91**	0.22	0.52	4.1	**4.84**
evaporation of D5 included	internal	0.85	0.84	4.1	**5.79**	0.25	0.42	4.1	**4.77**
	LOAEL				**100**				**100**
	min MoE				**16.9**				**20.7**

It should be noted, that the exposure via inadvertent ingestion of oral and lip care products is likely to be overestimated due to a high level of conservatism adopted in the calculations of exposure from these products. In the tier 2 assessment it is shown that the realistic exposure to D5 contained in these products is much lower (see Paragraph I-4.2.2.3).

Figure I: 4-2 illustrates that the key contributors to aggregate chronic exposure to D5 are:

- via inhalation route: hair care, sun care products and deodorants;
- via dermal application: body care, skin care, sun care products and deodorants;
- via oral (inadvertent) ingestion: oral care and lip care products.

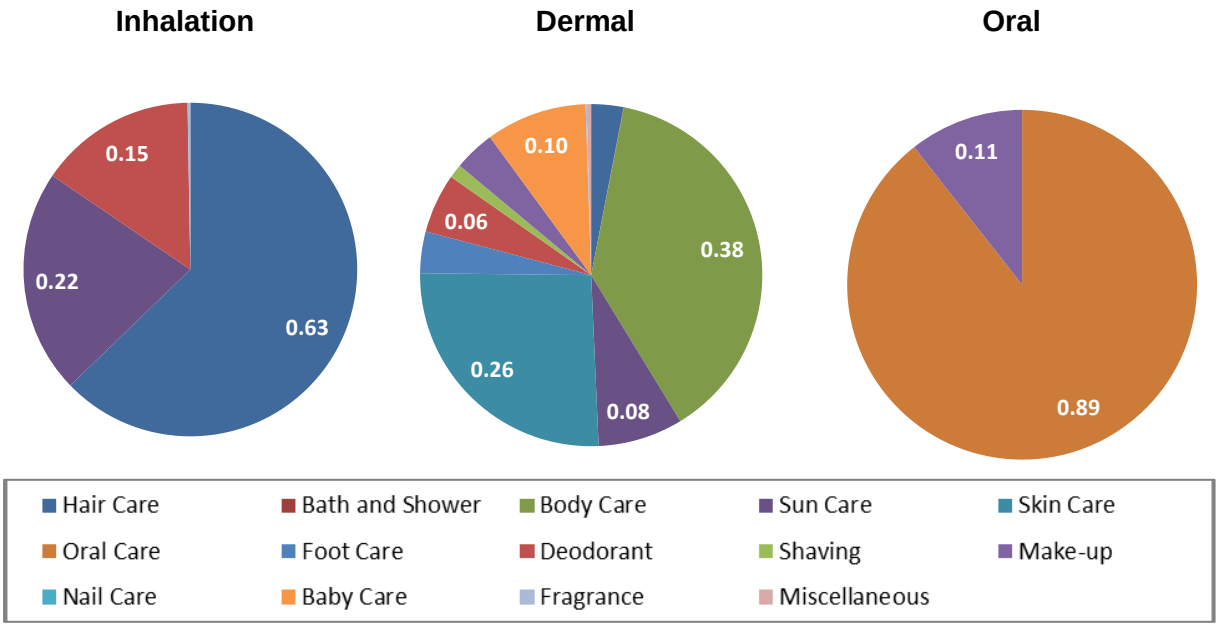


Figure I: 4-2. Contribution (fractions) of different C&PCPs categories into aggregate external chronic exposure to D5 calculated in tier 1 assessment.

The interpretation of the results gained in the tier 1 aggregate exposure assessment is best illustrated when using them in a risk assessment. Here, the specific LOAEL is divided by the total internal exposure estimates to obtain the margin of exposure (MoE) (Table I: 4 – 2). The current LOAEL of 100 mg/kg bw/day was derived from the subchronic rat study that showed organ weights increase after oral administration (Jäger and Hartmann, 1991). The assumption is that there is a 100% oral absorption in that study. The MoE for D5 is significantly lower than the assumed 'safe' MoE. Since the effect dose of 100 mg/kg bw/day is obtained from a LOAEL in a subchronic rat study, the MoE should be equal or larger than the product of the assessment factors accounting for LOAEL-to-NOAEL, subchronic-to-chronic, interspecies and intraspecies extrapolation to be considered sufficiently large. The comparison of the tier 1 estimate with LOAEL is provided here for reference purpose only.

Sensitivity analysis

A global sensitivity analysis for chronic dermal and inhalation external exposure to D5 (upper row in Table I: 4 – 2) was carried out using the One-at-a-Time (OAT) method (Daniel, 1973; Saltelli et al., 2000). With this approach any possible correlations between the input parameters are not taken into account. Whenever reliable information on correlations between exposure factors is available, it should be included, however. Omission of the relationship between the input parameters can result in the overestimation of actual consumer exposure if the parameters are negatively correlated, or underestimation if positive correlations exist.

In addition, it should be noted that this method is not able to evaluate the degree of conservatism in the tier 1 model, as the contribution of information on variability and uncertainty in the input parameters is not explicitly accounted for. Uncertainty is believed to be to some extent included in the assessment by adhering to the 'reasonable' worst-case scenario assumptions.

In our case the independently varied input parameters were:

- D5 concentrations in the product subcategories;
- Body weight of a consumer (60 kg by default);
- Inhalation rate of a consumer (26 m^3/day by default);
- Exposure time relevant for inhalation exposure (1 hour by default);
- Product amounts;
- Frequency of product use.

The sensitivity of the model to its input parameters is directly related to its underlying equations if the correlations between the parameters are neglected. In simple linear models a change in the input values (one parameter at a time) of e.g. 50% would lead to the same 50% change of the output. This is illustrated in Figure I: 4-3 (note the horizontal axis for inhalation runs from right to left). Our tier 1 model is equally sensitive to the constant variation (±50%) of all input parameters. A small remark on the body weight: since it appears in the denominator of the exposure equations (inverse-linear relationship), it contributes inversely to the variance of the aggregate exposure, resulting in a 100% increase of aggregate exposure if the body weight is cut by half.

In addition, we tested the effect of variation of the product weight fractions and the exposure time (for the inhalation model) on the default exposure estimates. The upper boundaries of these input parameters correspond to the conventional conservative values that are usually employed in the worst-case scenario assessment. As can be seen from Figure I: 4-3 the upper bound estimates result in a much higher exposure than the default (control) scenario suggests.

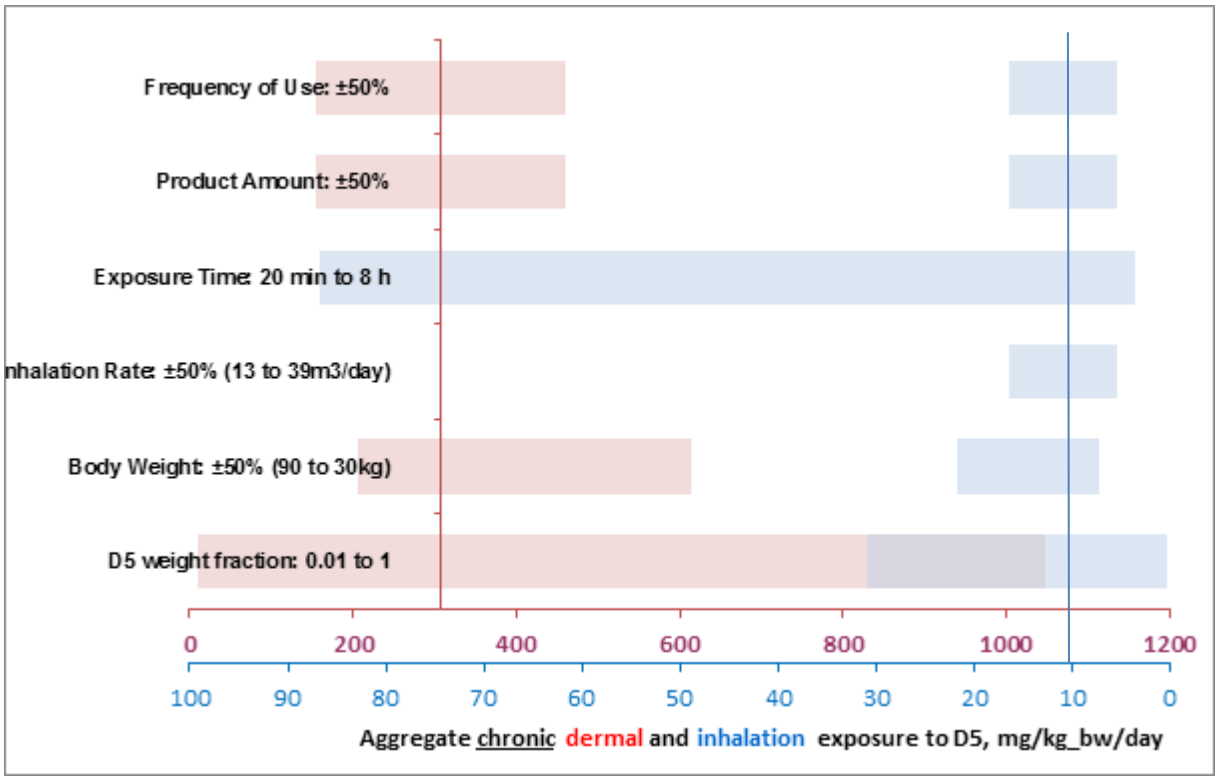


Figure I: 4-3. OAT sensitivity analysis of tier 1 aggregate chronic dermal and inhalation exposure to D5 (evaporation scenario is not included). Solid vertical lines represent the estimates in the default (control) scenario.

I-4.2.2.3 Tier 2 probabilistic assessment

General scope and purpose of the assessment

The aim of the tier 2 assessment is to determine realistic estimates of aggregate consumer exposure to D5 from the application of C&PCPs. The results are presented in the form of a non-parametric distribution of exposure estimates and reflect the variability of exposure within the general (adult) European population. Refinement of aggregate exposure is achieved by taking into account individualized exposure factors and genuine C&PCPs co-use profiles.

Tier 2 exposure model description

The individual-based probabilistic exposure modelling (PACEM; see Chapter I-2.4.3 for details) was undertaken for a population sample (N=5,000) that was constructed from a set of 516 individuals who completed and submitted the questionnaire survey on C&PCPs use (Biesterbos et al., 2013). The use of C&PCPs occurs either on a daily (e.g. deodorant), weekly (e.g. nail polish, eye shadow) or monthly basis (e.g. sunscreen). Hence, it was sufficient to model the individual day-by-day exposure profiles over a period of 30 days.

The PACEM dataflow for D5 is illustrated in Figure A4 – 4.1 of Appendix 4 and briefly can be described with the following steps:

- generating a simulated population of the required size by random sampling from the survey population;
- acquisition of the product use-profiles from the survey-use table for each individual in the simulated population (distributions of product amounts and use frequencies);
- construction of the simulated daily use-profiles (i.e. product use profile on each day in the entire modelling time-period) for each individual in the simulated population. The product amounts on the day of use are determined by random sampling from individual amount distributions (where applicable). The frequency of product use per day and whether the product is used at all on a particular day are also determined by drawing random numbers from the corresponding distributions (where applicable). NOTE: the algorithm for determination of product use on a particular day can be further elaborated by taking into consideration the information on product use on the preceding days. The most suitable method would be to assign a posterior probability developed using Bayes' theorem for the random frequency event;

- calculation of single product exposures for each individual in a simulated population on each simulated day by multiplying the product use amounts and frequencies in the use profile by D5 product concentrations and corresponding exposure fractions.

The acute aggregate population exposure encompasses all individual aggregate acute exposures over the entire simulation timeframe, thus expressing the exposure in person-days and providing a realistic estimate of the acute exposure within population. Chronic population exposure was constructed from the predetermined mean individual exposures.

Preliminary statistical analysis of the questionnaire data revealed no correlations between any product use parameters (i.e. product amount and use frequency) and personal characteristics of the respondents. Therefore, no adjustments in the sampling algorithm in the tier 2 model were necessary.

Aggregation strategy

The model allows calculating individual product-specific exposure by route on each day of the simulated period. The aggregation of exposure is then performed for each simulated individual separately on a daily basis over the entire range of products he/she used on a particular day, thus taking into account genuine data on products co-use patterns at the very individual level.

Input data

Product weight fractions

In total 47 unique product subcategories studied in the questionnaire were considered in the follow-up probabilistic exposure assessment. For now we assumed that all cosmetics and personal care products that are available for consumers and used by our survey population contain D5. However, further refinement of exposure calculations (if needed) by inclusion of the substance prevalence in a particular product category is also implemented in PACEM when accurate and reliable data are available.

The weight fractions of D5 in C&PCPs were refined and, therefore, slightly differed from those used in the tier 1 assessment. In particular, where it was possible we updated the weight fractions using the data available from Dudzina et al. (2014). The product subcategories for which D5 weight fractions were amended are marked with letter superscripts in Table A4 – 4.1 of Appendix 4.

Product use amounts and frequencies

The database of the user-product contact profiles for the tier 2 model was developed based on the results from Biesterbos et al. (2013). For each respondent in the questionnaire an individual product contact profile was created. The profile contains information on the individual characteristics (e.g. body weight, age, gender), the number and the type of C&PCPs used by a respondent on a regular basis, the amounts and use frequencies for every product category in the profile, time and place of product application, et cetera. The uncertainty associated with 'imprecise' answers given by the respondents to the questions on product amounts and/or use frequencies (i.e. selecting photographs or choosing ranges, e.g. "2-3 times per week") is accounted for by assigning uniform distributions to these quantities in the respective range (here: a uniform distribution with minimum = 2/7 and maximum = 3/7 times per day).

Exposure fractions

To each product (sub-)category the most appropriate/suitable application scenario was assigned based on the expert judgment and common practice (e.g. ECHA, 2012; RIVM Cosmetics Fact Sheet by Bremmer et al., 2006). Based on these references ten general scenarios were included:

1. stay-on skin (e.g. leave-on products)
2. rinse-off skin (e.g. rinse-off products)
3. spray on skin (e.g. deodorant sprays)
4. diluted in bath (e.g. bathing foam)
5. dermal wipe (e.g. make-up wipes)
6. spray on hair (e.g. hair sprays)
7. stay on hair (e.g. styling gel)
8. brush teeth (e.g. oral care)
9. lip care products (e.g. lipstick, lip balm)
10. nail polish/remover (e.g. nail care products)

Each product subcategory was linked to a particular application-scenario (Table A4 – 4.2 of Appendix 4).

Since consumer exposure in any application scenario may occur simultaneously via different routes (e.g. use of deodorant-spray would contribute to both dermal and inhalation exposure), each application scenario was defined with the appropriate route-specific exposure fractions (see Table A4 – 4.3 of Appendix 4).

In turn, each exposure fraction that is product-, substance- and route-specific, was described with either a point value or a parametric distribution. Table A4 – 4.4 of Appendix 4 lists the exposure fractions used in the tier 2 assessment and provides some additional information on how they were calculated. The distributions of exposure fractions for the inhalation route were first obtained with ConsExpo v.5.0 probabilistic modelling and then fitted to beta distributions (see Appendix A4 - 5). In most cases the distributed exposure fractions describe the variability in the input parameters used to characterize the product application scenario. A more detailed discussion of the variability and uncertainty analysis is given in Table I: 4-4**.**

Finally, the tier 2 model matches the products, use scenarios and corresponding exposure fractions to calculate external exposure via different routes. In order not to overestimate aggregate exposure, the sum of the route-specific exposure fractions should be lower or equal to 1. This requirement was fulfilled by calculating route exposures using the equations shown in Table A4 – 4.2 of Appendix 4.

Results

Figure I: 4-4 below illustrates the individual day-by-day aggregate external exposures. Remarkably, many individuals in PACEM simulations (mostly men) did not apply any D5 containing C&PCPs on a number of days over the entire modelled 30-day period, thus yielding zero exposures. The cumulative distribution of the population's acute exposure, which includes the whole simulation time-period (red curve), as well as the chronic population exposure (black solid curve) are also shown in Figure I: 4-4.

The tier 1 estimate of the total chronic exposure (dashed vertical line) is approximately two orders of magnitude higher than the corresponding 95th percentile of the chronic exposure determined in tier 2. The reduction of exposure was accomplished by taking into account the variability in C&PCPs usage habits and practices, by improving the aggregation strategy and by ensuring the essential requirement for route-specific exposure fractions being lower or equal to 1.

The MoE computed based on the LOAEL of 100 mg/kg bw/day and the sum of the 95th percentiles of the route-specific internal exposures reaches 500, which is about 25-fold higher than the estimate obtained in the tier 1 assessment.

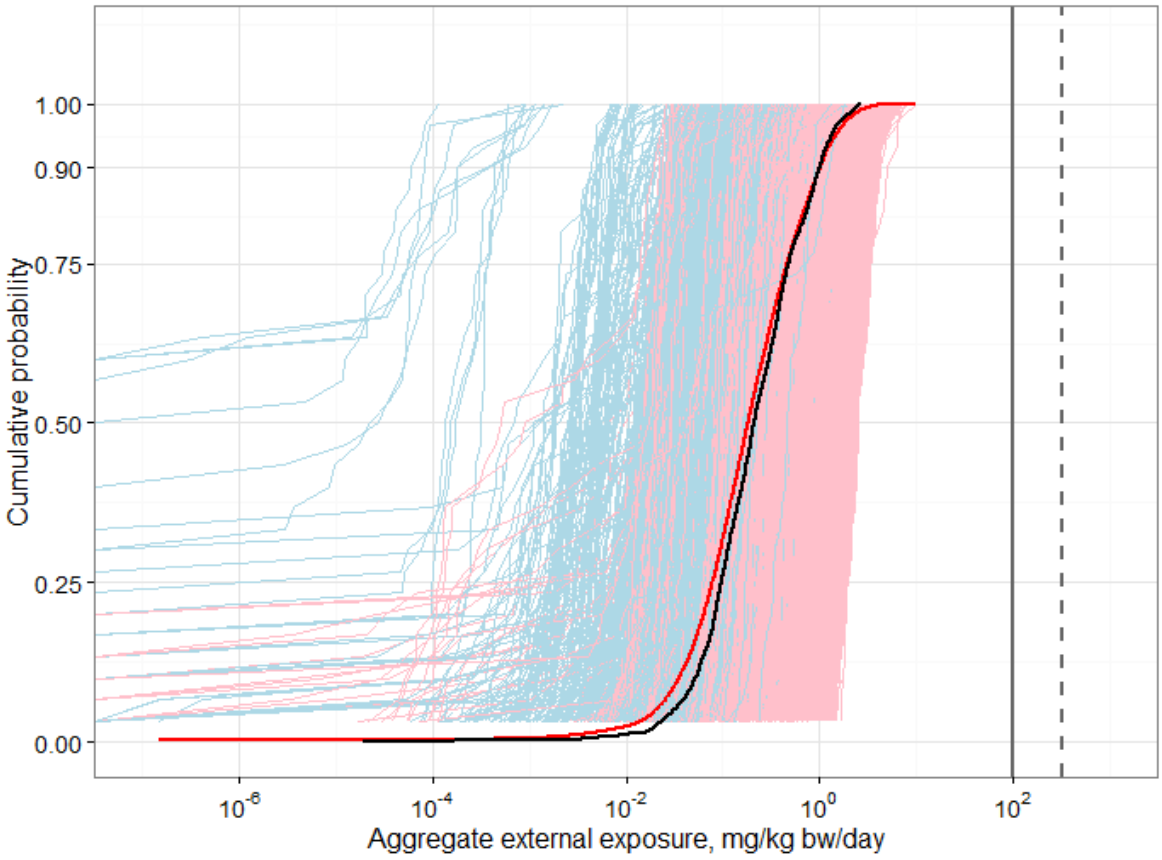


Figure I: 4-4. Results of the tier 2 exposure assessment for D5. Thin coloured lines are the individual cumulative distributions of the aggregate exposure (i.e. day-to-day aggregate exposure for every person in the simulations. Blue lines represent men; pink - women). Red and black solid curves are the cumulative distribution of the day-to-day acute and chronic aggregate population exposure, respectively. Vertical lines are the tier 1 estimate (dashed) and LOAEL (solid).

As can be seen from Figure I: 4-4 both acute and chronic population aggregate exposure to D5 are log-normally distributed. The summary statistics are provided in Table I: 4-3.

Table I: 4-3. Summary statistics of the population aggregate exposure to D5 modelled in tier 2 (median values and the 95% confidence intervals).

External aggregate exposure	Geometric mean	Geometric standard deviation	P50	P90	P95	P99
acute, mg/kg bw/persons/day	0.18 (0.039-0.55)	3.93 (4.21-3.44)	0.18 (0.033-0.55)	1.01 (0.14-3.02)	1.45 (0.25-3.96)	2.64 (0.42-6.87)
chronic, mg/kg bw/day	0.21 (0.042-0.63)	3.33 (4.08-3.38)	0.21 (0.046-0.63)	1.00 (0.21-2.97)	1.33 (0.27-3.88)	2.24 (0.48-6.53)

The variation observed in the population external exposure suggests that the variation in the internal doses will also be substantial. The baseline measurements of D5 in end-exhaled air of fifteen volunteers (see Part II, this report) support the findings of the tier 2 exposure modelling study.

To identify drivers of exposure, the relative contribution of a certain product category was calculated as a percentage of the aggregated mean population exposure per route (see Figure I: 4-5). Skin care, make-up and deodorants altogether contribute about 75% to the total chronic external exposure. Their high contribution can partially be assigned to the high amounts and use frequencies. In addition, they contribute significantly due to the fact that the amount applied stays in contact with the skin (i.e. leave-on products).

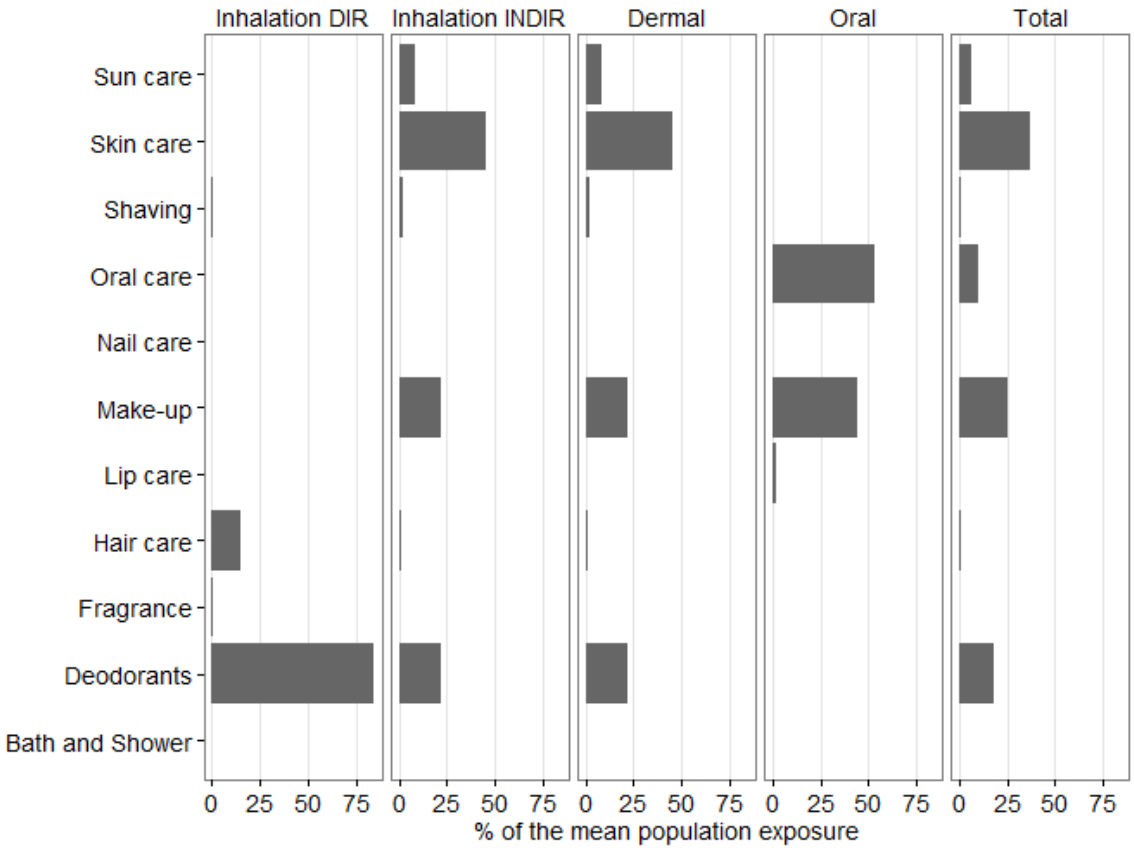


Figure I: 4-5. Relative contribution of C&PCPs categories to the chronic aggregate external population exposure to D5 calculated in the tier 2 assessment. Inhalation DIR and INDIR denotes direct (from spraying) and indirect (evaporated material) exposure, respectively.

Uncertainty analysis

Population consumer exposure cannot be fully described with a single point value and may vary spatially and temporally due to e.g. the inter- or intra-individual differences in consumer habits and application scenarios, as well as due to the seasonality, marketing policies, et cetera. For the sake of the realistic estimation of population exposure, in our model we focused only on the variability and uncertainty that are consumer-related, avoiding speculation on the uncertainty and variability associated with the product and its content. The uncertainty associated with 'imprecise' answers given by the respondents to the questions on product amounts and/or use is accounted for by assigning uniform distributions to these quantities in the respective range. The combined variability and uncertainty in the product application conditions (e.g. ventilation rate, room size) is reflected via random sampling from continuous parametric distributions assigned to the exposure fractions (see Appendix A4 -5).

The joint effect of uncertainty and inter-individual variation in exposure factors on the population exposure was examined by considering two extreme cases, i.e. the upper and the lower boundaries of exposure were modelled, which correspond to the 97.5^{th} and the 2.5^{th} confidence bounds for the total chronic exposure distribution, respectively. This was achieved by choosing the highest (or lowest) values for the product amounts and use frequencies, whereas the 97.5^{th} (or 2.5^{th}) quantile was drawn from exposure fractions distributions, if applicable. The product weight fractions of D5 were kept fixed. The results of the simulations are shown in Figure I: 4-6.

As discussed in Biesterbos et al. (2013) the mean age of the questionnaire population sample was 50 years old. The mean bodyweights for men and women questionnaire subpopulations were 85.8 and 81.0 kg, respectively. The difference in male and female body weights alone cannot explain a 5-fold discrepancy in the exposure estimates (see Figure I: 4-6). Rather, the use and co-use of C&PCPs are influenced by gender. The statistical analysis of the questionnaire data confirmed the absence of significant correlations between the product frequencies/amounts and consumer's age or bodyweight for any type of product. However, a slight but significant correlation of the product use frequency with consumer's gender was detected.

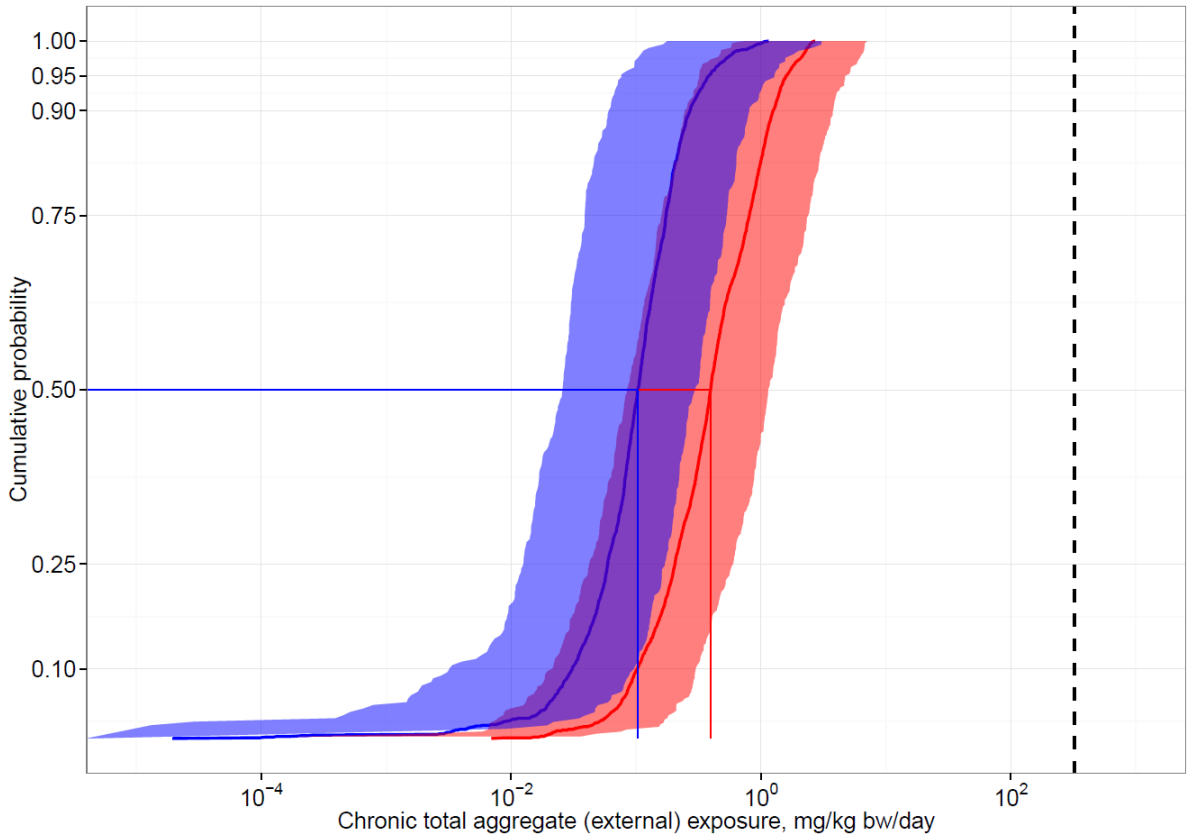


Figure I: 4-6. The medians (solid curves) and the 95% confidence intervals (shaded regions) of the chronic aggregate exposure to D5 for men (blue) and women (red) subpopulations. The dashed black line is the tier 1 estimate.

The exposure factors that can introduce uncertainty and variability into the exposure calculations are provided in Table I: 4-4 together with a description of how uncertainty and variability are propagated in the probabilistic model.

Table I: 4-4. Variability and uncertainty in exposure factors in tier 2 for D5.

Exposure factor	**Uncertainty reflected by**	**Variability reflected by**
product amounts reported by consumers / questionnaire respondents	uniform distributions assigned to each individual in the questionnaire	individual values chosen for every person in the simulated population
product use frequencies reported by consumers / questionnaire respondents	uniform distributions assigned to each individual in the questionnaire	individual values chosen for every person in the simulated population

Exposure factor	**Uncertainty reflected by**	**Variability reflected by**
product weight fractions	measurement uncertainty is not included	parametric distributions assigned to each product category in the model to account for variability among different product brands and names
market share of D5-containing products	uncertainty in the estimation is not included	variability among product categories, countries, time is not included
exposure/intake fractions	uncertainty associated with the input parameters used to calculate exposure fractions plus the uncertainty from fitting is not included	uniform or beta distributions assigned to corresponding exposure scenarios in the model (see Appendix A4 - 5)
body weight	self reported values: not considered	individual values for every person in the simulated population

The uncertainties that currently have not been taken into account are considered negligible in relation to the uncertainties that were accounted for.

I-4.2.3 Validation of exposure modelling

Comparison to the baseline measurements from the volunteer study

In order to validate the exposure modelling results obtained with PACEM we used a so-called forward dosimetry approach, i.e. the external chronic aggregate exposure data are fed into the human PBK model in order to estimate the internal exposure. Consequently, the chemical concentration can be predicted in various biomatrices (e.g. blood, exhaled air) at any time point following an exposure event.

The output of PACEM was modified to yield average individual dermal exposure in mg/day by combining dermal and indirect inhalation of D5 vapour (see Figure I: 4-7). Direct exposure from spray products was not considered because the relevant information available from the volunteer study was not sufficient to estimate the direct inhalation exposure to D5 from spraying.

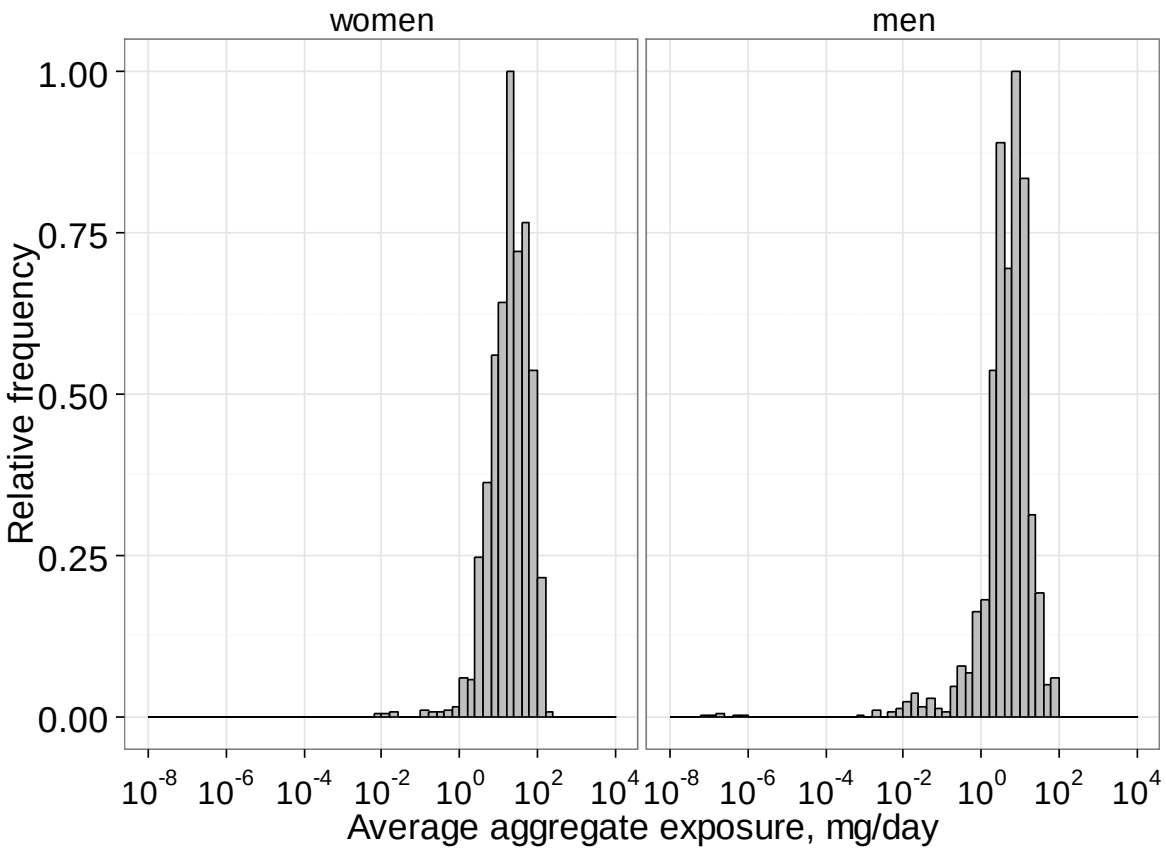


Figure I: 4-7. Average aggregate exposure distributions to D5 (dermal + indirect inhalation) for men and women simulated in PACEM.

Concentration-time curves of free D5 in venous blood obtained with PBK modelling for 5,000 individuals simulated in PACEM are plotted in Figure I: 4-8. Horizontal lines represent blood concentration equivalents derived from the baseline measurements of end-exhaled air of those volunteers, who used D5-containing C&PCPs, although excluding those who used deo-sprays (see Table II: 2-4 in Part II for details). The free D5 concentrations in the blood were calculated by dividing the D5 concentration measured in an end-exhaled air sample by the sample volume and multiplying it with the blood:air partition coefficient (0.41, Reddy et al., 2007). The mean concentrations found in the first and the second samples (see Table II: 2-5 in Part II for details) were plotted for each selected volunteer.

As Figure I: 4-8 suggests, the inter-individual variation of D5 concentrations in the blood is high and can reach up to four orders of magnitude. However, the comparison of baseline observations with the results obtained with forward dosimetry reveals that PACEM tends to slightly underpredict aggregate population exposure. This possibly indicates the presence of an additional pathway of exposure, e.g. via inhalation of background air. Another explanation could be that the PBK modelling was based on the application of pure D5, while volunteers

applied formulated D5. This probably influenced the simulations, because formulation is expected to slow down the evaporation kinetics of D5 (Dudzina et al., in preparation).

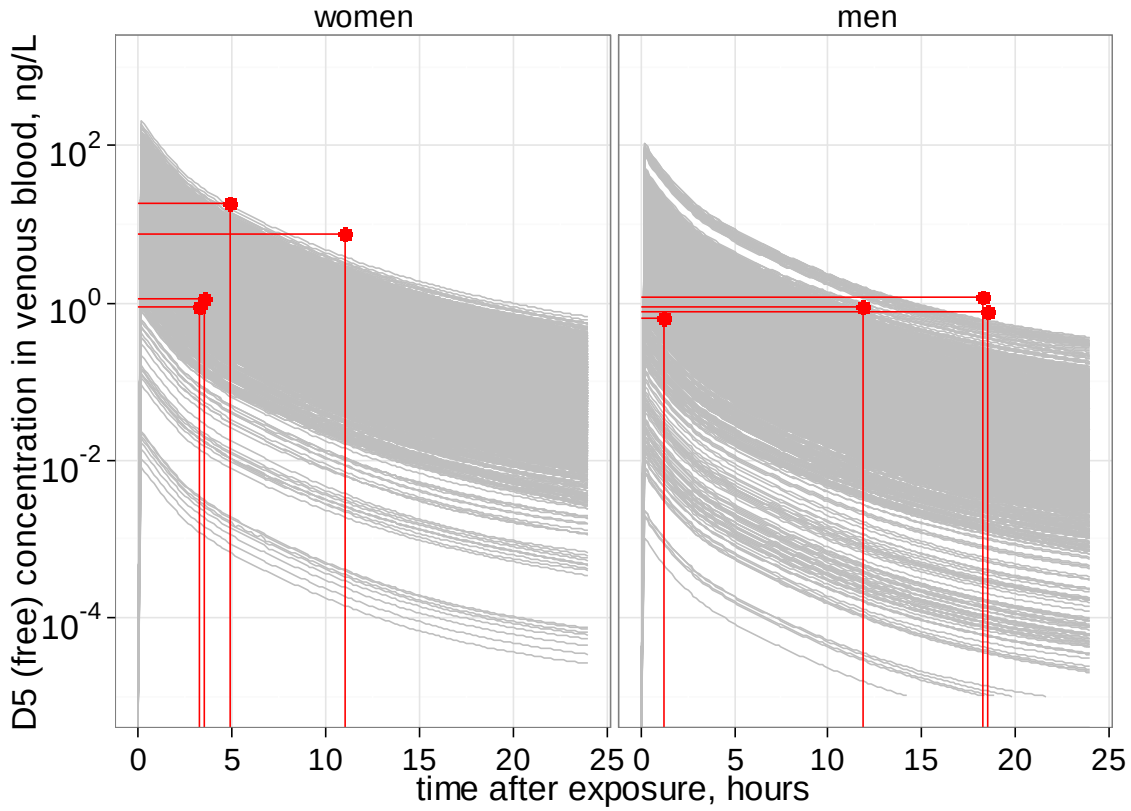


Figure I: 4-8. Modelled D5 (free) blood concentrations plotted against time for 5,000 individuals in PACEM. Red dots represent the experimentally determined values for 9 volunteers who participated in the baseline biomonitoring study and for whom the use of D5-containing C&PCPs was documented. Vertical red lines indicate the time interval between air sampling and the last direct exposure.

Comparison to the blood plasma data from Hanssen et al. (2013)

To further investigate the capability of PACEM to predict population exposure distributions we compared its output for D5 to other human biomonitoring data available from Hanssen et al. (2013). In this study the authors measured D5 concentrations in blood plasma samples from two women cohorts in Norway. The NOWAC cohort included samples from 94 postmenopausal women between 48 and 62 years old and the mean age of 55 years (Hanssen et al., 2013). The women in the MISA cohort (n=17) were selected for the study based on the pregnancy criteria and were on average 33 years old (range: 25-40 years). D5 presence in the blood plasma was not pronounced, as it was detected in only 18% samples of the middle-aged women cohort at median and maximum levels of 1.94 and 3.94 ng/mL, respectively. The concentrations of D5 in all blood samples of the pregnant women cohort

were below the LOQ (1.67 ng/mL). Therefore, for a more accurate comparison, only female individuals from PACEM simulations that fall in the older age category (i.e. between 48 and 62 years old) were selected for PBK modelling to produce blood plasma concentration-time curves. The total number of women taken into the validation assessment was 1,054.

For every female individual the input for the full PBK model was the total average dermal dose (i.e. combined dermal and indirect inhalation exposure to D5 vapour). In addition, we attempted to account for direct inhalation exposure from D5-containing spray products (e.g. spray deodorants). This was achieved by conversion of the individual exposures from spraying into the time-dependent air concentrations in the inhalation zone (C_{in}). A conservative value of 2 m^3 for the inhalation zone volume was assumed. The rate of chemical removal from the inhalation zone was randomized by drawing numbers from a uniform distribution with min = 5 and max = 10 times/hour (making an allowance for turbulence). The concentrations of bound D5 in blood plasma were calculated based on the assumption that approximately 55% of the total blood volume consists of plasma.

For each of the 1,054 individual concentration-time curves obtained with PBK modelling we selected three ('characteristic') time points, i.e. the time of the peak concentration (about 1 hour after exposure), 12 hours and 24 hours after the exposure. The distributions of blood plasma concentrations at these time points are presented in the form of probability density functions in Figure I: 4-9 (area under the curve is scaled to one). The vertical solid line represents the median D5 concentration detected in the blood plasma samples of the NOWAC cohort.

A few features depicted in Figure I: 4-9 are remarkable. Considering the 12h-density function (red curve), about 60% of the simulated individuals have predicted D5 concentrations above the median concentration determined in the Norwegian study for postmenopausal women. If calculated for a shorter time after the exposure event this proportion will be higher. The main difficulty for validating exposure modelling with the spot sample data is that the modelled D5 blood concentrations are very sensitive to the timing and magnitude of external exposure. Steady state is achieved slowly due to the relatively short elimination half-life time of D5 in the blood compared to the time intervals between individual exposure events. Higher time resolution in the PACEM model would be required to accurately predict the internal exposure of an individual.

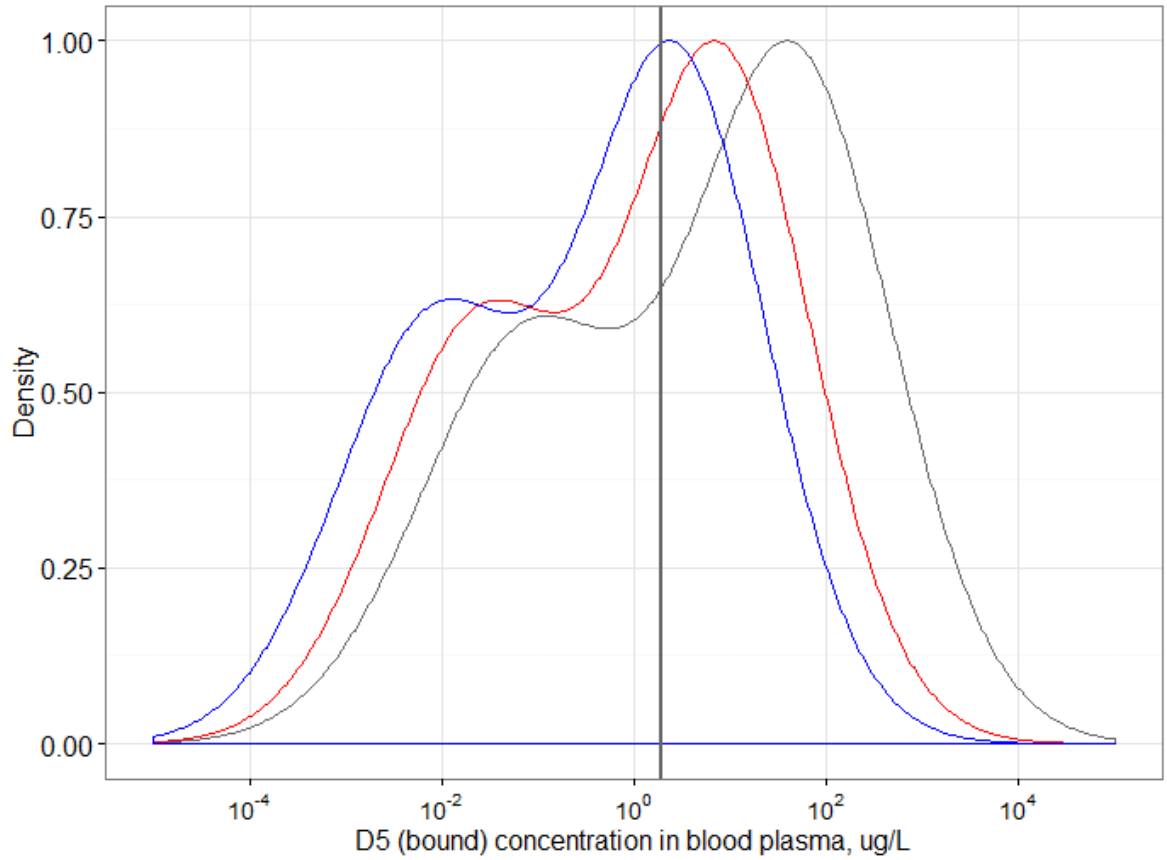


Figure I: 4-9. Modelled distributions of D5 (bound) blood plasma concentrations at the time of the peak concentration (black curve), at t=720 min (red curve) and t=1440 min (blue curve) for women in PACEM that fall in 48-62 years age category. The vertical black line represents the median D5 concentration in blood plasma measured in NOWAC women cohort (Hanssen et al., 2013).

I-4.3 Case study 2: Triclosan (TCS)

I-4.3.1 Substance profile

Physicochemical properties

5-chloro-2-(2,4-dichlorophenoxy)phenol (Triclosan, TCS; CAS 3380-34-5) is a chlorinated aromatic compound. Its functional groups include both phenols and ethers. The chemical structure of triclosan (Figure I: 4-10) is similar to organic environmental pollutants, such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs).

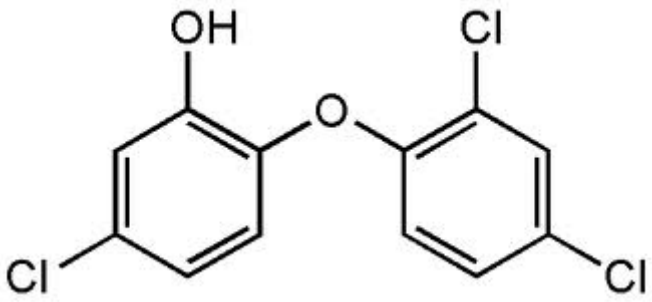


Figure I: 4-10. Chemical structure of triclosan.

The key physicochemical properties of triclosan are summarized in Table A4 – 2.2 of Appendix 4.

Kinetics

Gilbert and Williams (1987) investigated the oral retention and pharmacokinetics of [^{3}H]-TCS in antimicrobial toothpaste. Twelve healthy male volunteers between 19 and 37 years old were recruited for the study and asked to brush their teeth with 1 g of toothpaste containing 0.02% of [^{3}H]-TCS. The oral retention was found to be 36.6 ± 1.4%. Triclosan remained in dental plaque for at least 8 hours after dosage and in oral mucosa for 3 hours.

The buccal absorption of triclosan from 0.03% mouthwash was calculated by Lin (2000). Subjects were given 15 mL of triclosan oral mouthwash or a placebo oral rinse to be used twice a day. Blood and dental plaque samples were collected 1 and 4 hours after rinsing, respectively. The average oral retention dose was 7.3%. The peak concentrations of triclosan in blood plasma were attained after 2 days following exposure and returned to baseline 8 days after the last treatment.

Most recently Sandborgh-Englund (2006) examined the pharmacokinetic pattern of triclosan in humans after a single oral administration. In this study the subjects were given 13 mL of a

0.03% mouthwash solution, equivalent to 4 mg oral dose of triclosan. Blood and urine levels were monitored prior to exposure and up to 8 days after exposure, and baseline levels of triclosan in plasma and urine were determined for each subject. Plasma concentrations increased rapidly after dosing attaining peak levels within 1-3 hours, resulting in a terminal half-life of 21 hours. In plasma 30-35% of triclosan was present in the conjugated form. The cumulative excretion of triclosan was 54%, occurring 4 days after exposure.

The data from numerous animal studies suggest that triclosan rapidly penetrates the skin and is widely distributed in the body with having high affinity to gall bladder, liver, lung, adipose tissue and blood (Kanetoshi et al.,1992; Moss et al., 2000). Excretion with faeces and urine constitute the principal removal pathways (Moss et al., 2000). In both, urine and faeces triclosan is mainly present in the form of conjugates – TCS glucuronide and sulphate (DeSalva et al., 1989). An additional elimination pathway for TCS could be its metabolism in skin (Moss et al., 2000). The amount entering systemic circulation after dermal application over a 24-hour period in a rat study in vivo was 21%. Data from other percutaneous absorption studies indicate that triclosan is well absorbed through the skin in all species tested with the extent of absorption being dependent on the formulation in which it was delivered (Black and Howes, 1975; Kanetoshi et al.,1992; Trimmer, 1994; Burns, 1997). In the study by Black and Howes (1975) with rats in vivo, percutaneous absorption was approximately 23 to 28% of the applied dose of triclosan in ethanol, ethanol/ water, soap suspension, or a cream formulation.

Similar behaviour of TCS was observed in humans by Queckenberg et al. (2009) after dermal administration of TCS-containing hydrophobic cream for 12 hours. Percutaneous absorption calculated from urinary excretion was 5.9% + 2.1% of the dose (mean + standard deviation). Of the TCS absorbed the majority was excreted within 24 hours. The half-life was calculated to be 10.8 hours. This value is consistent with the previous study by Sandborgh-Englund (2006), who determined the median half-life of TCS based on urinary excretion to be 11 hours following single oral dose in human volunteers.

Geens et al., (2012) investigated triclosan concentrations in 11 samples of human adipose tissue, brain and liver. They observed that total triclosan (i.e. parent compound and conjugates) were found predominantly in liver (in 10 samples) with a mean concentration of 3.14 ng/g, followed by adipose tissue (7 samples; mean concentration of 0.61 ng/g), while it could be detected in only one brain sample at 0.03 ng/g.

As uptake fractions for the different routes 100% were chosen for the dermal route (due to a limited number of appropriate studies), 100% for inhalation and 40% for ingestion.

Toxicity

Triclosan is being increasingly studied after concerns emerged that it might be harmful to human health and the environment. It has been ubiquitously detected in surface water, sediment, biosolids, soils and aquatic species (Chu and Metcalfe, 2007; Chalew and Halden, 2009; Reiss et al., 2009; Nakada et al., 2010). During the wastewater treatment process triclosan is not completely removed and in the aquatic environment it is mainly present in the ionized form. Sorption, biodegradation and photolytic degradation mitigate the availability of triclosan to aquatic biota; however, the by-products such as methyltriclosan, dioxins and chlorinated phenols may be more resistant to degradation and have higher toxicity than the parent compound. Triclosan was also detected in humans world-wide (Calafat et al., 2008; Geens et al., 2012). Potential health issues associated with the use of triclosan include antibiotic resistance, skin irritations, endocrine disruption, increasing rates of allergies and the formation of carcinogenic by-products (Schweizer, 2001; Adolfsson-Erici et al., 2002; Latch et al., 2003, 2005; Ishibashi et al., 2004; Axelstad et al., 2013).

The information on the mode of action in mammals and associated relevant dose metrics is limited for triclosan. The mechanism of antibacterial activity of triclosan has been reported to involve the inhibition of lipid synthesis (McMurry et al., 1998; Heath et al., 1999). Inhibition of fatty acid synthesis in parasites has also been documented (Surolia et al., 2001; Samuel et al., 2003). Furthermore, it has been demonstrated that this chemical prevents bacterial cell growth and proliferation by interfering with the formation of new cell membranes (Levy et al., 1999). However, the relevance or ability of these mechanisms to lead to adverse health effects in humans has not been demonstrated (Sullivan et al., 2003; Sandborgh-Englund et al., 2006).

The current NOAEL, set by the SCCS after careful review of numerous animal toxicity studies in its opinion on triclosan, is 12 mg/kg bw/day (SCCS, 2009). The NOAEL was based on hematotoxicity as well as decreases in absolute and relative spleen weights observed in rats; at higher doses, mild clinical chemistry and/or hematological changes, together with histopathological changes in the liver were reported (EC, 2009; Ciba-Geigy, 1986; NICNAS, 2009). Although there is no conclusive information on the mode of action or relevant dose metrics for the triclosan-induced effects in rats, it seems that the parent chemical is likely to be the toxic form, given that triclosan does not undergo any oxidative metabolism or bioactivation reaction.

In its current opinion the SCCS (SCCS, 2009) concluded that taking into account the provided toxicological data, the use of triclosan as a preservative at the current concentration limit of maximum 0.3% in all cosmetic products is not safe for the consumer because of the

magnitude of the aggregate exposure. However, its use at a maximum concentration of 0.3% in toothpastes, hand soaps, body soaps/shower gels and stick-deodorants is considered safe. Any additional use of triclosan in face powders and blemish concealers at this concentration is also considered safe but the use of triclosan in other leave-on products (e.g. body lotions) and in mouthwashes is not considered safe for the consumer due to the resulting high exposures. Exposure from spray-deodorants was not assessed. Importantly, before a final conclusion on the safety of triclosan in cosmetic products can be reached, the potential development of resistance to triclosan and cross-resistance by certain micro-organisms must be assessed. This aspect is covered in another SCCS document (SCCS, 2010b), according to which it is not possible to quantify the risk associated with triclosan (including its use in cosmetics) in terms of development of antimicrobial resistance, genetic basis for resistance and dissemination of resistance based on the currently available scientific information. The SCCS can only recommend the prudent use of triclosan, for example in applications where a health benefit can be demonstrated

I-4.3.2 Aggregate consumer exposure assessment

I-4.3.2.1 Tier 0 qualitative assessment

General scope and purpose of the assessment

The purpose of the tier 0 exposure assessment is to provide a qualitative overview of all possible exposure sources, pathways and routes for the chemical of interest. The information collected in tier 0 will provide the basis for the subsequent tiers.

Exposure sources

Because of its antimicrobial activity, triclosan is widely incorporated into textiles (e.g. socks, shoe insoles, towels, swimwear, sportswear, wool bedding), medical devices (e.g. surgical scrubs, fake teeth), plastics (e.g. toothbrushes, toys, toilet seats, litter bins, pet accessories), paints, household cleaning and personal care products intended for everyday use (e.g. dishwashing detergents, laundry detergents, bathroom and kitchen surface cleaners, toothpastes, mouthwashes, deodorants and soaps) (Adolfson-Erici et al., 2002; Bhargava and Leonard, 1996; Perencevich et al., 2001).

Triclosan can appear on the product ingredients list under different names, such as:

- 2,4,4’-trichloro-2’-hydroxydiphenyl ether
- Cloxifenolum
- Triclosanum
- Irgasan DP-300
- Lexol 300
- CH-3565

Articles that have triclosan incorporated may be referred to as Ultra-Fresh, Microban, Amicor and Sanitized (Adolfsson-Erici et al., 2002).

Triclosan has a worldwide production of 1,500 metric tons (Bester, 2005) with 350 metric tons produced in Europe (Singer et al., 2002) and 450 metric tons in the USA (von der Ohe et al., 2011). These production volumes are consistent with Dye et al. (2007) who reported annual production and import volumes of triclosan in the order of 10 to 1,000 metric tons for the EU. The Scientific Committee on Consumer Safety (SCCS, 2010) estimated an annual consumption of 450 metric tons within the EU.

The primary application of triclosan is in the personal care sector (NICNAS, 2009; SCCS, 2010). In the EU, about 80-85% of triclosan is used in personal and household care products, compared to 5-15% in textiles (BI, 2004) and 5-10% in plastics and food contact materials.

The use of triclosan as an antimicrobial substance in cosmetics in the EU is currently regulated by Annex VI entry 25 of the Cosmetics Directive 76/768/EEC. Since March 2010 the use of triclosan as a disinfectant/preservative in food and feed production, as well as in the manufacturing of food contact materials (e.g. cutting boards, food storage containers, and other kitchen utensils) is prohibited in the EU. Triclosan is used in biocidal products for veterinary hygiene but it is banned as a preservative in animal food. Under the new EU Biocidal Products Regulation, which came into force in September 2013, it is no longer permitted to place biocidal products on the EU market unless the active ingredients are approved for the intended application.

The exposure scenarios to TCS that are most relevant for consumers include:

- exposure from the use of C&PCPs containing triclosan;
- exposure from the use of household cleaning products containing triclosan;
- exposure to triclosan from the articles into which it was incorporated (e.g. textiles, plastics);
- exposure to triclosan migrating from surfaces that were treated with cleaning products;

- exposure from the use of veterinary hygiene products containing triclosan.

Exposure pathways

The main routes of consumer exposure to triclosan are dermal absorption after the application of triclosan-containing products and dermal contact with triclosan-containing articles; inadvertent oral ingestion of oral care products (e.g. toothpaste) or ingestion of triclosan residues in food, which was in contact with surfaces cleaned with triclosan-containing household products. Inhalation exposure may occur through breathing aerosols generated from the use of C&PCPs and cleaning products containing triclosan, or indoor dust and the dust generated from the use of powders containing triclosan (Geens et al., 2009).

I-4.3.2.2 Tier 1 worst-case scenario assessment

General scope and purpose of the assessment

The aim of the tier 1 assessment is to determine a realistic upper bound of the aggregate consumer exposure to TCS in a population from the application of consumer products. The results of such a reasonable worst-case assessment can be further used in e.g. chemical safety assessment, risk assessment or in defining regulatory values. Furthermore, the screening assessment can help to identify the exposure sources, routes and/or pathways, for which the refinement in higher tiers should be a priority.

Tier 1 exposure model description

The tier 1 consumer exposure assessment for triclosan was carried out for the general European subpopulation (adults) using the default worst-case scenario exposure factors (i.e. consumer body weight = 60 kg, instant release of the substance from a consumer article, upper bounds of product amounts, substance weight fractions, et cetera).

Consumer exposure to triclosan from C&PCPs was calculated using a model analogous to the one used for D5 (see Paragraph I-4.2.2.2 for details).

Consumer exposure to triclosan from household cleaning products (direct and indirect) was calculated using the A.I.S.E. REACT (Reach Exposure Assessment Consumer Tool) *(http://www.aise.eu/reach/?page=exposureass_sub3*).

Consumer exposure to triclosan from veterinary hygiene products was modelled with ConsExpo v.5.0.

Aggregate consumer exposure was calculated by summing up the source-related exposures by exposure route.

Aggregation strategy

Similar to that one used in Case Study 1 (Chapter I-4.2.2.2).

Input data

Product weight fractions

The concentration of TCS in C&PCPs, household cleaning and veterinary hygiene products in the tier 1 model was set to 0.3% (i.e. to the maximum allowed concentration).

The content of TCS in other product categories varies across different products and ranges from 7 to 195 mg/kg_textile in textiles (Rastogi et al., 2003), <1.4-8.4 ng/g_food in food (Remberger et al., 2002; Adolfsson-Erici et al., 2007), 0.025-3.0 μg/g_dust in indoor dust (Canosa et al., 2007; Fan et al., 2010; Geens et al., 2012). The worst-case scenario weight fractions of TCS in these products employed in the tier 1 assessment are indicated directly in the exposure calculations sections below.

Product amounts and use frequencies

In the calculations of consumer exposure from C&PCPs use, the main data sources were similar to the case study on D5, i.e.:

- Cosmetic Europe publications on European consumer exposure to cosmetic products (Hall et al., 2007, 2011);
- SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation (SCCS, 2012); and
- RIVM report 320104001/2006 Cosmetics Fact Sheet (Bremmer et al, 2006).

The input data for exposure modelling from household cleaning products were taken from the HERA project (2005), i.e. worst-case default values in the AISE REACT.

The default exposure parameters from ConsExpo v.5.0 were used to calculate consumer exposure from the use of veterinary hygiene products.

Results

Both acute (i.e. on the day of use) and chronic (i.e. yearly average) aggregate consumer exposures were calculated for all identified sources and pathways and each route separately. The outputs are either external or internal route-specific doses. The internal doses were calculated by multiplying external exposures with corresponding route-specific uptake rates. Each route was aggregated separately. The results of the tier 1 assessment for different consumer products are presented below in the corresponding subsections.

Cosmetics and personal care products

Although TCS as an antimicrobial agent is predominantly used in rinse-off products to provide a cleansing and antimicrobial effect, for the 'reasonable' worst-case scenario assessment all 46 C&PCP categories were considered. The results of aggregate consumer exposure assessment from selected C&PCPs per route are presented in Table A4 – 3.3 of Appendix 4.

Household cleaning products

The AISE REACT model allows quantitative estimation of consumer exposure to substances that are present in household care preparations used by consumers. The tool was used to calculate TCS exposure via inhalation, dermal, and oral routes separately. Both direct (i.e. during the product use) and indirect dermal (i.e. skin contact with TCS residues in laundry) exposure was calculated. The input parameters required to calculate indirect dermal exposure with AISE REACT were as follows:

Weight fraction absorbed through skin (mandatory for indirect skin contact calculation)	1
Is amount of substance deposited on fabric (Sdep) available or not?	yes
Amount of substance deposited on 1 cm^2 of fabric, Sdep (mg)	2.93E-03 *

* - the value was estimated assuming the fabric density of 150 g/m^2 and triclosan concentration of 195 mg/kg_textile.

For the acute exposure calculation, the maximum amounts and use frequencies were used; typical values (as denoted in the AISE REACT tool) were employed in the calculations of chronic exposure. The results are shown in Table A4 – 3.4 of Appendix 4.

Tiles and surfaces

Dermal exposure to triclosan may also occur from contact of the skin with tiles and surfaces (e.g. in bathrooms, showers, kitchen) treated with triclosan-containing products. The external dermal exposure via this pathway is calculated according to the ConsExpo v.5.0 'rubbing-off

scenario', i.e. when a product is initially applied to a surface and consequently transferred to the skin by dermal contact with the surface. The equation for the external dose calculation is:

$$D = S_{area} \times F_{dislod} \times Wf \times M / BW, \text{ where } S_{area} = max(R_{trans} \times t, S_{max})$$

The input parameters were as follows:

- Rubbed surface (S_{area}), i.e. the area of the treated surface that can potentially be rubbed
- Dislodgeable amount (F_{dislod}), i.e. the amount of a cleaning agent applied on a surface area that may potentially be wiped off, per unit of surface area = 30 g x 7 times/day / 10 m^2 = 21 g/m^2
- Triclosan content in the products (*Wf*) – 0.3% w/w
- Migration rate of triclosan from treated surfaces to skin (*M*) – 100%
- BW: body weight – 60 kg
- Transfer coefficient (R_{trans}), i.e. the surface area treated with product that is in contact with the skin per unit of time – palms and soles (one third of the surface area of the adult feet) = 858 cm^2 + 1/3 x 1061 cm^2 = 1212 cm^2 or 0.12 m^2 per second
- Contact time (*t*), i.e. the time per day spent in the kitchen (worst case for rubbing kitchen surfaces) = 260 min or 15,600 sec (US EPA, 2011)
- Surface area treated with a cleaning agent (S_{max}), i.e. the maximal area that can be rubbed during exposure – 10 m^2

The acute and chronic dermal external exposure for adults is 10.5 mg/kg_bw/day.

<u>Textiles</u>

The worst-case dermal exposure from wearing triclosan-incorporated clothes is calculated based on the following assumptions:

- Skin area exposed – whole body except for head = 16,340 cm^2 (US EPA, 2011)
- Concentration of TCS in clothes – 195 mg/kg_textile x 0.15 kg/m^2 = 29.3 mg/m^2
- Time period of exposure – 1 day (worst-case scenario)
- Migration rate of TCS from treated surfaces to skin – 100% (worst-case scenario).

The acute and chronic dermal external exposure for adults (body weight 60 kg) is 0.8 mg/kg_bw/day.

Veterinary hygiene products

The exposure via this pathway was calculated using ConsExpo v.5.0 based on the exposure factors and parameters set by default (Prud'homme de Lodder et al., 2006). Triclosan weight fractions in these products were set to 0.3%. The results are presented in Table I: 4-5.

Table I: 4-5. Tier 1 worst-case scenario assessment of consumer exposure to TCS from the application of veterinary hygiene products.

Product Subcategory	Acute exposure, mg/kg/day					
	Inhalation		Dermal		Oral	
	ext	Int	ext	int	ext	int
birds accommodation (fumigation) [a]	1.1E-05	1.1E-05	8.3E-07	8.3E-07		
animal accommodation (powder)			2.2E-06	2.2E-06		
animal accommodation (tablets)			8.3E-07	8.3E-07		
animal accommodation (wipes) [a]			9.5E-01	9.5E-01		
animal transportation (powder)			2.2E-06	2.2E-06		
animal transportation (tablets)			1.7E-06	1.7E-06		
animal transportation (spray) [a]	1.8E-03	1.8E-03	4.5E-01	4.5E-01	7.6E-03	3.0E-03
Aggregate acute exposure:	**1.8E-03**	**1.8E-03**	**1.4E+00**	**1.4E+00**	**7.6E-03**	**3.0E-03**
	Chronic exposure, mg/kg/day					
birds accommodation (fumigation) [a]	3.5E-07	3.5E-07	2.7E-08	2.7E-08		
animal accommodation (powder)			1.2E-08	1.2E-08		
animal accommodation (tablets)			4.5E-09	4.5E-09		
animal accommodation (wipes) [a]			5.2E-03	5.2E-03		
animal transportation (powder)			3.6E-08	3.6E-08		
animal transportation (tablets)			2.7E-08	2.7E-08		
animal transportation (spray) [a]	3.0E-05	3.0E-05	7.4E-03	7.4E-03	1.3E-04	5.2E-05
Aggregate chronic exposure:	**3.0E-05**	**3.0E-05**	**1.3E-02**	**1.3E-02**	**1.3E-04**	**5.2E-05**

[a] – this product category was chosen for the calculation of aggregate exposure

Food

Since March 2010 the use of triclosan as a disinfectant/preservative in food and feed production, as well as in the manufacturing of food contact materials, is prohibited in the EU. However, a few researchers detected triclosan in food. In the past Remberger et al. (2002) demonstrated that triclosan levels could reach <1.4-8.4 ng/g in different types of fatty food. The results by Adolfsson-Erici et al. (2007) indicate lower content of triclosan in food, showing that pool samples of dairy products, meat, fish and egg composed on the basis of

Swedish per capita consumption data contained <0.02-0.15 ng/g triclosan, which would account for an average triclosan intake of 16 ng/day via food for humans in Sweden (Allmyr, 2009).

Dust

Another source of background human exposure to triclosan was suggested by the finding of triclosan in indoor dust samples. A study from households in Spain reports triclosan concentration in dust at an average level of 1.1 μg/g (Canosa et al., 2007). In Canada the median concentration was lower by a factor of two, i.e. 0.57 μg/g (range 0.087-3.0 μg/g) (Fan et al., 2010). Finally, Geens et al. (2012) detected triclosan in indoor dust of 18 residential/domestic premises in Belgium at the lowest median concentration of 0.22 μg/g (range 0.025-1.83 μg/g). Assuming the average dust intake of 0.02 g/day for adults (Jones-Otazo et al., 2005) and 100% bioavailability, the dust would hence account for a relatively low average triclosan intake of 22.0, 11.4, and 4.4 ng/day for the adult population in Spain, Canada and Belgium, respectively. Using the higher estimate of 0.05 g/day of daily dust intake (Jones-Otazo et al., 2005) and the upper bound of triclosan concentration found in the dust (i.e. 3.0 μg/g in Canada) the worst-case exposure would raise to 150 ng/day.

Aggregate exposure

Neglecting the intake of triclosan from food and dust, which would not contribute much to the aggregate exposure (see above), the aggregate external consumer exposure to triclosan calculated over all other relevant sources and pathways is shown below in Table I: 4-6.

Table I: 4-6. Tier 1 aggregate exposure modelling results for TCS by different sources.

Products	Acute exposure, mg/kg bw/day							
	Inhalation		Dermal		Oral		Total	
	ext	int	ext	int	ext	int	ext	int
C&PCPs	1.16E-01	1.16E-01	3.87E+00	3.87E+00	1.10E+00	4.38E-01	**5.08E+00**	**4.43E+00**
Household products	1.84E-02	1.84E-02	1.88E+00	1.88E+00	2.98E-05	1.19E-05	**1.90E+00**	**1.90E+00**
Treated surfaces			1.05E+01	1.05E+01			**1.05E+01**	**1.05E+01**
Textiles			8.00E-01	8.00E-01			**8.00E-01**	**8.00E-01**
Veterinary hygiene	1.81E-03	1.81E-03	1.40E+00	1.40E+00	7.60E-03	3.04E-03	**1.41E+00**	**1.40E+00**
Aggregate exposure	**1.36E-01**	**1.36E-01**	**1.85E+01**	**1.85E+01**	**1.10E+00**	**4.41E-01**	**1.97E+01**	**1.90E+01**
	Chronic exposure, mg/kg bw/day							
Selected C&PCPs	7.44E-02	7.44E-02	2.50E+00	2.50E+00	1.09E+00	4.36E-01	**3.66E+00**	**3.01E+00**
Household products	1.81E-03	1.81E-03	1.42E+00	1.42E+00	2.98E-05	1.19E-05	**1.42E+00**	**1.42E+00**
Treated surfaces			1.05E+01	1.05E+01			**1.05E+01**	**1.05E+01**
Textiles			8.00E-01	8.00E-01			**8.00E-01**	**8.00E-01**
Veterinary hygiene	3.04E-05	3.04E-05	1.26E-02	1.26E-02	1.30E-04	5.20E-05	**1.28E-02**	**1.27E-02**
Aggregate exposure	**7.62E-02**	**7.62E-02**	**1.52E+01**	**1.52E+01**	**1.09E+00**	**4.36E-01**	**1.64E+01**	**1.57E+01**
NOAEL								**12**
MoE								**0.76**

It should be noted that the dermal exposure to TCS from the contact with treated surfaces and from wearing textiles is relevant for both users and non-users of household care products. Considering the users only, these two pathways account for about 70% of the total chronic internal dose. Direct use of personal and household care products seems to be a less important source of exposure, contributing roughly 30% to the total aggregate consumer exposure to triclosan.

Overall, the aggregate chronic internal dose derived in the tier 1 exposure assessment for triclosan is comparable to its current NOAEL level of 12 mg/kg_bw/day enforced in the EU (SCCS, 2010). The low MoE indicates that a risk cannot be excluded, and higher tier exposure estimation is triggered.

Sensitivity analysis

As discussed in the corresponding paragraph of case study 1, the sensitivity of the exposure model to its input parameters is directly related to the underlying equations if the correlations between the parameters are disregarded. Therefore, changing any of the numerical input

parameters of the tier 1 exposure model by 50% while fixing the other parameters would result in 50% change in aggregate exposure.

The uncertainty in the tier 1 model is accounted for by means of the worst-case scenario assumptions adopted in the calculations. The highest level of conservatism was admitted in the calculations of exposure to TCS from wearing clothes and from residue transfer after skin contact with surfaces. To date reliable input data for these scenarios are lacking.

The smallest contribution to variability and uncertainty will be by the weight fraction of TCS, since its concentration in many consumer products is currently limited to 0.3% (w/w). The product weight fractions are not expected to vary largely between products, perhaps between 0.01% in mouthwashes and 5% in textiles, thus not contributing much to the uncertainty. A reasonably conservative value of 0.3% w/w for TCS was chosen in the tier 1 worst-case scenario assessment. On the other hand, the market share of the TCS-containing products (i.e. prevalence) is a more substantial contributor to both variability and uncertainty of the assessment, although predominantly relevant for higher tiers. For the worst-case approximation we assumed that all the products used by a hypothetical person contain triclosan (i.e. market share of 100%).

I-4.3.2.3 Tier 2 probabilistic assessment

General scope and purpose of the assessment

The aim of the tier 2 assessment is to determine realistic estimates of aggregate consumer exposure to TCS from the application of C&PCPs and household cleaning agents. The results are presented in the form of a non-parametric distribution of exposure estimates and reflect the variability of exposure within the general (adult) European population. Refinement of aggregate exposure is achieved by constructing individual product use and co-use profiles based on the information from previous studies and taking into account the variation in the exposure factors within population.

Tier 2 exposure model description

In the absence of the input data on exposure factors at the individual level it was decided to run a population-based version of the tier 2 probabilistic exposure model (PACEM), meaning that the data on exposure parameters are used in the form of parametric distributions

ascribed to a (sub)population as a whole. These distributions are believed to reflect the true variability in product usage-patterns within the entire (sub)population. Another distinct feature of the PACEM for triclosan is that the product co-use profiles are not genuine, since no co-use data were available for household cleaning products. Rather, the exposure profiles have been constructed for every individual based on the probability of product use (both cosmetics and household cleaning products) within the general population (see section *'Input data'* below for explanation).

The model algorithm comprises the following steps:

1. constructing the simulated population by sampling the required number of individuals from the population distribution with fixed parameters (i.e. age and body weight). For each individual his(her) age and body weight are specified;
2. creating a product co-use profile for every individual in a simulated population. All the products are assumed to contain TCS;
3. assigning the timeframe for exposure simulations (e.g. 30 days) and constructing the individualized product-contact profiles on each day of exposure simulations: random sampling similar to the algorithm described in Paragraph I-4.2.2.3.;
4. aggregating exposure across product subcategories which are used by every individual on each day of exposure simulations. The acute and chronic population external exposure can be constructed based on the individual aggregate exposures.

Here, we report the results of exposure modelling for 5,000 simulated individuals (men and women of 18-74 years old) over a 30-day time period. The probabilistic assessment was carried out for the selected personal and household care products only. Exposure from wearing clothes and exposure from touching surfaces was neglected in this project because (1) no studies exist that have determined realistic transfer rates, which presumably are much smaller than the 100% assumed in tier 1 and (2) the PACEM model is aimed at direct exposure from consumer products only (not indirect exposure from treated surfaces), but currently does not include textiles. The selection of consumer products for the realistic tier 2 assessment was based on the recommendation of the SCCS for "justified use" of TCS in consumer products (SCCS, 2010a). In particular, toothpaste, spray-deodorant and a few rinse-off personal care products were chosen (body wash, hand soap, facial cleanser, shaving gel). Amongst household cleaning agents we chose the most frequently/extensively used products, i.e. dishwashing liquid and all-purpose cleaner (Weegles and van Veen, 2001; Moran et al., 2012; VerbraucherAnalyse database (*www.verbraucheranalyse.de*)). Other consumer product-categories considered in the tier 1 assessment according to an online ingredients database did not list TCS among their ingredients

(*http://www.whatsinproducts.com/chemicals/view/1/95/003380-34-5/Triclosan*), and therefore were excluded from further (realistic) exposure assessment.

Inhalation exposure to TCS was modelled only for spray products, because inhalation of vapour can be neglected due to the small vapour pressure of TCS ($5.3*10^{-4}$ Pa at 20°C). The exposure fractions for TCS were modelled with ConsExpo v.5.0 and fitted to parametric distributions (see Appendix A4 - 5).

Aggregation strategy

The aggregation approach was in principle similar to that one described in Chapter I-4.2.2.3, i.e. aggregation of exposure was performed for every simulated individual separately on a daily basis over the entire range of products he/she used on a particular day. The aggregate population exposure was then constructed based on the individual aggregate exposures.

Input data

In this report we justified the use of different data sources/databases based on their comprehensiveness and representativeness for the general European population. The input data for the realistic tier 2 exposure assessment of TCS were obtained from numerous sources, namely:

- the StatLine database of the Dutch Statistics Bureau (Statistics Netherlands, 2013) on population characteristics (population stratification by age and body weight);
- the questionnaire data for consumer C&PCPs usage-patterns (Biesterbos et al., 2013);
- the HERA project (HERA, 2005) and the paper of Weegels and van Veen (2001) for consumer use of household cleaning products;
- VerbraucherAnalyse database (*www.verbraucheranalyse.de*) for the product use intensity and the data on product types preferred by consumers (e.g. liquid, gel, spray).

The characteristics of the 'true' European population, upon which the simulated population was built, are listed in Table A4 – 4.6 and Table A4 – 4.7 of Appendix 4.

The product co-use profiles were determined on an individual basis based on the consumer's gender. No further stratification by any other socio-economic descriptors (e.g. age, education, income) was made, as other factors were shown to have no or little influence on

consumer behaviour with regard to the selected products. The procedure for assigning individual product co-use profiles was as follows: First of all, for each generic product category in the assessment the probability of use within the general population was initially specified as the percentage of product users identified in the questionnaire surveys for men and women separately (Moran et al., 2012; Biesterbos et al., 2013). The essential assumption was that the estimates reported in these studies were the true probabilities of products use occurring within the general population. An individual person was assumed to use a product, if the initial probability for using the product was greater or equal to a random number drawn from a standard uniform distribution (i.e. U(0,1)).

Overall, Table A4 – 4.8 of Appendix 4 summarizes the exposure factors employed in the probabilistic tier 2 exposure modelling for TCS. The product weight fractions of TCS were assumed as 0.3% (w/w) for each generic product category. The amount and use frequency distributions for the selected household care products were taken from the table of habits and practices for consumer products in Western Europe developed by AISE (HERA, 2005). The corresponding data for the selected C&PCPs were obtained from the panel questionnaire (Biesterbos et al., 2013) by parametric bootstrapping. Namely, the specified ranges of product amounts and use frequencies were repeatedly sampled (N_{samp}=500) for every respondent and each product he(she) uses. Where possible the resulting data were parameterized as continuous (non-uniform) distributions (see Table A4 – 4.9 of Appendix 4). The use data for the hand soap subcategory were obtained from a survey on liquid hand soaps (Danish EPA, 2006).

Results

The results of the probabilistic exposure modelling for TCS are shown in Figure I: 4-11. Several ‘light’ users who have very low exposure (mostly men) can be identified.

Similarly to the results obtained in the case study on D5, the 95th percentile of the modelled chronic external exposure to triclosan (black curve in Figure I: 4-11) is approximately two orders of magnitude lower than the corresponding tier 1 estimate (dashed vertical line).

The MoE computed based on the NOAEL of 12 mg/kg bw/day for TCS and the sum of the 95th percentiles of the route-specific internal doses is around 50, which is almost 70-fold higher than the one obtained in the tier 1 assessment.

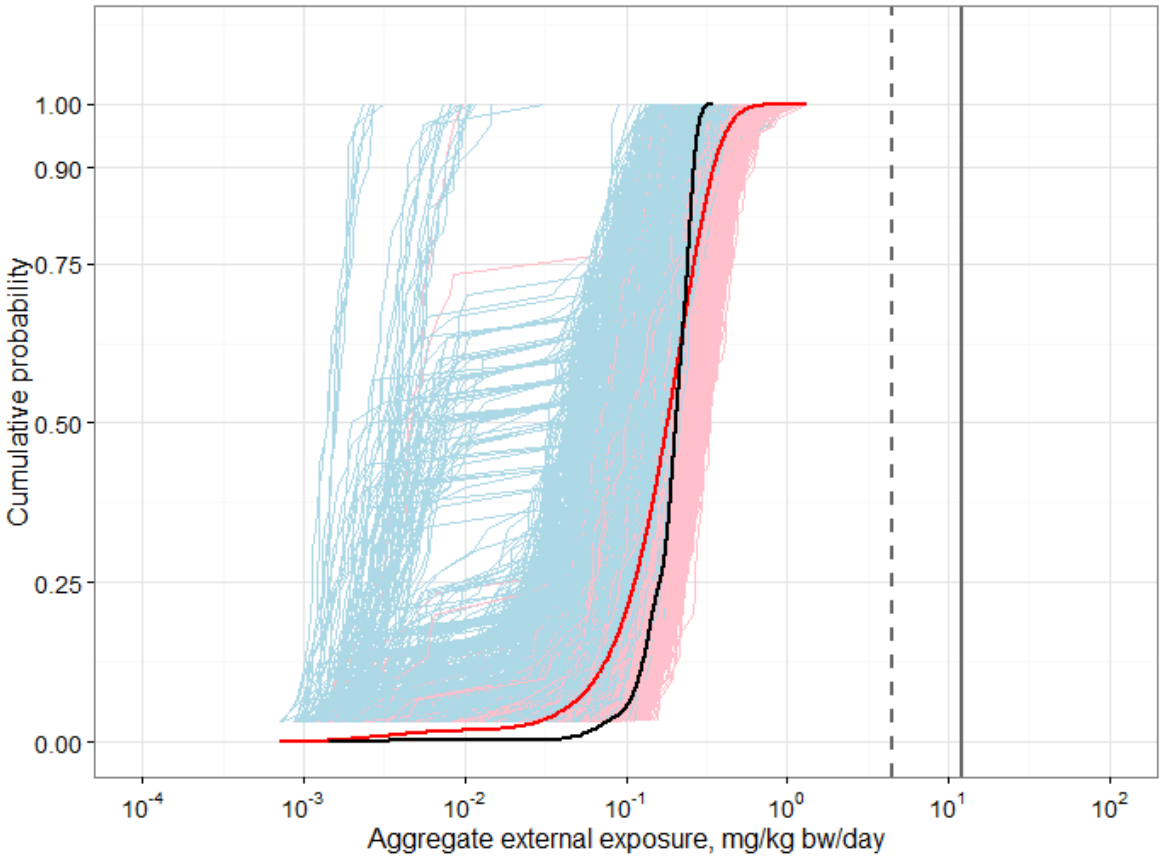


Figure I: 4-11. Results of the tier 2 exposure assessment for TCS. Thin coloured lines are the individual cumulative distributions of the aggregate exposure (i.e. aggregate exposure for every person in the simulations. Blue lines represent men; pink - women). Red and black solid curves are the cumulative distribution of acute and chronic aggregate population exposure, respectively. Vertical lines are the tier 1 estimate (dashed) and NOAEL (solid).

The main contributing products to the aggregate consumer exposure to TCS are spray-deodorants, toothpastes and surface cleaning sprays (Figure I: 4-12). Only direct inhalation exposure from spraying products was calculated for TCS.

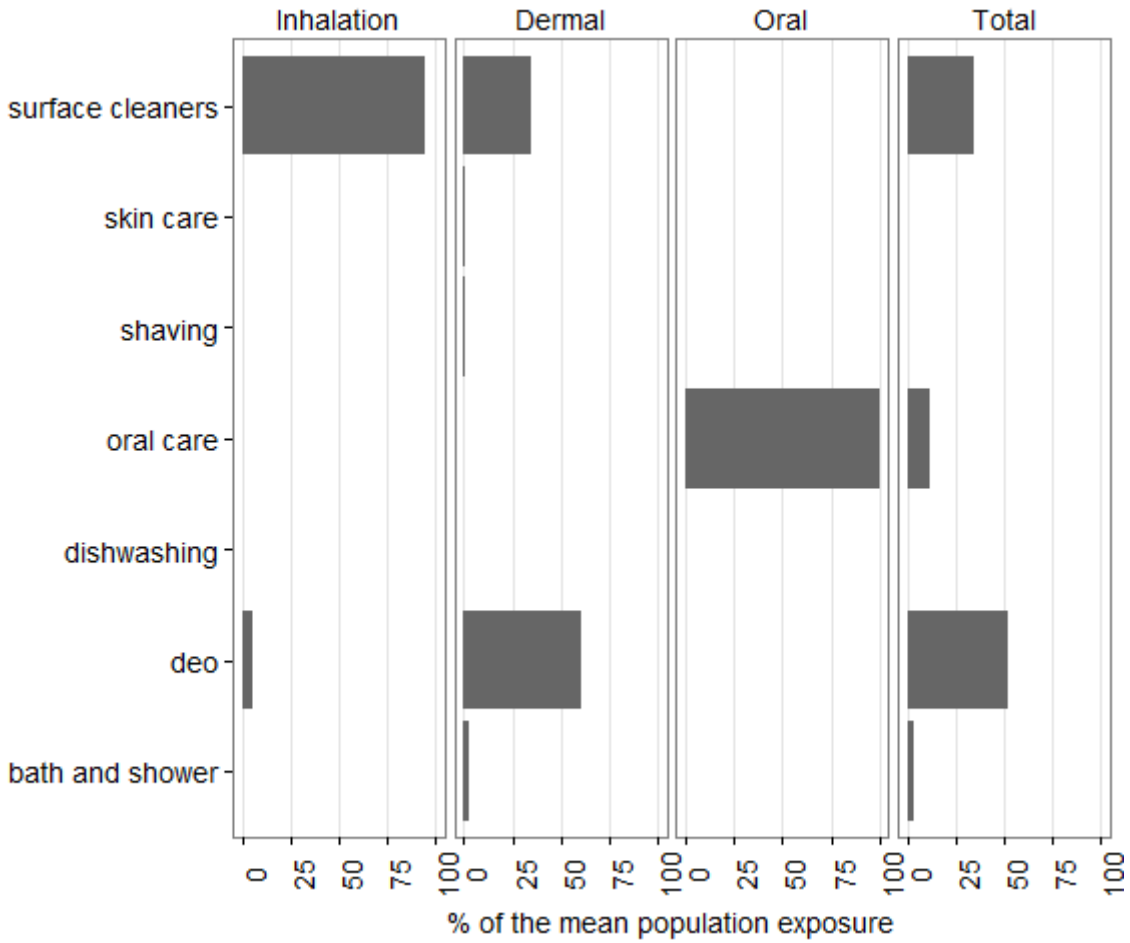


Figure I: 4-12. Relative contribution of different product categories to the chronic aggregate external population exposure to TCS calculated in the tier 2 assessment.

Uncertainty analysis

The uncertainty analysis of tier 2 results for triclosan was carried out analogously compared to chapter I-4.2.2.3. The upper and the lower boundaries of exposure were modelled, which span the 95% confidence interval for the exposure distribution. This was achieved by choosing the highest (or lowest) values for product amounts and use frequencies, whereas the 97.5th (or 2.5th) quantile was drawn from exposure fractions distributions, where applicable. The product weight fractions of triclosan were fixed at 0.3% w/w. The results of the simulations are shown below in Figure I: 4-13.

I-4.3.3 Validation of exposure modelling

Due to its toxicity profile triclosan is a fairly well-studied substance. There is an ample selection of human biomonitoring datasets. Table I: 4-7 lists a few studies in which information on baseline urinary concentrations of TCS can be found.

Table I: 4-7. Baseline urinary concentrations of TCS in the several (sub-)populations.

Country	Number of samples (population)	Urine concentrations, ng/mL	Reference
US	2749 (≥6 y.o.)	GM 14.5; median 10.7	NHANES, 2013
US	30 (adults)	median 12.5	Ye et al., 2005
US	90 (girls 6-8 y.o.)	GM 10.9; median 7.2	Wolff et al., 2007
China	287 (3-24 y.o.)	GM 3.8; median 3.4	Li et al., 2013
Belgium	131 (1-75 y.o.)	GM 2.7	Pirard et al., 2012
Belgium	193 (14–15 y.o.)	adolescents: GM 2.19; median 1.3	den Hond et al., 2013
Sweden	10 males and females (26-42 y.o)	GM 25.3 (10.3); median 57.6 (29.4) [a]	Sandborgh-Englund et al., 2006
Korea	1870 (18-69 y.o.)	GM 1.68	Kim et al., 2011

[a] – the values reported are baseline urinary concentrations observed a week (or 3 days) before the controlled exposure study

As can be noted from Table I: 4-7, the population urinary triclosan levels are well below the current biomonitoring equivalent (BE) of 2600 ng/mL for urinary concentrations of total TCS (free plus conjugates) corresponding to the EC-identified margin of safety target from the NOAEL of 12 mg/kg_bw/day (Krishnan et al., 2010).

Other human biomonitoring data available for triclosan include:

- breast milk samples from Australian women (Toms et al., 2011);
- breast milk samples from US (Dayan, 2007);
- blood plasma and milk samples from nursing women in Sweden (Allmyr et al., 2006)
- blood plasma from 10 Swedish adults (Sandborgh-Englund et al., 2006)
- blood serum samples from Australian women (Allmyr et al., 2008).

In the absence of a valid PBK model for triclosan the validation of the aggregate consumer exposure modelling results was performed using the biomonitoring equivalent approach discussed by Krishnan et al., 2010, applied to the urinary concentration data. The latter were obtained from the 4th national report on human exposure to environmental chemicals in the U.S. (NHANES, 2013) and from Sandborgh-Englund et al. (2006). The equivalent total

external dose was calculated from the urinary concentration data assuming 100% absorption/uptake (all routes considered), a mean body weight of 60 kg (if data for the biomonitored individuals were not available like e.g. for NHANES, 2013), an average 24-h urinary volume of 1.7 L and the urinary excretion fraction for triclosan of 0.54 (both values taken from Krishnan et al., 2010). The calculated equivalent chronic doses are provided in Table I: 4-8 and Table I: 4-9.

Table I: 4-8. Baseline TCS urinary excretion data from NHANES, 2013 and respective calculated equivalent chronic doses.

Value	Factor	Geometric mean	Selected percentiles			
			50th	75th	90th	95th
Urinary concentration, ug/L	Total	14.5	10.7	51.2	238	483
Equivalent dose, mg/kg/day	Total	0.0008	0.0006	0.0027	0.0125	0.0253
	Gender					
Urinary concentration, ug/L	males	14.8	10.9	55.1	243	455
	females	14.2	10.5	50	235	488
Equivalent dose, mg/kg/day	males	0.0008	0.0006	0.0029	0.0128	0.0239
	females	0.0007	0.0006	0.0026	0.0123	0.0256
	Age					
Urinary concentration, ug/L	>20 years	15.5	11.1	61.8	262	544
Equivalent dose, mg/kg/day	>20 years	0.0008	0.0006	0.0032	0.0137	0.0285

Table I: 4-9. Baseline TCS urinary excretion data from Sandborgh-Englund et al. (2006) and respective calculated equivalent chronic doses.

Subject			Excretion baseline from 24-h urine collection, μg/day		Equivalent chronic dose, mg/kg/day	
Gender	Age, years	Body weight, kg	First extract (6-5 days before the study)	Second extract (3-2 days before the study)	First	Second
f	26	69	64	71	0.0017	0.0019
f	26	51	189	73	0.0069	0.0027
f	27	54	191	77	0.0066	0.0026
f	30	77	0.1	0.1	0.000002	0.000002
f	28	57	21	4.1	0.0007	0.0001
m	26	76	743	91	0.0181	0.0022
m	29	95	29	18	0.0006	0.0004
m	42	80	3.1	1.4	0.0001	0.0000
m	33	78	218	55	0.0052	0.0013
m	27	79	133	44	0.0031	0.0010
statistics:						
f		median	64.0	71.0	0.0017	0.0019
f		95th percentile	190.6	76.2	0.0068	0.0026
m		median	133.0	44.0	0.0031	0.0010
m		95th percentile	638.0	83.8	0.0155	0.0020
all		median	98.5	49.5	0.0024	0.0012
all		95th percentile	506.7	84.7	0.0130	0.0026

The results of the validation are demonstrated in Figure I: 4-13. Deterministic worst-case estimates from the tier 1 assessment (dashed vertical line) and the cumulative distribution of the total chronic external exposure (solid curve) with the 95% confidence interval (grey shaded area) modelled in the tier 2 assessment are evaluated against the results obtained from the baseline urinary data (red and blue dots). As can be seen, the modelling uncertainty for the population exposure is rather large and spans around three orders of magnitude.

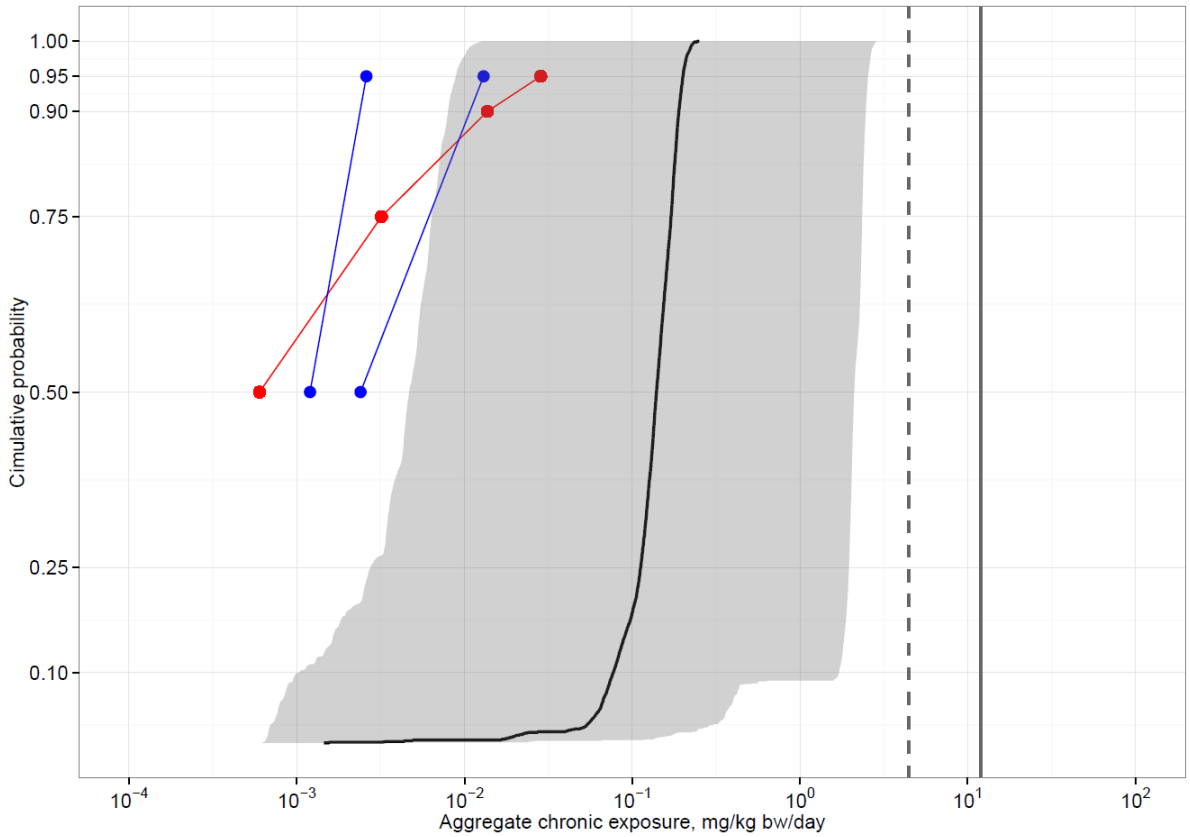


Figure I: 4-13. The median (black curve) and the 95% confidence interval (grey shaded region) of the chronic aggregate population exposure to TCS. Vertical lines are the tier 1 estimate (dashed) and NOAEL (solid). Red and blue pointed lines depict the selected percentiles of the equivalent chronic doses derived from NHANES and Sandborgh-Englund et al. (2006) data, respectively.

The discrepancy between the modelled and the observed values most probably originates from a significant overprediction of exposure mainly due to the conservative assumption for the market share of the triclosan-containing products (currently 100%). If market shares are available on a product category level, the exposure modelling results can be refined.

Furthermore, the external exposure calculated from human biomonitoring data is itself a subject to uncertainty. The biomonitoring equivalent (BE) approach, which was used to translate urinary concentration data into the external exposure, employed the excretion fraction of TCS derived in a single oral dose study with a limited number of individuals (N=10). For the derivation of urinary BE for TCS the median excretion fraction (54%) reported in this study was used (Sandborgh-Englund et al., 2006). The ratio between the maximal and the median value of the excretion fraction for TCS was less than a factor of two. The intersubject variability could result from e.g. variation of bioavailability, distribution kinetics, metabolic clearance and/or fraction of TCS eliminated via renal clearance.

Additional uncertainty associated with the use of a single oral dose human study for deriving urinary BE appeared to be low, since the dose-normalized area under curve was similar for ingestion of TCS following single or multiple exposures (EC, 2009).

Moreover, in addition to the uncertainty introduced in the method of relating TCS biomarker data to the actual exposure, there is a statistical uncertainty in the biomarker data due to the limited sample size in the study of Sandborgh-Englund et al. (2006), where only five men and five women were examined. Owing to the limited sample size the uncertainty in the estimated 95^{th} percentile will be high. Contrariwise, the NHANES percentiles data were calculated from urinary concentration data obtained from a large number of participants (N>2,000), however, the reported results are based on the measurements from single spot urine samples (Calafat et al., 2008), and are expected to be influenced much more than the samples collected for a 24h period by both variations in hydration status and creatinine excretion. This also disseminates additional uncertainty into the calculated equivalent doses, since the collection time of the urinary spot sample is not known.

In summary, the comparison with biomonitoring equivalents shows that the tier 2 calculations are conservative. However, for a substance like TCS that is only used in a small fraction of products the market share has to be included in the exposure model in order to enable validation with population biomarker data. At present, given the conservatism in the model and the uncertainty in biomonitoring, the results agree reasonably well and are judged to be in accordance at least for higher percentiles of the population exposure.

I-4.4 Conclusions

The key conclusions that can be drawn from the findings of the case studies are summarized below:

1. The performance of the tiered approach to modelling (realistic) aggregate consumer exposure was demonstrated: for both case substances the 95th percentiles of chronic population exposure modelled in the tier 2 assessment were almost two orders of magnitude lower than the tier 1 estimates.
2. For the realistic estimation of aggregate exposure within the general population the information on product use and co-use profiles is essential, because the assumption of using all products simultaneously (tier 1) results in a large overestimation of exposure. In addition, other factors influencing the outcome of exposure modelling should be properly described (e.g. percent of product users, prevalence of a substance in a product category).
3. Both the tier 1 and the tier 2 models proved to be reasonably conservative: the modelled exposure was higher compared to the baseline levels, with the probabilistic results nearly approaching the realistic exposure values observed in higher percentiles of the population.
4. On average, men tend to have lower exposure to the substances present in consumer products than women due to the differences in habits and practices of C&PCPs use.

Detailed analysis of the case studies revealed a few substance-related particularities in exposure modelling that can be formulated as follows:

1. The results of the aggregate consumer exposure assessment for D5 suggest that for external exposure the dermal route of exposure dominates over inhalation and inadvertent ingestion. In contrast, the internal exposure results primarily from inhalation of (re)evaporated D5. Inhalation contributes more to the internal exposure due to the relatively high inhalation absorption rate compared to the dermal absorption rate.
2. For D5 the tier 2 exposure modelling results agree well with the baseline levels (i.e. realistic values) determined for the general population.
3. For TCS the tier 2 exposure modelling is higher than the BM equivalents by two orders of magnitude, presumably because the true prevalence of TCS in products is much less than the one assumed in the exposure modelling.

I-5. References

Adolfsson-Erici, M., Pettersson, M., Parkkonen, J., Sturve, J., 2002. Triclosan, a commonly used bactericide found in human milk and in the aquatic environment in Sweden. Chemosphere; 46:1485–1489.

AISE (Association Internationale de la Savonnerie, de la Détergence et des Produits d'Entretien), 2009. [Available online at http://www.aise.eu/reach/?page=exposureass_sub3 ((last accessed 01.06.2013)].

Allmyr, M., Adolfsson-Erici, M., McLachlan, M.S., Sandborgh-Englund, G., 2006. Triclosan in plasma and milk form Swedish nursing mothers and their exposure via personal care products. Sci Total Environ; 372:87–93.

Allmyr, M., Harden, F., Toms, L.M.L., Mueller, J.F., McLachlan, M.S., Adolfsson-Erici, M., Sandborgh-Englunda, G., 2008. The influence of age and gender on triclosan concentrations in Australian human blood serum. Sci of the Total Env; 393:162-167.

Allmyr, M., 2009. On the fate of triclosan. Doctoral thesis. [Available online at http://publications.ki.se/xmlui/bitstream/handle/10616/38133/thesis.pdf?sequence=1 (last accessed 01.06.2013)].

Arnold S.F., Price P.S. (2007). The LifeLine Group, Modelling mixtures resulting from concurrent exposures to multiple sources, Toxicology and Applied Pharmacology, Volume 223, Issue 2, 121-124.

Axelstad, M., Boberg, J., Vinggaard, A.M., Chritiansen, S., Hass, U., 2013. Triclosan exposure reduces thyroxine levels in pregnant and lactating rat dams and in directly exposed offspring. Food and Chem Tox; DOI: http://dx.doi.org/10.1016/j.fct.2013.06.050.

Bennett D.H., Margni M.D., McKone T.E. and Jolliet O. (2002). Intake Fraction for Multimedia Pollutants: A Tool for Life Cycle Analysis and Comparative Risk Assessment. Risk Analysis, 22: 905–918. doi: 10.1111/1539-6924.00260.

Bester, K., 2005. Fate of triclosann and triclosan-methyl in sewage treatment plants and surface waters. Arch Environ Contam Toxicol; 49:9-17.

Bhargava, H.N., Leonard, P.A., 1996. Triclosan, applications and safety. Am. J. Infect Control 24, 209–218.

Biocide Information (BI), 2004. Biocides in textiles. Biocide Information Services.

Biesterbos, J.W.H., Dudzina, T., Delmaar, C.J.E., Bakker, M., Russel, F.G.M., von Goetz, N., Scheeprs, P.T.J., Roelevend, N., 2013. Usage patterns of personal care products: important factors for exposure assessment. Food and Chem Tox. 55, 8-17.

Black, J.G., Howes, D., 1975. Percutaneous absorption of Triclosan from toilet preparations. J Soc Cosmet Chem 26:205-215.

Bennett, D.H., Wu, X.M., Teague, C.H., Lee, K., Cassady, D.L., Ritz, B., Hertz-Picciotto, I., 2012. Passive sampling methods to determine household and personal care product use. J of Exp Sci and Env Epid 22:148-160.

Bremmer H.J. and van Veen M.P., 2002. Children`s Toys Fact Sheet, RIVM report 612810012.

Bremmer, H.J., Prud'Homme de Lodder, L.C.H., van Engelen, J.G.M., 2006b. General Fact Sheet. Limiting conditions and reliability, ventilation, room size, body surface area. Updated version for ConsExpo 4. RIVM report 320104002/2006.

Bremmer H.J., Prud'homme de Lodder L.C.H., van Engelen J.G.M. (2006b). Cosmetics Fact Sheet To assess the risks for the consumer. Updated version for ConsExpo 4.RIVM report 320104001/2006.

Burns. J., 1997. 14-Day repeated dose dermal study of Triclosan in Rats. CHV 6718-102. Corning Hazleton Inc. Vienna, Virginia. April 28, 1997.

Burns-Naas, L.A., Mast, R.W., Klykken, P.C., McCay, J.A., White, K.L., Mann, P.C., Naas, D.J., 1998a. Toxicology and humoral immunity assessment of decamethylcyclopentasiloxane (D5) following a 1-month whole body inhalation exposure in Fischer 344 rats. Toxicol Sci. 43: 28-38.

Burns-Naas L.A., Mast R.W., Meeks, R.G., Mann, P.C., Thevenaz, P., 1998b. Inhalation toxicology of decamethylcyclopentasiloxane (D5) following a 3-month nose-only exposure in Fischer 344 rats. Toxicol Sci. 43(2): 230-240.

Buser, A.M., Kierkegaard, A., Bogdal, C., MacLeod, M., Scheringer, M., Hungerbühler, K., 2013. Concentrations in ambient air and emissions of cyclic volatile methylsiloxanes in Zurich, Switzerland. Environmental Science & Technology 47(13):7045-7051, (doi: 10.1021/es3046586).

Calafat, A.M., Ye, X., Wong, L.Y., Reidy, J.A., Needham, L.L., 2008. Urinary concentrations of triclosan in the US population: 2003–2004. Environ. Health Perspect. 116(3):303–307.

Canosa, P., Perez-Palacios, D., Garrido-Lopez, A., Tena, M.T., Rodriguez, I., Rubi, E., 2007. Pressurized liquid extraction with in-cell clean-up followed by gas-chromatography-tandem mass spectrometry for the selective determination of parabenes and triclosan in indoor dust. J. of Chrom A; 1161:105-112.

Centre Européen des Silicones (CES), 2013. Description of cyclic siloxanes. [Available online at http://www.cyclosiloxanes.eu/index.php?page=cyclic-siloxanes (last accessed 01.07.2013].

Chalew, T.E.A,, Halden, R.U., 2009. Environmental exposure of aquatic and terrestrial biota to triclosan and triclocarban. J. Am. Water Resour. Assoc. 45(1): 4–13.

Chu, S., Metcalfe, C.D., 2007. Simultaneous determination of triclocarban and triclosan in municipal biosolids by liquid chromatography tandem mass spectrometry. J. Chromatogr. 1164: 212–218.

Chung, D., Papadakis, S. E., Yam, K. L., 2003. Evaluation of a polymer coating containing triclosan as the antimicrobial layer for packaging materials. International Journal of Food Science and Technology; 38:165–169.

Cowan-Ellsbery C. and Robison S.H. (2009). Refining Aggregate Exposure: Example using Parabens, Regulatory Toxicology and Pharmacology 55, 321–329. doi:10.1016/j.yrtph.2009.08.004.

Crofoot S.D., Stanton E., Siddiqui W., Zimmer M.A. (1990) A 14-day subchronic gavage study with decamethylcyclopentasiloxane in rats. Unpublished data, submitted by SEHSC to Cosmetic Ingredient Review Expert Panel [cited in AR14]

CropLife America (CLA), (2010). Cumulative and Aggregate Risk Evaluation System (CARES). http://www.ilsi.org/ResearchFoundation/Pages/CARES.aspx, (accessed July 2011)

Daniel, C. 1973. One-at-a-time-plans. J. Am. Statist. Assoc.; 68:353-360.

Danish Ministry of the Environment (Environmental Protection Agency (EPA)), 2006. Survey of liquid hand soaps, including health and environmental assessments. Survey of Chemical Substances in Consumer Products, No. 69. [Available online at http://www2.mst.dk/udgiv/publications/2006/87-7052-062-3/pdf/87-7052-063-1.pdf (last accessed 25.01.2014)].

Dayan, A.D., 2007. Risk assessment of triclosan [Irgasan] in human breast milk. Food Chem Toxicol;47:125–129.

Delmaar, J.E., Park, M.V.D.Z., van Engelen, J.G.M., 2005. ConsExpo 4.0 Consumer Exposure and Uptake Models. Program Manual. RIVM report 320104004/2005.

Delmaar, J.E., Park, M.V.D.Z., van Engelen, J.G.M., 2006. RIVM report 630700001/2006 Aggregating human exposure to chemicals: An overview of tools and methodologies.

den Hond, E., Paulussen, M., Geens, T., Bruckers, L., Baeyens, W., david, F., Dumont, E., Loots, I., Morrens, B., Nemery de Bellevaux, B., Schoeters, G., Van Laraveke, N., Covaci, A., 2013. Biomarkers of human exposure to personal care products: Results from the Flemish Environment and Health Study (FLEHS 2007-2011). Sci of the Total Env; 463-464:102-110.

Dow Corning Corporation, 1996a. In Vitro Percutaneous Absorption of 14C-D5 in Rat Skin. Report no.1995-10000-41226, August 14, 1996.

Dow Corning Corporation, 1996b. In Vitro Percutaneous Absorption of 14C-D5 in Rat Skin. Report no. 1996-10000-41225, September 30, 1996.

Durango Software LLC, 2008. Calendex: http://www.exponent.com/calendex_software/ (accessed July 2011)

Dye, C., Schlabach, M., Green, J., Remberger, M., Kaj, L., Palm-Cousins, A., et al., 2007. Bronopol, Resorcinol, m-Cresol and Triclosan In the Nordic Environment. Copenhagen: Nordic Council of Ministers.

European Chemical Agency (ECHA), 2008. Guidance on information requirements and chemical safety assessment, chapter R.19: Uncertainty analysis, Guidance for the implementation of REACH.

European Chemical Agency (ECHA), 2010. Guidance on information requirements and chemical safety assessment, chapter R.15: Consumer Exposure Estimation, Guidance for the implementation of REACH.

European Chemical Agency (ECHA), 2012. Guidance on information requirements and chemical safety assessment. R.15: Consumer exposure estimation. Version 2.1. [Available online at

http://echa.europa.eu/documents/10162/13632/information_requirements_r15_en.pdf (last accessed 01.06.2013)].

Environ International Corporation. 2006. Evaluation of exposure to D5 for consumers, workers and the public. Prepared for the Silicones Environmental Health and Safety Council. [cited in OEHHA 2007].

European Commission (EC), 2008. The European Union System for the Evaluation of Substances (EUSES). [Available online at http://ihcp.jrc.ec.europa.eu/our_activities/health-env/risk_assessment_of_Biocides/euses/ (last accessed on 25.01.2014)].

European Commission (EC), 2009. Scientific committee on consumer products (SCCP). Opinion on triclosan. COLIPA No. P32 (May 21st, 2009). [Available online at http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_166.pdf (last accessed 04.02.2014).

Fan, X., Kubwabo, C., Rasmussen, P., Jones-Otazo, H., 2010. Simultaneous quantitation of parabens, triclosan, and methyl triclosan in indoor house dust using solid phase extraction and gas chromatography-mass spectrometry. J Environ Monit; 12(10):1891-1897.

Geens, T., Roosens, L., Neels, H., Covaci, A., 2009. Assessment of human exposure to Bisphenol-A, Triclosan and Tetrabromobisphenol-A through indoor dust intake in Belgium. Chemosphere 76, 755-760.

Geens, T., Neels, H., Covaci, A., 2012. Distribution of bisphenol-A, triclosan and n-nonylphenol in human adipose tissue, liver and brain. Chemosphere; 87:796-802.

Gilbert, R.J., Williams, P.E.O., 1987. The oral retention and antiplaque efficacy of triclosan in human volunteers. Br. J. Clin. Pharmacol. 23(5):579–583.

Heath, R.J., Rubin, J.R., Holland, D.R., Zhang, E., Snow, M.E., Rock, C.O., 1999. Mechanism of triclosan inhibition of bacterial fatty acid synthesis. J. Biol. Chem. 274, 11110–11114.

HERA, 2005. Guidance document. Methodology. [Available online at http://www.heraproject.com/files/HERA%20TGD%20February%202005.pdf (last accessed on 20.01.2014)].

International union of pure and applied chemistry (IUPAC), 2007. Glossary of terms used in toxicology. 2nd edition (IUPAC Recommendations 2007). Pure Appl. Chem., Vol. 79, No. 7, pp. 1153–1344. doi:10.1351/pac200779071153

Ishibashi, H., Matsumura, N., Hirano, M., Matsuoka, M., Shiratsuchi, H., Ishibashi, Y., Takao, Y., Arizono, K., 2004. Effects of triclosan on the early life stages and reproduction of medaka Oryzias latipes and induction of hepatic vitellogenin. Aquat. Toxicol. 67(2): 167–179.

Jäger, R., Hartmann, E., 1991. Subchronische toxikologische Untersuchungen an Ratten (Magensondenapplikation über 13 Wochen). Bayer AG. Report no. 20204, May 3, 1991.

Johnson, W., Bergfeld, W.F., Belsito, D.V., Hill, R.A., Klaassen, C.D., Liebler, D.C., Marks, J.G., Shank, R.C., Slaga, T.J., Snyder, P.W., Andersen, F.A., 2011. Safety Assessment of Cyclomethicone, Cyclotetrasiloxane, Cyclopentasiloxane,

Cyclohexasiloxane, and Cycloheptasiloxane. International Journal of Toxicology 30(6 suppl.), 149S-227S.

Jones-Otazo, H.A., Clarke, J.P., Diamond, M.L., Archbold, J.A., Ferguson, G., Harner, T., 2005. In house dust the missing exposure pathway for PBDEs? An analysis of the urban fate and human exposure to PBDEs. Env Sci and Tech; 39:5121-5130.

Jovanovic M.L., McMahon JM, McNett DA, Tobin JM, Plotzke KP (2008) In vitro and In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane (14C-D4) and 14Cdecamethylcyclo-pentasiloxane (14C-D5). Regul Toxicol Pharmacol. 50: 239–248.

Junker, M.L., Hay, A.G., 2004. Effects of triclosan incorporation into ABS plastic on biofilm communities. J of Antimicrobial Chemotherapy; 53(6):989-996.

Kalyon, B. D., Olgun, U., 2001. Antibacterial efficacy of triclosan-incorporated polymers. American Journal of Infection Control; 29:124–126.

Kanetoshi, A., Katsura, E., Ogawa, H., Ohyama, T., Kaneshima, H., Miura, T., 1992. Acute toxicity, percutaneous absorption and effects on hepatic mixed function oxidase activities of 2,4,4′-trichloro-2′-hydroxydiphenyl ether (Irgasan® DP300) and its chlorinated derivatives. Arch. Environ. Contam. Toxicol.; 23(1):91–98.

KEMI (Swedish Chemicals Agency), 1997. Chemicals in textiles - report of a Government Commission: The Swedish National Chemicals Inspectorate. [Available online at http://www.kemi.se/Documents/Publikationer/Trycksaker/Rapporter/Report_5_97_Chemicals_in_textiles.pdf (last accessed 01.07.2013].

KEMI (Swedish Chemicals Agency), 2012. Antibacterial substances leaking out with the washing water - analyses of silver, triclosan and triclocarban in textiles before and after washing. [Available online at http://www.kemi.se/Documents/Publikationer/Trycksaker/PM/PM1_12_Antibact_eng.pdf (last accessed 01.07.2013)].

Kim, K., Park, H., Yang, W., Lee, J.H., 2011. Urinary concentrations of bisphenol A and triclosan and associations with demographic factors in the Korean population. Env Res; 111:1280-1285.

Krishnan, K., Gagne, M., Nong, A., Aylward, L.L., Hays, S.M., 2010. Biomonitoring equivalents for triclosan. Reg Tox and Pharm; 58:10-17.

Latcha, D.E., Packer, J.L., Arnold, W.A., McNeill, K., 2003. Photochemical conversion of triclosan to 2,8-dichlorodibenzo-p-dioxin in aqueous solution. J. Photochem. Photobiol. A Chem.; 158(1): 63–66.

Latcha, D.E., Packer, J.L., Stender, B.L., VanOverbeke, J., Arnold, W.A., McNeill, K., 2005. Aqueous photochemistry of triclosan: formation of 2,4-dichlorophenol, 2,8-dichlorodibenzo-p-dioxin, and oligomerization products. Environ. Toxicol. Chem.; 24(3): 517–525.

Levy, C.W., Roujeinikova, A., Sedelnikova, S., Baker, P.J., Stuitje, A.R., Slabas, A.R., Rice, D.W., Rafferty, J.B., 1999. Molecular basis of triclosan activity. Nature 398, 383–384.

Li, X., Ying, G.G., Zhao, J.L., Chen, Z.F., Lai, H.J., Su, H.C., 2013. 4-nonylphenol, bisphenol-A and triclosan levels in human urine of children and students, and the effects of drinking these bottled materials on the levels. Env Int; 52:81-86.

Lin, Y.J., 2000. Buccal absorption of triclosan following topical mouthrinse application. Am. J. Dent. 13(4):215–217.

Lorenz C., von Goetz N., Scheringer M., Wormuth M., Hungerbühler K. (2011). Exposure of German consumers to engineered nanoparticles in cosmetics and personal care products, Nanotoxicology, 5, 12-29.

McMurry, L.M., Oethinger, M., Levy, S.B., 1998. Overexpression of marA, soxS, or acrAB produces resistance to triclosan in laboratory and clinical strains of Escherichia coli. FEMS Microbiol. Lett. 166, 305–309.

Meek, M.E., Boobis, A.R., Crofton, K.M., Heinemeyer, G., Van Raaij, M., Vickers, C., 2011. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework, Regulatory Toxicology and Pharmacology, Volume 60, Issue 2, Supplement 1, Risk Assessment of Combined Exposure to Multiple Chemicals: A WHO/IPCS framework - WHO Supplement, 1 July 2011, Pages S1-S14, ISSN 0273-2300, DOI: 10.1016/j.yrtph.2011.03.010.

Moran, R.E., Bennet, D.H., Tancredi, D.J., Wu, X.M., Ritz, B., Hertz-Picciotto, I., 2012. Frequency and longitudinal trends of household care product use. Atm Env; 55:417-424.

Morgan, M.G., and Henrion, M., 1990. Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis, New York: Cambridge University.

Moss, T., Howes, D., Williams, F.M., 2000. Percutaneous penetration and dermal metabolism of triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether). Food Chem. Toxicol. 38(4):361–370.

Nakada, N., Yasojima, M., Okayasu, Y., Komori, K., Suzuki, Y., 2010. Mass balance analysis of triclosan, diethyltoluamide, crotamiton and carbamazepine in sewage treatment plants. Water Sci. Technol. 61:1739–1747.

NHANES (National Health and Nutrition Examination Survey), 2013. The Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2013. [Available online at http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Mar2013.pdf (last accessed 01.06.2013)].

NICNAS (National Industrial Chemical Notification and Assessment Scheme), 2009. Priority Existing Chemical Assessement Report No. 30 for Triclosan. Australian Government, Department of Health and Ageing. [Available online at http://www.nicnas.gov.au/__data/assets/pdf_file/0017/4391/PEC_30_Triclosan_Full_Report_PDF.pdf (last accessed 01.07.2013)].

NPIRS (National Pesticide Information Retrieval System), 2012. [Available online at http://ppis.ceris.purdue.edu/ (last accessed 01.07.2013)].

Orhan, M., Kut, D., Gunesoglu, C., 2007. Use of triclosan as antibacterial agent in textiles. Indian J Fibre Text Res; 32:114–8.

Perencevich, E.N., Wong, M.T., Harris, A.D., 2001. National and regional assessment of the antibacterial soap market: a step toward determining the impact of prevalent antibacterial soaps. Am. J. Infect. Control 29, 281–283.

Pirard, C., Sagot, C., Deville, M., Dubois, N., Charlier, C., 2012. Urinary levels of bisphenol A, triclosan and 4-nonylphenol in a general Belgian population. Env Int; 48:78-83.

Price, P.S., Curry, C.L., Goodrum, P.E., Gray, M.N., McCrodden, J.I., Harrington, N.W., Carlson-Lynch, H., Keenan, R.E., 1996. Monte Carlo modelling of time-dependent exposures using a microexposure event approach. Risk Anal., 16 (3), 339–348.

Prud'homme de Lodder, L.C.H., Bremmer, H.J., van Engelen, J.G.M., 2006a. Cleaning Products Fact Sheet.To assess the risks for the consumer. RIVM report 320104003/2006.

Prud'homme de Lodder, L.C.H., Bremmer, H.J., Pelgrom, S.M.G.J., Park, M.V.D.Z., van Engelen, J.G.M., 2006b. Disinfectant Products Fact Sheet to assess the risks for the consumer. RIVM report 320005003/2006.

Queckenberg, C., Meins, J., Wachall, B., Doroshyenko, O., Tomalik-Scharte, D., Bastian, B., Abdel-Tawab, M., Fuhr, U., 2010. Absorption, pharmacokinetics, and safety of triclosan after dermal administration. Antimicrob. Agents Chemother. 54(1):570–572.

Rastogi, S.C., Krongaard, T., Jensen, G.H., 2003. Survey of chemical substances in consumer products: antibacterial compounds in clothing articles. Survey No. 24. Copenhagen: Danish Environmental Protection Agency.

Reddy, M.B., Looney, R.J., Utell, M.J., Plotzke, K.P., Andersen, M.E., 2007. Modelling of human dermal absorption of octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5). Toxicological Sciences 99(2): 422–431.

Reiss, R., Lewis, G., Griffin, J., 2009. An ecological risk assessment for triclosan in the terrestrial environment. Environ. Toxicol. Chem; 28(7):1546–1556.

Remberger, M., Sternbeck, J., Strömberg, K., 2002. Screening av triclosan och visa bromerade fenoliska ämnen i Sverige. [Screening of triclosan and some brominated phenolic compounds in Sweden]. IVL report no B1477-2.

Saltelli, A., Chan, K., Scott, E.M., 2000. Sensitivity Analysis. Wiley Series in Probability and Statistics Wiley & Sons: Chichester. ISBN 0-471-99892-3.

Samuel, B.U., Hearn, B., Mack, D., Wender, P., Rothbard, J., Kirisits, M.J., Mui, E., Wernimont, S., Roberts, C.W., Muench, S.P., Rice, D.W., Prigge, S.T., Law, A.B., McLeod, R., 2003. Delivery of antimicrobials into parasites. Proc. Natl. Acad. Sci. USA 55, 14281–14286.

Sandborgh-Englund, G., Adolfsson-Erici, M., Odham, G., Ekstrand, J., 2006. Pharmacokinetics of triclosan following oral ingestion in humans. J. Toxicol. Environ. Health: Pt A; 69(20):1861–1873.

SCCS (Scientific Committee on Consumer Safety), 2010a. Opinion on cylcomethicone, octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5). [Available online at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_029.pdf (last accessed on 01.02.2013)].

SCCS (Scientific Committee on Consumer Safety), 2010b. Opinion on triclosan (antimicrobial resistance). Brussels: Scientific Committee on Consumer Safety.

SCCS (Scientific Committee on Consumer Safety), 2012. The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation. 8th revision. SCCS/1501/12. [Available online at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf (last accessed on 01.02.2013)].

Schuur, A.G., Delmaar, C.E., van Engelen, J.G.M., 2009. Geaggregeerde blootstelling in verschillende kaders en toekomstige mogelijkheden/ Aggregate exposure. Use in different frameworks and future possibilities. RIVM Briefrapport 320015003 (in Dutch).

Schweizer, H.P., 2001. Triclosan: a widely used biocide and its link to antibiotics. FEMS Microbiol. Lett.; 202(1):1–7.

Siddiqui, W.H., Stump, D.G., Reynolds, V.L., Plotzke, K.P., Holson, J.F., Meeks, R.G., 2007. A two-generation reproductive toxicity study of decamethylcyclopentasiloxane (D5) in rats exposed by whole-body vapor inhalation. Reprod Toxicol. 23(2): 216-225.

Singer, H., Mueller, S., Tixier, C., Pillonel, L., 2002. Triclosan: occurrence and fate of a widely used biocide in the aquatic environment: field measurements in wastewater treatment plants, surface waters, and lake sediments. Environ Sci Technol; 36:4998–5004.

Statistics Netherlands, 2013. [Available online at http://statline.cbs.nl/StatWeb/?LA=en (last accessed on 01.07.2013)].

Sullivan, A., Wretlind, B., Nord, C.E., 2003. Will triclosan in toothpaste select for resistant oral streptococci? Clin. Microbiol. Infect. 9, 306–309.

Surolia, N., Ramachandra Rao, S.P., Surolia, A., 2001. Paradigm shifts in malaria parasite biochemistry and anti-malarial chemotherapy. Bioessays 31, 192–196.

The Lifeline Group, Annandale, VA (2006). LifeLine v5.0™ (version 5.0) [software]. [Available at www.thelifelinegroup.org (last accessed 01.07.2011)].

Tiered Aggregate Exposure Assessment (TAGS), (2011). [Available online at http://www.tags.cperi.certh.gr/ (last accessed 01.07.2011)].

Tobin, J.M., McNett, D.A., Durham, J.A., Plotzke, K.P., 2008. Disposition of decamethylcyclopentasiloxane in Fischer 344 rats following single or repeated inhalation exposure to 14C-decamethylcyclopentasiloxane (14C-D5). Inhal Toxicol. 2008 Mar;20(5):513-31. doi: 10.1080/08958370801935075.

Toms, L.M.L., Allmyr, M., Mueller, J.F., Adolfsson-Erici, M., McLachlan, M.S., Murby, J., Harden, F.A., 2011. Triclosan in individual human milk samples from Australia. Chemosphere; 85:1682-1686.

Trimmer, G.W., 1994. 90-day Subchronic dermal toxicity study in the rat with satellite group with Irgasan DP300 (MRD-92-399): 139910B. EXXON Biomedical Sciences Inc. Mettlers Road, CN 2350, New Jersey. July 14, 1994

Trudel, D., Scheringer, M., von Goetz, N., Hungerbühler, K., 2011a. Total Consumer Exposure to Polybrominated Diphenyl Ethers in North America and Europe, Environ. Sci. Technol., 45, 2391–2397.

Trudel, D., Tlustos, C., von Goetz, N., Scheringer, M., Reichert, P., Hungerbühler, K., 2011b. Exposure of the Irish population to PBDEs in food: consideration of parameter uncertainty and variability for risk assessment, Food Additives and contaminants, available online, doi:10.1080/19440049.2011.572082.

US-EPA (United States Environmental Protection Agency), 1997. Standard Operating Procedures (SOPs) for Residential Exposure Assessments [Available online at http://www.epa.gov/pesticides/trac/science/trac6a05.pdf (last accessed 01.07.2011)].

US-EPA (United States Environmental Protection Agency), 2001. General Principles For Performing Aggregate Exposure And Risk Assessments. [Available online at http://www.epa.gov/pesticides/trac/science/aggregate.pdf (last accessed 01.07.2011)].

US-EPA (United States Environmental Protection Agency), 2011. Exposure Factors Handbook.

VerbraucherAnalyse [Consumer Analysis] Klassik [Classic] and Jugend [Youth]. [Available online at http://www.verbraucheranalyse.de/inhalte (last accessed 03.02.2014)].

Von der Ohe, P.C., Schmitt-Jansen, M., Slobodnik, J., Brack, W., 2011. Triclosan-the forgotten priority substance? Environ Sci Pollut Res; 19:585–91.

Von Goetz N., Wormuth M., Scheringer M., Hungerbühler K., 2010. Bisphenol A: How the most relevant exposure sources contribute to total consumer exposure, Risk Analysis, 30(3), 473-487.

Walser, T., Demou, E., Lang, D.J., Hellweg, S., 2011. Prospective environmental life cycle assessment of nanosilver T-shirts. Environ Sci Technol; 45:4570–8.

Watterson, B., 1999. Antimicrobial Fibreglass Reinforced Plastic Composite. Microban Products Company. [Available online at http://www.google.com/patents/US5919554 (last accessed on 01.06.2013)].

Weegels, M.F., van Veen, M.P., 2001. Variation of consumer contact with household products: a preliminary investigation. Risk Analysis 21(3):499-511.

WHO - IPCS (2004). Risk Assessment Terminology Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment. Part 2: IPCS Glossary of Key Exposure Assessment Terminology.

WHO - IPCS (2008). Uncertainty and Data Quality in Risk Assessment. [Available online at http://www.who.int/ipcs/publications/methods/harmonization/exposure_assessment.pdf (last accessed 25.01.2014)].

WHO - IPCS (2009). Assessment of combined exposures to multiple chemicals. Report of a WHO/IPCS international workshops. [Available online at http://www.who.int/ipcs/methods/harmonization/areas/workshopreportdocument7.pdf (last accessed 25.01.2014)].

Windler, L., Height, M., Nowack, B., 2013. Comparative evaluation of antimicrobials for textile applications. Env Int; 53:62-73.

Wolff, M.S., Teitelbaum, S.L., Windham, G., Pinney, S.M., Britton, J.A., Chelimo, C., 2007. Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. Environ Health Perspect; 115:116–121.

Zartarian V.G., Özkaynak H., Burke J.M., Zufall M.J., Rigas M.L., Furtaw Jr E.J., 2000. A modelling framework for estimating children's residential exposure and dose to chlorpyrifos via dermal residue contact and nondietary ingestion. Environ. Health Perspect., 108 (6), 505-514.

Zartarian, V.G., Ott, W.R., and Duan, N., 2007. Basic concepts and definitions of exposure and dose. In: Exposure Analysis. edited by Ott, W.R., Steinemann, A.C., Wallace, L.A. RC Press, Boca Raton. ISBN 1-56670-663-7.

Part II: Biomonitoring Study

II-1. Guidance to human biomonitoring for the assessment of consumer exposure

II-1.1 Introduction

Human biological monitoring (HBM) was used in large population-based studies such as NHANES, GERES and COPHES in programs primarily aimed at exposures from the ambient environment (Kirman et al., 2012; Schulz et al., 2007; Joas et al., 2012). There is also increasing interest to apply HBM in connection to a chemical incident or disaster (Scheepers et al., 2011; Eggens et al., 2012, Müller and Schmiegen, 2012; Scheepers et al. 2014a; 2014b). However, there is limited experience on how to use biological monitoring in the process of risk characterization and management of exposures resulting from the use of consumer products in the general population (Boogaard et al. 2011). This guidance aims at describing the merits and limitations of the concept of biomonitoring for the assessment of consumer exposure.

II-1.1.1 *Terminology*

In the context of this guidance biomonitoring is defined as ‘the standardized and repeated systematic collection, pretreatment, storage, and analysis of body tissues to assess the internal dose of a xenobiotic substance by analysis of the parent substance and/or a product of biotransformation’ (Scheepers et al., 2011). As will be shown, biomonitoring is much more than just the analysis of the internal dose of a chemical substance, which is also called ‘biomarker’ (Manno et al., 2010). The biomarkers themselves are useful tools in the assessment of exposure, susceptibility or effect in the context of human health risk assessment of xenobiotic substances (Zielhuis and Henderson, 1986). This use of biomarkers in a public health setting (i.e. in a biomonitoring study) is different from the use of clinical biomarkers in a healthcare setting aimed at prognosis, diagnosis or treatment of disease in an individual patient. Biomonitoring studies are usually performed in populations of healthy individuals who are exposed to environmental factors, which may or may not have health consequences. This application of biomonitoring is suited to address primary prevention of exposure and potential forthcoming disease.

In this guidance a biomarker can be the parent chemical substance (parent), as a chemical ingredient of a consumer product. It can also be a biotransformation product of this parent (metabolite) or the product of covalent binding of the parent, a reactive intermediate or a metabolite to an endogenous molecule (e.g. DNA, RNA or protein). This is called 'addition product', abbreviated as 'adduct'. The relationship between these substances is shown in Figure II: 1-1. The intermediate itself cannot be a biomarker due to its intrinsic reactivity, which makes it not stable enough for being analysed.

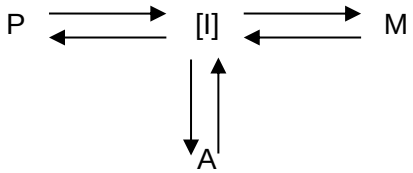


Figure II: 1-1. Relationship between the parent (P), a metabolite (M) and/or an adduct (A) which can all be used as a biomarker of exposure. The intermediate ([I]) cannot be used as biomarker.

II-1.1.2 *Scope*

The scope of this document is to support assessment of personal internal exposure as part of a human health risk assessment related to the *normal* use of chemical products on a day-to-day basis in the general population, i.e. use of consumer products. Therefore, only biomarkers of exposure will be included rather than other, equally useful, biomarker applications such as biomarkers of susceptibility, biomarkers of biochemical effects or biomarkers of health effects (Zielhuis and Henderson, 1986). A biomarker of exposure is defined as '*a chemical or its metabolite or the product of an interaction between a chemical and some target molecule or macromolecule that is measured in a compartment or the fluid of an organism'* (Manno et al., 2010).

This guidance will cover the use of biomonitoring in both experimental and observational study designs. The way biomarkers are used in such studies and the contextual information, which is collected in these studies, will determine the added value of this field of applied research.

II-1.1.3 *Merits and limitations*

There are several merits and limitations to the concept of biomonitoring. A first limitation is that biomonitoring is of limited value for those chemicals that have (only) a local effect in the tissue in direct contact with the chemical product. This may be the skin in the case of dermal

contact, the oral cavity and oesophagus in the case of oral uptake or the airways if inhalation is the most prominent route of uptake. In these cases an estimate of the local tissue concentration is the most relevant dose parameter on short-term or long-term. Chemicals have systemic effects, sometimes in addition to local effects. Before deciding on the method of exposure assessment it is important to decide which effect is considered to be critical to health. A systemic exposure should be measured e.g. by determination of the concentration of the chemical substance or a product of biotransformation in the (blood) circulation or a parameter that reflects this concentration. For this so-called systemic exposure the use of biomarkers may be of added value compared to environmental monitoring. More particular merits and limitations of biomonitoring will be further discussed below.

An important merit is the capability of biomonitoring studies to positively identify (by chemical analysis) the presence of xenobiotics in body tissues. Depending on the type of tissue and the level of chemical substance(s) observed, this information can be used to assess the possible risk of this presence to induce health effects on short or long-term. Biomonitoring is often the most reliable exposure assessment methodology in the case of exposures in the general public because of the complex nature of such exposure, involving multiple exposure pathways, routes of uptake and contact media (Boogaard et al., 2011). The added value of the measurement of internal exposure to the more conventional determination of external exposure by source-to-dose modelling combined with environmental monitoring is that biomonitoring integrates the uptake from different routes of uptake, of different exposure events and from different sources over a defined period of time (e.g. from different environmental compartments, micro environments attenuated by personal habits/behavioural and activity patterns).

If the exposure is part of a complex mixture, other substances in that mixture may change the fate of the substance of interest in the human body. This influence is also integrated in the biomarker data that are collected. The variability in biomarker levels combines exposure-related and host-related factors into a single parameter, which shows a much wider inter-individual and intra-individual variability than parameters indicating environmental exposure only (Manno et al., 2010). Such inter-individual variation in the level of a biomarker provides an accurate assessment of individual exposure and also provides information on the changes of the internal dose over time within an individual. This makes biomonitoring more attractive than source-to-dose-modelling for assessing the total internal exposure of an individual, provided that the toxicokinetics and toxicodynamics of the biomarker are sufficiently understood.

Source-to-dose modelling may be preferred to study research questions related to preventive interventions, i.e. for the determination of the most relevant source of exposure (von Goetz et

al., 2010). Here, biological monitoring sometimes offers an alternative approach, but in most cases just provides a complementary research tool (Manno et al., 2010).

An important limitation of the concept of biomonitoring is that, depending on the choice of a biomarker, it is sometimes not possible to discern if the finding of a substance in a body tissue is truly the result of external (exogenous) origin, since some substances (either parent or metabolite) may also be formed in the body i.e. are of internal (endogenous) origin. In such cases it is only possible to interpret a biomonitoring outcome with reference to a background level that reflects a baseline exposure in each individual, in a sub-population or in the entire population. This requires an intelligent study design that will be discussed in this guidance. Also, it may not be known which source of exposure may have contributed to an internal dose reflected by a biomarker of exposure or which routes of uptake may be involved. Therefore, an isolated finding of a biomarker in body tissues or body fluids does not provide much information on exposure other than the identity of the biomarker (i.e. the chemical structure), the biological medium where it was found (e.g. detection in urine is relevant for toxicity to the kidney) and its the concentration level in the analysed tissue or fluid. For the use of biomarkers as a useful source of information in exposure assessment it is necessary to define an appropriate sampling strategy such as repeated collection of samples in the same individual at pre- and post-exposure moments in time. Biomonitoring is considered to be less useful for chemical substances for which the toxicology is unknown or for which the significance of certain biomarkers to health is unclear (Manno et al., 2010).

II-1.1.4 *Structure of the guidance*

This guidance is structured in such a way that it follows the procedure when conducting a biomonitoring study, i.e. from the determination of the objective of a biomonitoring campaign until the communication of the outcome. Before following this stepwise process of preparing a biomonitoring study, some basic concepts of toxicokinetics and toxicodynamics are introduced in chapter II-1.2, as far as they are of direct concern to the subject of this guidance.

Chapter II-1.3 discusses some possible aim(s) of a biomonitoring study. Chapter II-1.4 discusses what should be done to prepare a biomonitoring study before and in order to obtain approval from the ethics committee (chapter II-1.5). In chapters II-1.6 to II-1.11 the performance of a biomonitoring study from recruitment of the study subjects and sample collection to interpretation of results and communication to the study participants is discussed in a stepwise manner. In chapter II-1.12 the interpretation of biomonitoring results

is discussed and chapter II-1.13 addresses the way the results of a biomonitoring study can be communicated to the participants.

II-1.2 Basic toxicology considerations

II-1.2.1 *Toxicokinetics*

Toxicokinetics describe the absorption, distribution, metabolism and excretion of chemical substances and their metabolites. Below, some examples of these processes will be discussed to demonstrate the relevance of these aspects to the health risk of an exposure to a chemical constituent of a consumer product. In each of these events the possible role of biomonitoring as a research tool will be discussed, including some limitations to the availability and interpretation of biomonitoring data.

II-1.2.1.1 Influence of route of uptake

Depending on the consumer product of interest, chemical substances may be taken up via inhalation, skin absorption or absorption in the gastrointestinal tract. The toxicity of a substance may depend on this route of uptake. If a chemical substance is absorbed in the digestive system it will reach the liver before being distributed to other organs by the circulation. If the liver reduces the toxicity of the substance by metabolizing the chemical to a less toxic metabolite (the so-called first pass effect), oral uptake of this chemical is expected to have much lower toxicity compared to the uptake of the same substance by inhalation or by dermal absorption. Determination of the concentration of the parent substance and/or a metabolite will show in what forms the chemical is systemically available and how the ratio of parent to metabolite(s) may attenuate the probability of health effects to occur. Uptake via two or three different routes may lead to a systemic exposure that is difficult to predict. In such cases the determination of one or more biomarkers may show the influence of the toxicokinetic processes on the target dose of one or more bioactive species (parent, intermediate or metabolite).

II-1.2.1.2 Bioavailability

Biomonitoring is most useful to assess the probability of a systemic effect of a toxicant. Before a chemical substance can cause such an effect, it must enter the circulation and (in some but not all cases) be activated. If and to what extent the use of a consumer product leads to uptake in the circulation depends on many substance-specific properties, on the way

the product is used and on the physiology of the exposed individual. The uptake resulting from some generic use patterns may be modelled but many use patterns are too specific and/or complicated to predict. In such cases biomonitoring may be used to describe the integrated outcome of all of these phenomena (Boogaard et al., 2011). The most frequently used parameter to predict systemic toxicity is the biomarker level in the blood plasma. For this body fluid it is important to know if the substance is free in solution or bound to plasma proteins. If accurate data are needed e.g. to refine TK and PBPK or PBTK models, such uptake and bioavailability processes may be studied by the use of biomonitoring. This will stimulate the use of biomarkers that reflect the *effective dose* following a chemical exposure.

II-1.2.1.3 Bioactivation of chemical substances

Some chemicals (e.g. strong bases and acids) have high chemical reactivity, causing immediate lesions. Other substances (such as biocides) may bind to specific receptors disrupting physiological functions or biochemical pathways. Some chemical substances also may have a low toxicity by themselves but need to be activated in the body. Uptake of these substances usually results in altered toxicity after having been chemically changed and thereby activated through biotransformation (e.g. polycyclic aromatic hydrocarbons, benzene). The liver is the primary site of activation by metabolism but other organs (e.g. lung, kidney, skin) may also contribute to the formation of metabolic products. These products can be metastable molecules that may readily bind to DNA, RNA or proteins. Consequently, the place of metabolic activation is the most important target tissue for biomonitoring. A chemically more stable metabolite may interfere with physiological functions or biochemical pathways to exert its toxicity. The necessity of bioactivation and the type of activation will determine the choice of a biomarker because ideally the biomarker reflects the level of activation in a specific target.

II-1.2.1.4 Time-course of exposure (peak exposures) and dynamics of internal exposure of a target (organ)

For the toxicity of a chemical substance the highest concentration reached in the circulation and/or in a target tissue may determine if and how the exposure is tolerated by the organism (Manno et al., 2010). Using a suitable biomarker will show to what extent the concentration of a toxic substance or its metabolite(s) will be able to reach a critical value or not, depending on phase 1 metabolism that may yield more or less toxic metabolites or on phase 2 mechanisms that neutralize reactive electrophilic intermediates such as enzymatic conjugation. At very high exposure levels an oversaturation may change the

biotransformation pathway that is expected at an intermediate or low exposure. Such events can be identified and studied by the use of biomonitoring (Scheepers et al., 2011).

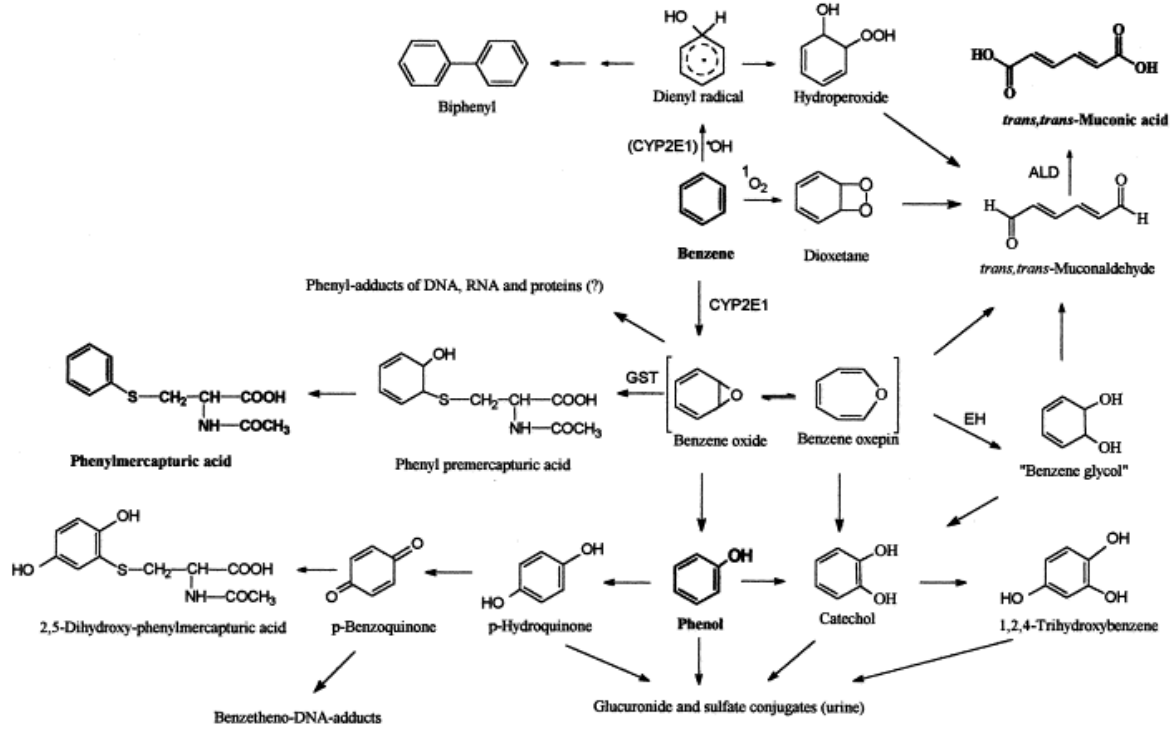
II-1.2.1.5 Aggregate exposures

If a single chemical substance occurs in different consumer products, the health risk for this substance is determined by the target dose resulting from the contribution of the combined exposures to these products. Due to the type of products and the way they are used, the exposure may involve two or more uptake routes and be a combination of two or more aforementioned scenarios: Formulation of product A may lead to different absorption kinetics of a specific chemical substance compared to uptake of the same substance used in another product B with a different formulation or use pattern. Certain products (e.g. rinse-off products such as a shower gel) may lead to peak exposures whereas the uptake pattern for stay-on products, such as a cream or deodorant is much less dynamic. Use of more than one product may lead to simultaneous or intermittent exposures to the same substance. Intra- and inter-individual variability in the resulting pattern of internal exposure can be characterized by the determination of suitable biomarkers.

II-1.2.2 *Toxicodynamics*

Toxicodynamics describe the interaction of a chemical substance and/or its metabolites/adducts with an organism and (preferably) also the toxicity mechanism involved. Exposure to a substance can lead to a reversible or irreversible effect, a molecular or physiological effect, a non-adverse or adverse effect and an effect that occurs on short-term or long-term. Depending on the aim of the biomonitoring study it is important to decide which is the most suitable biomarker, with respect to the toxicodynamics of the chemical substance of interest. This means that even when considering exposure (and thus using a biomarker of exposure) it may be preferred to analyse body tissues for a metabolite rather than the parent substance, e.g. in the case that the health effect of interest is known to be caused by one or more metabolite(s) rather than by the parent substance. If a metabolite is preferred over the parent substance as a biomarker, it is important to verify that the metabolite is sufficiently specific for the exposure to the parent substance as a metabolite may also be the product of biotransformation in a different, sometimes endogenous pathway and may also result from another parent substance. This dilemma is discussed using the example of benzene exposure and cancer risk in Figure II: 1-2.

Figure II: 1-2. Choosing the most suitable biomarker of exposure to benzene. Benzene is present in gasoline fuels and can also be present in exhaust fumes from spark ignition engines. For exposure to benzene there are different health concerns. Short-term exposure to high concentrations may lead to depression of the central nervous system. In epidemiological studies long-term exposure to low concentrations of benzene is associated with an increased risk of cancer. If aimed at short-term neurotoxic effects, determination of the parent substance in blood, exhaled air or urine is a suitable biomarker. If aimed at the cancer risk the determination of metabolites of benzene is more suitable as the carcinogenicity is attributed to metabolites and not to the parent substance. There are two well-established methods for the determination of metabolites of benzene: t,t-muconic acid and S-phenyl mercaputuric acid. Both are conjugates formed from metastable intermediates (such as benzene oxide benzene oxepin) and benzene that are thought to be involved in the cancer risk. S-phenyl mercapturic acid is a metabolite very specific to benzene exposure, whereas t,t-muconic acid is equally sensitive but no exclusively the result of benzene metabolism. This substance may also be formed as a result of bacterial metabolism of dietary sorbic acid intake (Scherer et al., 1998).



II-1.2.3 *Biomarkers of exposure*

Biomarkers are divided into three categories: biomarkers of exposure, biomarkers of susceptibility and biomarkers of effect (Zielhuis and Henderson, 1986). Below, different options for the choice of a biomarker are discussed: the parent substance, a product of biotransformation (metabolite) or an addition product (adduct).

II-1.2.3.1 Parent substance

The chemical substance that is used as a constituent in a consumer product can be measured in a biological tissue. The parent substance can be used as a biomarker and may thus be equivalent to the xenobiotic substance involved in the exposure. This is often the case when choosing a biomarker of exposure. The parent substance may be a suitable biomarker as long as the level of the parent substance is a reflection of the level of a bioactive species (parent, intermediate or metabolite) in the target organ.

II-1.2.3.2 Metabolite

A product of metabolism (metabolite) may also represent a suitable biomarker. Especially in those cases where the parent substance is not involved in the most relevant health effect, it is more suitable to consider the choice of a product of biotransformation. In those cases where the toxicity is equivalent to reactivity it may not be possible to measure the reactive intermediate itself, because the intermediate is not chemically stable or cannot be isolated from biological tissues before it is converted to a chemically stable product.

The biomarker can also be a metabolite proportionally related to the ultimate toxicant (Boogaard et al., 2011). A good example is a conjugate which if formed by reaction of an ultimate electrophilic reactive intermediate with an endogenous nucleophilic entity that protects the cellular components from any adverse lesions. Such nucleophilic substrates are e.g. gluthatione, glucuronides or sulphates.

II-1.2.3.3 Adducts

The classification of Zielhuis and Henderson (1986) has its limitations for biomarkers that reflect exposure and also have a clear relationship with the health effect. The classical example of such a biomarker is carboxyhemoglobin (COHb). For genotoxic chemicals DNA is the molecular target and the level of DNA-adducts reflects the biologically effective dose (Scheepers, 2009; Manno et al., 2010). In addition to the uptake of a chemical substance

these adducts also reflect to what extent a parent chemical may be metabolized to an ultimate reactive intermediate which binds to a DNA—base and which may result in a distorted replication (a mutation) or modified expression of certain genes like oncogenes and tumour suppressor genes. The DNA-adduct level also shows to what extent recent damage was repaired by DNA-repair enzymes. A limitation to this approach is that the level of DNA adducts cannot always be measured in the target tissue (i.e. the tissue were tumour induction is expected for a specific chemical substance). Often peripheral lymphocytes are used as a source of DNA for the determination of adducts. Because of the discrepancy of adduct levels in the lymphocytes and the probability of tumour formation, most adduct levels are better indicators of a biochemical effect than of an adverse health effect (Boogaard, 2009).

In recent years also protein-binding products (protein adducts such as adducts to albumin or hemoglobin)were developed for an increasing number of chemical exposures (Törnqvist et al., 2002; Scheepers et al., 2005, 2008, 2011, 2014). Similar to DNA adducts, these adducts also reflect the biological effective dose of a xenobiotic substance. An important difference is that there is no known mechanism to remove amino acids from proteins after a covalent bond with a xenobiotic substance has been introduced. Therefore a protein adduct persists until it is digested and its native amino acids are reused in synthesis of new proteins. At that stage adducted amino acids are excreted. The formation of a covalent binding product is a demonstration of reactivity in a molecular target. Most of the proteins are determined systemically, in blood plasma (albumin) or erythrocytes (haemoglobin). In some cases protein adducts have also been determined in target tissues (Hukkelhoven et al., 1985). Because of the toxicological relevance, DNA and protein adducts may be called ‘multifunctional’ biomarkers rather than being placed in the categories exposure, susceptibility or effect (Manno et al., 2010).

II-1.3 Determination of the aim of a biological monitoring study

The aim of a biomonitoring study implies many choices that will have to be made as part of a comprehensive protocol (see chapter II-1.4).

Below four generic categories of aims are presented:

1. Observational research: population studies describing the relationship of a biomarker to an environmental exposure or the relationship of a biomarker level to a health endpoint (observational studies)
2. Experimental research and clinical studies: volunteer studies carried out to collect data on toxicokinetic parameters and/or on some specific health-related endpoints (experimental studies)
3. Emergency response: research that provides data that can be used in the treatment of an individual with clinical signs of intoxication (clinical studies).
4. Risk assessment studies: these studies are carried out to prevent health effects related to the use of chemicals in specific situations. These are studies carried out for regulatory purposes (regulatory/preventive studies) e.g. to derive a safe dose or biological equivalent (see chapter II-1.12).

These generic aims will be discussed below in more detail.

II-1.3.1 *Observational research*

In the context of an epidemiological study biomarkers can be valuable since they represent parameters reflecting the dose in target tissues. For these studies biomonitoring is preferred to environmental exposure data, because ideally the individual internal exposure should be linked to the individual effect. Biological and exposure modelling/environmental monitoring should not be treated as alternatives but rather as complementary approaches (Manno et al., 2010).

II-1.3.2 *Experimental research*

Healthy subjects may be recruited for a laboratory-based volunteer study. Such a study may be carried out to collect data on specific kinetic parameters describing the absorption, distribution, metabolism and/or excretion in humans. Administered exposures in these studies are in a range that is generally thought to be safe. Some subjects with certain a priori

defined characteristics are excluded from participation because of known increased susceptibility (e.g. pregnancy). Studies may also be performed to study early/mild reversible health effects at concentrations that are considered safe. These types of studies require approval by an ethics committee.

II-1.3.3 *Clinical studies*

An individual healthy person or patient can benefit from biomonitoring when data can be supplied, complementing or supporting the correct interpretation of clinical tests in the case of a suspected intoxication (Scheepers et al., 2011). Biomarkers often have a much better sensitivity and specificity than clinical tests. Also a biomarker is usually more valuable to the individual if the biomarker is closer to the critical target and supports the test of an adverse effect or a disease (Manno et al., 2010). In such cases biomonitoring can help to provide the most optimal healthcare to the patient (Eggens et al., 2012).

II-1.3.4 *Emergency response*

If patients are admitted to hospital and have clinical signs of an intoxication, biomonitoring may be used to confirm the identity of specific chemical substances and this information may be used to determine the most suitable treatment or to communicate possible health effects. The use of biomonitoring in the case of a chemical incident is discussed by Scheepers et al. (2011), and a guideline was recently published in The Netherlands (Eggens et al., 2012; Scheepers et al., 2014).

II-1.3.5 *Risk assessment oriented studies*

If the relationship between a biomarker level and the potential risk of health effects was previously established in a relevant human or animal study it may be possible to use biomonitoring data for the prediction of health risk and standard setting. Usually such exposure-response data is presented on a group level and should not be used for the assessment of an individual health risk. However, exposure to substances so high that clinical toxic effects are expected may require an individual exposure assessment e.g. in the case of exposure to toxicants derived from a chemical incident, medical treatment or medical device (Scheepers et al., 2011; Latini et al., 2005; Polyzois, et al., 2012).

II-1.3.5.1 Hazard identification

Biomonitoring may provide the supporting evidence for the involvement of a specific chemical substance in producing an adverse health effect effect by confirmation of the identity of the parent or a metabolite of adduct, specific for the parent.

II-1.3.5.2 Dose-response characterization

Sometimes the relationship between dose and response is described in animal studies mostly for one specific route of exposure. For realistic exposure scenarios involving humans using consumer products such studies have limited value. If the dose parameters are well-defined and the response is characterized as a reversible early and mild health effect it may be more useful to study this relationship in human subjects under well-defined and controlled, but (compared to animal-exposures) more realistic exposure conditions, such as in a laboratory-based experimental study, involving small numbers of volunteers as human subjects. Alternatively, biomonitoring could be used in an observational study involving selected or randomly chosen human subjects from the general population. From these subjects biomonitoring data are collected as well as data on health, based on real life exposures to chemical substances from one or more consumer products.

II-1.3.5.3 Exposure assessment

Biomonitoring is preferably used to study consumer exposure scenarios where complicated processes are involved that are too complex to assess by source-to-dose modelling. However, inhalation or dermal exposure monitoring are to date not sufficiently validated to describe uptake from consumer exposure scenarios (Boogaard, 2008; Boogaard et al., 2011).

Biomonitoring may help to establish the internal dose level in one or more of the following generic exposure scenarios:

- Involvement of different sources of exposure resulting from the use of different consumer products such as e.g. an antioxidant component.
- Involvement of different routes of exposure e.g. the uptake of a component in sunscreen in a young child by different routes.
- Simultaneous exposures involving different chemical substances, which may show non-additive interactions in metabolic pathways, e.g. interference of a component in a consumer with a commonly prescribed medical drug (Campbell et al., 1987).

- Integration of two or more of the above mentioned exposure scenarios

II-1.3.5.4 Risk characterization

If a quantitative relationship between the level of a biomarker of exposure and the probability of an adverse biological effect is known, the biomarker level can provide an estimate of the risk at group level (Manno et al. 2010). In this context, biomonitoring reveals specific otherwise inaccessible components of risk such as polymorphism in metabolic enzymes, induction and inhibition of metabolic pathways by co-exposures to chemical substances that use the same (iso)enzymes (Hansen et al., 2004).

II-1.4 Preparation of a study protocol

II-1.4.1 *Study designs*

The design of the study depends on the type of research question(s) that need to be answered. In the following different study designs are discussed in the light of the research question to be answered.

II-1.4.1.1 Observational studies

An observational design is suitable to study the use of consumer products on a population level. In contrast to the lab-based experimental situation a field study in a real life setting is much more challenging because of the many variables that will influence the exposure (Boogaard et al., 2011). To describe this complex exposure setting a reasonably large number of human subjects should participate. Depending on the aim of the study it may be useful to perform statistical power analysis to determine the required size of the study population..

If the study results should be translated to the general population, random selection of the study subjects from this population is required. In contrast, the researcher may also determine the constitution of a study population, e.g. based on prior knowledge on the influence of characteristics believed to be relevant. Such a design is called a panel-study and may relate to a subgroup from the general population such as pregnant women exposed to consumer products containing reproductive toxic ingredients.

Depending on the aim of the study in addition to the biomonitoring data, additional information should be collected to describe the exposure conditions. These data constitute contextual information, which is important for the interpretation of the biomarker levels in the light of the research question.

For the sake of simplicity two distinct designs will be discussed: a cross-sectional study and a prospective study. The first design can be used to address a specific well-described exposure situation such as the use of one or more products across a well-defined (potentially large) study population and in a well-defined period of time (e.g. a day). The number of biological samples may be limited to one pre-exposure and one post-exposure or even be limited to a single measurement (post-exposure). In a prospective study each of the participants is followed over time (day, week, month, year) to collect more detailed information on the use of one or more products. Usually this design is applied to study a small number of participants, perhaps a specific and relevant target population. It is also possible to combine both designs, but this will lead to a potentially very large-scale study. To avoid such a large research effort, a prospective study can be performed in (only) a selection of the participants of a cross-sectional study. Alternatively, a prospective study could also be extended by involving additional study participants (e.g. a control group), from which exposure data are collected at a well-defined moment in time. This is a so-called nested study design. Another refinement of a prospective observational study is a cross over design. In this design two well-defined exposure scenarios are compared, e.g. an intervention scenario (A) is compared to a reference scenario (B, 'no intervention'). The study participants are randomly assigned in two study groups. In one of the groups scenario A is followed by scenario B. In the other group the sequence is reversed (scenario B is followed by scenario A).

II-1.4.1.2 Experimental studies

In an experimental setting such as a clinical lab study, a regulatory preventive study or a risk assessment-oriented study, biomonitoring can be used to validate a new biomarker method by determining the toxicokinetics following exposure to a chemical substance and one or more biomarkers in human subjects. The most suitable study design is a prospective study, following a volunteer during three periods: pre-exposure, during exposure and post-exposure. During the pre-exposure period a baseline is established. During the administration of a chemical substance the kinetics of uptake can be monitored, usually until a steady state is reached. After cessation of exposure the pattern of elimination is determined. An experimental setting allows standardization of many study parameters such as the administered dose, uptake route and the duration of the exposure, level of physical activity during each of the aforementioned phases, control of the environment and follow-up period following the end of exposure.

A prospective lab-based study allows the collection of repeated samples. This considerably increases the statistical power of a study, reducing the need to involve many human subjects in such a study. If the study population is small it is important to consider which inclusion and exclusion criteria should be used (see 4.3) and how the most important independent personal characteristics such as gender and age are distributed within the study population.

II-1.4.2 *Selection of the most suitable biomarker*

This guideline is limited to biomarkers of exposure but the use of a biomarker will determine whether it is useful to estimate exposure rather than the intrinsic properties (Watson and Mutti, 2004). There are several different perspectives which can be used to select a biomarker: the relationship with a health effect, accessibility of biological tissues, chemical persistence of the biomarker, life span of a binding product to a macromolecule, sensitivity of analysis, et cetera. In Figure 2 this issue is illustrated using benzene as an example.

II-1.4.2.1 Relationship with health effect

A biomarker may be equivalent to the chemical substance of interest. If exposure is the primary interest this may be a good choice as long as the role of the parent substance in the occurrence of health effects is known. If not the parent substance but a product of biotransformation is known to be the (more) relevant marker for health effect, this may be a reason to consider use of a product of biotransformation as the preferred biomarker of exposure.

II-1.4.2.2 Accessibility of biological tissues

In an experimental study performed in a laboratory with volunteers, there are many options to collect tissues as long as ethics are well balanced with the aim of the study. If the study duration is not too long virtually all accessible tissues are acceptable. In an observational study there may be more limitations as to the availability and accessibility of biological materials for determination of biomarker levels, especially if repeated collection of such materials is desired. Exhaled air, saliva, urine and hair are tissues, which can be collected without much problems for the participants. Only if the researchers would like the study subjects to perform collection of these materials by themselves there may be limitations to the possibility to train and motivate the study participants to perform these collections repeatedly and also keep a written administration of the times and conditions of sample collection. In healthy subjects, there may also be limitations to the type of biological tissues

collected. This may be the case for collection of blood samples especially if sample collection is repeated. The collection method may comparatively be too high a burden and also a risk for potential infection. Repeated blood sampling is difficult without good motivation towards the study participant and the ethics committee. It may be appropriate to consider placing a venal cannula, from which repeated blood samples can safely be collected without unacceptable burden and infection risk for the study participants.

II-1.4.2.3 Sensitivity of analytical methods

The possibility to determine a low level of a biomarker in a biological fluid is not only dependent on the detection limit of the analytical instrument used, but also on the volume of the sample, possible enrichment and clean-up steps during sample pre-treatment, sample properties, separation of the analyte of interest from other components in the sample (not removed during pre-treatment), et cetera. The ability to detect a biomarker is represented by the limit of detection or the limit of determination, abbreviated as LOD. Below this value it is not possible to confirm the presence of the biomarker and the result of the analysis is usually reported as ‘not detected (ND)’ or (better) ‘below the limit of detection (< LOD)’. Even if the biomarker can be detected it is not always possible to report a concentration with sufficient reliability because the precision at a concentration level close to the LOD may be unacceptable. The precision is expressed as the coefficient of variation (CV) or relative standard deviation (RSD), which is determined in a series of duplicate analysis of real life samples or matrix-mixed standards (Pocklington, 2009). Normally the uncertainty increases with a lower reported value for the biomarker level, resulting in a higher RSD (Scheepers, 2009; Allison et al., 2000). It is difficult to provide general limits of acceptance for a RSD or CV value because this also depends on the aim of the study. Criteria for an acceptable CV are dependent on the concentration level (Pocklington, 1990). As a rule of thumb the limit of quantification (LOQ) is twofold the LOD.

II-1.4.2.4 Half-life of excretion

For making a planning for sample collection, toxicokinetic data of the chemical of interest can be used to estimate the time interval between the end of an exposure (period) and the time point when the biomarker level has decreased to below the LOQ of the analytical method. A simple algorithm can be used for the calculation of this time interval for collecting biological materials. When the biomarker follows first order kinetics, the biomarker concentration (C_t) at any time-point after cessation of the exposure (t) can be calculated as

$$C_t = \frac{C_e}{2^{\frac{t_s}{t_{0.5}}}} \quad (1)$$

in which C_e is the concentration of the biomarker at the end of the exposure (estimated by e.g. dispersion modelling), $t_{0.5}$ is the half-life of this parameter in hours and t_s is the time (in hours) that has elapsed between the end of the exposure at the chemical incident location and the time when the biomarker level is expected to reach C_t. For C_t ~ LOQ, equation 1 can be rewritten to

$$t_s = t_{0.5} \cdot log_2(\frac{C_e}{LOQ}) \quad (2)$$

Equation 2 shows that reducing the LOQ for the analysis of the biomarker will increase the time available to collect the biological materials, if LOQ<<C_e. For biomarkers that follow zero order elimination (such as haemoglobin adducts) this equation can be simplified to

$$t_s \cong 2 \cdot t_{0.5} \quad (3)$$

II-1.4.3 *Inclusion and exclusion criteria for participation*

Before the recruitment of study participants, the researchers should prepare a list of desired characteristics i.e. inclusion criteria, which are coherent with the aim of the study. Exclusion criteria describe the characteristics of individual subjects for which the researcher anticipates potential problems for the safety of the participant. This may also lead to discontinuation of the participation, which is not in the interest of the researcher either. The inclusion and exclusion criteria, which were defined a priori should be included in the study report.

II-1.4.4 *Blinding and randomization*

When performing a lab-based study it is recommended to randomize the participants within the planned testing program to avoid dependence of the finding on the timing and sequence of experiments. If groups are compared, the human subjects should be randomly assigned to each of the groups. In an experimental setting blinding can be applied as a measure to prevent observer's bias. Blinding can be full double blinding, e.g. in the case of comparing two different products (of which one may be a placebo). Single blinding may be a useful strategy to prevent bias in laboratory personnel who have a role in the analysis of the biomarkers.

II-1.4.5 *Collection of contextual information*

For the interpretation of the outcome of a biological monitoring study information should be collected to describe the exposure conditions.

II-1.4.5.1 General person characteristics

Some general characteristics of persons such as age and date and place of birth are already collected during the recruitment phase. A questionnaire can be used to collect more characteristics that can be used to describe the study population.

II-1.4.5.2 Use of consumer products

Data on the type of products that are used and information on how these products are used can be collected by questionnaire or by interview (or both).

II-1.4.5.3 Life style factors

In addition to general personal characteristics it is useful to collect data on several lifestyle factors that may modify the biomarker levels or are of general interest to interpretation of the biomonitoring outcome. Most used life style factors are related to diet (food components or contaminant which may explain elevated biomarker levels such as consumption of seafood in the determination of urinary total arsenic). Related to the dietary pattern is the use of alcoholic beverages. Alcohol consumption may affect induction of liver enzymes or lead to competitive inhibition such as CYP2E1 (Van Rooij et al., 1994). The smoking status and smoking history is often used for stratification of smokers and non-smokers. Current smoking may also be verified by analysing urinary cotinine.

II-1.4.5.4 Medication

The use of prescribed and non-prescribed medication is also recorded, even if there is no a priori knowledge on metabolic interactions. Interactions of medication use with attenuated biomarker levels have been described (Campbell et al., 1987).

II-1.4.5.5 Sample collection information

During a biomonitoring campaign study participants can be asked to keep record of the dates and times of collection of urine and exhaled air samples. This information is important if the

timing of sample collection is not standardized. In addition to collection of information on sampling also other information can be collected such as the use of certain products, changes in ventilation by opening of windows, et cetera. For such information a diary can be used.

II-1.5 Obtaining approval from the ethics committee

If an exposure study is planned and the use of biomonitoring is involved it is important to consider the possible need of ethical approval of the study protocol. Ethical approval of a biological monitoring campaign may not be required if the consumer has direct personal benefit of the result of such a study. Such benefits may be similar to workers (Manno et al., 2010):

- Possible relationship with a health effect or disease that can be avoided or treated such as e.g. exposure to a chemical substance, to which an individual may be sensitized or for which an individual may have a higher sensitivity
- Estimate of past exposure that can be used in risk communication about the determination of a medical intervention such as metals that leached from a metal-on-metal hip prosthesis or silicones that leached from a breast implant.

II-1.6 Recruitment of participants

For recruitment of the participants short announcements can be made public to invite individuals to participate. Concise information should be provided such as the purpose of the study, inclusion and exclusion criteria for potential participants and complete information about what the participants are asked to invest in terms of time and effort.

Table II: 1-1. Information to be relayed to study participants prior to their participation in a biomonitoring campaign (from Scheepers, 2009).

Subject	Contents
Purpose	The purpose of the study should be clearly stated.
Parameters	The parameters that will be investigated should be specified and the relationship of these parameters with the goal of the study should be clarified.
Role of participants	The role of the participants should be made clear, specifying in detail when and how samples will be collected, how and when questionnaires will be completed and what other requests are made to the participants. It should be made clear that participation is on a voluntary basis.
Privacy	Clarify how the privacy of the participants will be protected during and after the study. Will the data collection be anonymous and who will keep the biological samples and the data and for what period of time? Also restrictions and procedures for future use of biological samples or data (by third parties) should be described.
Recruitment	The procedure for recruitment of participants should be explained (e.g. the use of inclusion/exclusion criteria) and the informed consent procedure should be explained.
Results	The moment and the way of presenting the study outcome to the participants should be made clear. It is important to inform the participants of any plans to disseminate the information to health authorities or to the scientific community or by uploading the data into a specific computer database.
Compensation	It should be made clear to what extent participants will be compensated for efforts and expenses.
Financial support	It should be stated how the study is financially supported and which parties are involved.
Contact	Names and contact information of the study coordinator(s).

II-1.6.1 *Introduction of the study*

It is suggested to introduce the study personally to each potential participant and also supply information in writing. In some cases it may be possible to introduce the study to a group e.g. during an announced meeting. In Table II: 1-1 the information that needs to be provided to potential participants during an initial introductory meeting is specified.

II-1.6.2 *Informed consent procedure*

A decision about participation should not be part of the initial meeting when the study is introduced. The invited subjects should be given time to consider their decision to participate and make their decision known preferable during a follow-up visit or by returning a signed informed consent form to the researcher. This form should contain the information provided in Table II: 1-2. However, in the meantime the potential participant should have the possibility to ask questions about the information that was provided during the introduction of the study. Because of the possibly personal nature of the questions, the participants should have direct access to the researcher to discuss these issues.

Table II: 1-2. Minimum requirement for items included in the informed consent form.

Subject	**Content**
General	Study title and study period.
Objectives	The purpose of the study should be clearly stated.
Biological tissues	The biological tissues, which will be collected, should be described.
Parameters	A description of the biomarkers and other study parameters should be provided.
Withdrawal	It should be clearly stated that even after signing the informed consent form the study, participants have the right to withdraw from participation at any moment and without reason.
Compensation	It should be made clear to what extent participants will be compensated for efforts and expenses.
Protection of privacy	Information should be provided on what information is kept by the researcher and how long this information will be kept and who has access to information that identifies the study participants.
Dates and signatures	The supervising researcher should write the date on the form and sign. The participant is also asked to write the date on the form and sign.

II-1.6.3 *Protecting privacy of participants*

As soon as the recruitment process is completed the researcher assigns a person code to each of the individual participants. This code may not contain any personal information such as gender or birth date. The list of names and person codes is kept by the study coordinator or any other person. Their identities have to be revealed to the study participants. The list with person codes may not be provided to any third parties and be kept in a secure place. Sometimes it is required to destroy the list that links the person code to a study participant after the study is completed.

II-1.7 Collection, pre-treatment and storage of biological samples

Most types of biological tissues need some kind of pre-treatment or preparation before long-term storage. This depends on the type of biological tissue and the properties of the biomarker. The requirement for the most used media will be discussed below.

II-1.7.1 *Exhaled air*

In exhaled air the gas-phase is the most used fraction for the determination of biomarkers present in the gas or vapour phase. These are often chemical substances that have exhaled air as the primary route of elimination, not only after inhalation but also following dermal uptake. Collection of the gas-phase of exhaled air is a suitable approach for simultaneous determination of concentrations of multiple volatile compounds and metallic mercury (Manno et al., 2010). For gases and vapours it is recommended to collect the last part of a complete exhalation, called ‘end-exhaled air’. This so-called alveolar air volume reaches the part of the lungs where gas exchange with blood occurs. The biomarkers present in this air volume have momentarily equilibrated with blood, a process, which is ruled by blood-air partitioning. The biomarker concentration in alveolar air thus reflects the arterial blood concentration as an approximation of the biomarker level in arterial blood that is supplied to the brain. If the central nervous system is the critical target organ, the alveolar concentration is proportional to the target dose, provided that the parent substance (and not the metabolite) is involved as the toxicant.

For the collection of end-exhaled air different materials can be used. Good results were reported by Dyne and co-workers (1997) with a device called BioVOC. For mixed exhaled air, bags made of the plastic Tedlar are commonly used.

For studies on consumer exposure biomarkers in exhaled air may be attractive because of the non-invasiveness of the method of sample collection (Scheepers and Heussen, 2002; Scheepers, 2009). Most organic biomarkers excreted via the lungs also have fast kinetics, which provides an opportunity to study pre- and post-exposure levels of the biomarker in connection to a realistic use scenario. The simplicity and low-burden type of sample collection also allows possible repeats in sample collection, which are not possible for urine (which cannot be repeated within short periods of time) or blood (which would be difficult to defend as a method of sample collection in healthy subjects in ethical approval). Exhaled air is an attractive non-invasive approach, which is simple and can be used also in children (Scheepers et al., 2009).

As an alternative an exhaled air condensate can also be collected for the determination of water-soluble biomarkers with a low volatility such as metal ions (Mutti and Corrado, 2006).

II-1.7.1.1 Pre-treatment

Before long-term storage it is advised to transfer biomarkers in the gas phase of breath preferably within a few hours to a solid sorbent to prevent losses due to diffusion, surface adsorption or reactivity of the biomarkers.

II-1.7.1.2 Storage

Because of the low concentrations of biomarkers in an exhaled air sample the ambient environment may be a source of contamination. Keeping exhaled air samples in a clean (office) environment is recommended, compared to storage in a laboratory environment. Since caps of adsorbent tubes are generally not guaranteed to be airtight it is recommended to store adsorbent tubes in double gastight sealed bags (Scheepers et al., 2009). For evaluation some clean tubes or tubes with selected standards may be stored alongside the sample tubes to verify how storage conditions may have affected the samples.

II-1.7.2 *Urine*

Water soluble parent substances and also metabolites may be excreted via urine. Also volatile organic compounds may be retrieved from urine, including substances with poor water solubility. An intrinsic property of a urinary biomarker is that it reflects the excretion over a time interval equivalent to the interval of formation and storage of urine in the bladder. For the planning of the sample collection it has to be recalled that urine samples cannot be collected at random. For adults a normal volume of urine over 24 h is 1.5-2.0 L, which is produced in different aliquots during the day. The most concentrated urine sample is produced in the morning after awakening. This is also a good time point for standardization regarding the influence of the circadian rhythm on biomarker levels. For biomarkers with a short excretion half-life this portion can be used to determine a pre-exposure baseline for most consumer products. Repeated urine collection is most useful when performing laboratory-based studies with volunteers. Collection of all urine aliquots during a day (a so-called 24 hour urine sample) may be used to study the kinetics of urinary excretion of the parent substance and of metabolites. For a study carried out among consumers it is hardly feasible to collect 24 h urine. In some cases for biomarkers with fast kinetics pre- and post-exposure spot samples may be collected if a researcher is interested to study the uptake of a

well-defined exposure event. This strategy may be also feasible if consumers are involved as part of a field study.

II-1.7.3 *Blood*

Blood is often used for the determination of biomarkers, but in studies with consumers it is not first choice because it is an invasive method that cannot be repeated without explicit approval from the ethics committee and cooperation of the study subject. However, there are some specific biomarkers that require the collection of blood samples such as biomarkers in blood plasma (butyrylcholinesterase activity, bromide, dioxin, hexachloromenzene, molybdene, lindane, hydrazine, pentachlorophenol, polychlorinated biphenyls) or serum (aluminum, thiocyanate) or erythrocytes (e.g. hexavalent chromium, aceylcholinesterase activity, hemoglobin adducts, etc.). For most other chemical substances there are good alternatives in urine or (end-)exhaled air.

II-1.7.4 *Other tissues*

Other less or non-invasive methods of sample collection include the use of buccal smears, saliva and hair. Buccal smears and saliva are mostly used to obtain mRNA or DNA for genotyping. Hair is sometimes used to determine exposure to metals (Marsh et al., 1987). More recently the determination of organic compounds in hair was also described (Mercadante et al. 2012).

II-1.8 Sending and storage of biological tissues

The materials that are used for sample collection may not be suitable for storage or sending (see Table II: 1-3). Regulations for international shipments have become stricter over the past few decades and require a lot of paper-work.

Since there are weight- and volume limitations per parcel it can be efficient to reduce the volume of the samples and the weight and volume of the materials used. Due to the use of new materials (no more need of glass), breakage risk is not an issue any more. Below these issues are discussed for blood, urine and exhaled air.

For the analysis of blood samples fractionation is usually required at some point. If fractionation is critical it is recommended to isolate the required fraction one the same day. If stored at 4 °C, pre-treatment may be postponed to the next day. If stored more than 24 h there may be some quality loss, e.g. some cell components may start to leak into plasma.

For urine samples a usual practice is to ask the study subjects to collect an aliquot of a few hundred millilitres in a labelled plastic jar with a screw cap. It is recommended to thoroughly mix and redistribute this volume in smaller portions before cooling or freezing. This allows taking an aliquot corresponding to the volume required for each analysis from the well-homogenized sample and transfer this to smaller tubes (one for each analysis). At this stage, it is possible to add a preservative and also take the precaution not to overfill the tubes if they will be frozen at a later stage or already during transportation. For some metabolites it is recommended to capture the metabolite of interest on a solid phase (e.g. when the metabolite tends to be chemically unstable or is highly volatile).

Repacking the biological samples also allows to re-label the sample using a more efficient and reliable method like use of a chip, barcode or engraving because some labels might come off during storage.

Table II: 1-3. Materials recommended for the collection, sending and storage of biological materials.

Type of biological material	For collection	For shipment	Pre-treatment	Storage	Additional precautions
Blood	Vacuum tube with anticoagulant	Cryotube with relevant blood fraction	Isolation of the required fraction from full blood	Frozen at -4 or -18 °C	Addition of an internal standard or inclusion of a matrix-mixed standard
Urine	250 mL bottle with screw cap	Tube with screw cap with small volume of urine required for analysis	Homogenization and addition of a preservative	Frozen at -4 or -18 °C	Addition of an internal standard or inclusion of a matrix-mixed standard
Exhaled air	Bio-VOC container or similar	Sorbent tube	None	At ambient temperature in clean office environment in sealed plastic bag	Include a blank sample and a sorbent tube with a known quantity of the substance of interest

Exhaled air samples have a limited integrity since chemical substances may be lost from the container used for collection, or surface absorption and/or chemical conversions may occur. Components in exhaled air can be transferred to a suitable solid sorbent immediately after collection. For this purpose a solid sorbent is often used. Since the gas tightness of most tube caps cannot be guaranteed it is recommended to use sealable plastic bags during shipment and storage. This will prevent losses but also possible contamination from the ambient environment.

There are some precautions that can be taken to prevent problems with the integrity/quality of the samples during sending and/or storage. The most important precautions are cooling or freezing of samples during transportation using cold pack or dry ice, respectively. In some cases, addition of a preservative is possible instead of cooling. For urine, adding an inorganic acid solution, such as analytical quality hydrochloric acid, can be an effective precaution to prevent growth of microorganisms in the sample. The use of other preservatives (e.g. azides) is not recommended because of the health hazard of these chemicals.

For quality assurance during sending and storage it is recommended to consider addition of an internal standard (i.e. a deuterated structure analogue) to the samples before shipment/storage. An alternative is to store standards with a known biomarker concentration together with the samples, preferably matrix-mixed standards.

II-1.9 Analysis of biomarkers

The entire set of samples is provided to the laboratory preferably in one batch, including possible reference standards and blanks. The samples have codes that do not reveal information about the identity of the study subjects or any information relating to specific groups of participants or exposure situations. For analyses with a tight range of calibration it may be useful to report the anticipated range of biomarker levels for different subsets of samples to prevent problems with outliers. The laboratory completes the analysis and reports raw data including information about the method of analysis (recovery during pre-treatment and extraction procedures), accuracy and calibration.

II-1.10 Validity and quality assurance

The validity of a biomarker measurement depends on the sensitivity and specificity of the method. The sensitivity is the ability to avoid false negative results, which is of particular value in risk assessment settings. The specificity is defined as the capability to avoid false positive results and may be more relevant if the biomonitoring is followed by medical treatment. The performance of a biomarker method can be expressed using a receiver operator curve (ROC). The performance of laboratories engaged in the analysis of biomarkers can be evaluated in external quality assurance programs.

II-1.11 Adjustments and calculations

Based on the raw data the researcher decides on how the data are treated for data analysis (Table II: 1-4). A decision should be taken how many digits are presented in the final report of a biomarker level (Allison et al., 2000). Some biomarkers may be normalized, such as by using the creatinine concentration for adjustment for for the density of urine (Garde et al., 2004). The preferred units for reporting biomarker levels adjusted for creatinine is µmol/mol of creatinine.

Table II: 1-4. Preferred units for reporting of biomarker levels.

Biological medium	**Raw data**	**Adjusted**
Free organic substance in urine	µmol per litre of sample	µmol per mol creatinine
Haemoglobin adducts	µmol per litre of haemoglobin solution	µmol per g of globin
Dioxin in serum	nmol per litre of serum	nmol per gram of serum fat

II-1.12 Data analysis and interpretation

The interpretation of the outcome of a biomonitoring study is usually not straightforward. Specifically in the case of consumer exposure the interpretation of biomarker levels may be complicated because of the complex exposure situation involving different sources of exposures and different frequencies in use of products (Boogaard et al., 2005; Boogaard and Money, 2008). As any result of measurement shows variability, biomarker levels will show variability within a person and between persons. In part this variability may not be explainable and show a random pattern. In another part this variability may also be an intrinsic property of the system. When interpreting biomonitoring data it is important to consider this variability as a potential source of information since many sources of variability may represent known or unknown parameters that may be related to the probability of health effects (Manini et al., 2007).

II-1.12.1 *Baseline excretion*

For some biomarkers the baseline excretion level is below the LOQ and some chemical substances may not be taken up by consumers. However, if chemical substances are studied, which are ubiquitous in the environment, uptake is likely and a baseline level above the LOQ is to be expected (provided that sufficiently sensitive methods are being used). For such chemical substances the baseline should be characterized for the population of interest and (ideally) for each individual who participates in a biomonitoring study. If the sources of a baseline exposure are known it is possible to determine at which moment in time the baseline level for each individual can be estimated. For example if there is uptake from the diet a sample for characterization can be collected directly after awakening and before the first meal. For consumer products used during the day, characterization of a baseline early in the morning after awakening could be suitable if the excretion half-life of the biomarker is such that a past exposure (e.g. of the previous day) is negligible. This may be the case, e.g. for a VOC which does not accumulate in adipose tissue and can be measured in exhaled air.

II-1.12.2 *Co-exposures and interferences*

For most biomarkers co-exposures and interferences are described in published biomonitoring studies. Below the most important factors to consider in consumer studies will be discussed.

II-1.12.2.1 Age

Stratified analysis of different age groups in large-scale biomarker studies in the general population indicated the contribution of age as a direct or indirect modifying factor in levels of most biomarkers (CDC, 2008; GerES, 2008). An obvious interference of age with a biomarker level is the accumulation of a persistent lipophilic biomarker during life (e.g. the pesticide DDT). Especially when comparing groups within the general population it is important to consider defining age criteria as inclusion/exclusion criteria for different subgroups of interest and also use age as an independent variable for stratification during data analysis.

II-1.12.2.2 Gender

Gender-based differences in activity patterns and differences in choice and usage of consumer products may be important reasons to perform studies in both male and female sub-populations, separately. It should be noted that gender and sex are also important covariates that may have a profound influence on the toxicokinetics of biomarkers. This can be based on genetic factors but also on environmental factors and their interactions. If a study involves both males and females it is recommended to decide in the planning stage of the study about the size of both sub-populations and perform a separate analysis of biomarker data in a subgroup analysis.

II-1.12.2.3 Smoking

The most studied co-exposure is active tobacco smoking. Tobacco smoke contains more than 5000 different chemical compounds. The ‘Hofmann-list’ identified 60 carcinogenic substances that were found in the main stream of tobacco smoke. In a recent literature review this list was updated and contains 98 entries of substances with a possible health risk (Talhout et al., 2011). In many biological monitoring studies smoking is considered to be an important covariate that may contribute to co-exposure or interfere with toxicokinetics of biomarkers (Van Rooij et al., 1994). In such cases study subjects are recruited from populations of smokers, non-smokers and of those subjects who stopped smoking recently.

II-1.12.2.4 Alcoholic beverages and use of drugs

Alcohol and drugs may have a profound influence on the toxicokinetics, in particular the metabolic fate of chemical substances and thus be a covariant to consider in the interpretation of biomonitoring studies. It is certainly worthwhile to perform a literature search

to identify any previously published reports on interference of use of alcoholic beverages or drug use with biomarkers. Even if there is no prior information to suspect any interference from use of alcohol or drugs it is recommended to ask study participants to report the use of these products before and during a biomonitoring study. A questionnaire or diary may include questions about the type, amount and time of use.

II-1.12.2.5 Medication

A questionnaire should be used to identify any use of prescribed and non-prescribed medical drugs. Based on a literature search it is possible to find out if the metabolic pathway of a certain drug may interfere with the metabolism of the chemical substance of interest. Medical drugs therapy may explain outliers and, if accurately recorded, could be the basis for discarding a single outlier from the study.

II-1.12.3 *Reference values*

Under REACH the most suitable reference value for consumer exposure is the derived no effect level (DNEL), defined as the level of a substance above which a human should not be exposed (EC, 2006). Hayes et al. (2007) introduced the concept of the biological equivalent (BE), which translates the DNEL or any other reference value that is defined as an internal dose, into a biomarker concentration. This is done by using the available toxicokinetic data of the substance to predict a steady state concentration of a biomarker, given the DNEL of the parent substance. A biological equivalent (BE) was defined by Hays and co-workers (2008) as *'the concentration or range of concentrations of chemical in a biological medium (…) that is consistent with an existing health-based exposure guidance value (…)'*. For consumers BEs are intended as screening values to allow interpretation of biomonitoring data. They are meant as a screening tool to determine the margin of safety of chemicals as large, small or none (Krishnan et al., 2010). For consumer exposures it would be appropriate to derive a BE at a steady-state dose, i.e. a biomarker level that is consistent with the reference dose as a day-average in mg/kg-day. This reference dose may be an RfD (USEPA) or an ADI (WHO).

A BE can be derived if the following information is available (Boogaard et al., 2011):

- A reliable biomonitoring method with sufficient specificity and sensitivity;
- A DNEL or another reliable reference value such as an occupational exposure level, acceptable daily intake (ADI), reference dose (RfD) or another value as long as it is health-based;

- Sufficient substance-specific data to allow toxicokinetic modelling or other calculations to extrapolate the biomarker concentration corresponding to the reference value, using e.g. available human or animal data.

BEs were already derived for acrylamide (Hays and Aylward, 2008), cadmium (Hays et al., 2008), triclosan (Krishnan et al. 2010) and di-isononyl phthalate (Hays et al. 2011).

II-1.13 Communication of results

Lakind and co-workers (2008) introduced a system for communicating the results of biomonitoring studies to the general public, based on the use of BEs. In communication about results obtained during a biomarker study the same principles apply as in any other risk assessment study. Important principles to consider are transparency and to address issues of confidence and uncertainty in the interpretation of the study outcome on a group basis but also in individual cases (Lakind et al. 2008). It is also important to realize that the analysis of body fluids may be perceived by the study subject to result in an interpretation of an individual's health status in terms of present or future health effect, even if there is only a direct link to exposure characterization. Even if this is communicated explicitly in advance of sample collection, participants of a biomonitoring study will have questions about the relationship between the biomarker outcome and their (future) health.

II-1.14 References

Boogaard PJ. Biomonitoring as a tool in the human health risk characterization of dermal exposure. Hum Exp Toxicol. 2008 Apr;27(4):297-305.

Boogaard PJ, Hays SM, Aylward LL. Human biomonitoring as a pragmatic tool to support health risk management of chemicals--examples under the EU REACH programme. Regul Toxicol Pharmacol. 2011 Feb;59(1):125-32. Epub 2010 Oct 7.

Boogaard PJ, Money CD. A proposed framework for the interpretation of biomonitoring data. Environ Health. 2008 Jun 5;7 Suppl 1:S12.

Campbell L, Marsh DM, Wilson HK. (1987) Towards a biological monitoring strategy for toluene. Ann Occup Hyg 31:121-133.

Dyne D, Cocker J, Wilson HK. A novel device for capturing breath samples for solvent analysis. Sci Total Environ. 1997 Jun 20;199(1-2):83-9.

Eggens ML, Bos PMJ, Grievink L, Nijhuis NJ, Scheepers PTJ, van de Weerdt DHJ, Wientjes AD, van der Woude I, van Brederode NE (2012) GGD-richtlijn medische milieukunde. Biomonitoring bij kleinschalige (chemische) incidenten. RIVM report 60930023/2012.

Ellison SLR, Rosslein M, Williams A (2000) EURACHEM/CITAC Guide. Quantifying uncertainty in analytical measurement. Second Edition, 126 pp.

Garde AH, Hansen AM, Kristiansen J, Knudsen LE. Comparison of uncertainties related to standardization of urine samples with volume and creatinine concentration. Ann Occup Hyg. 2004 Mar;48(2):171-9.

Hansen AM, Wallin H, Binderup ML, Dybdahl M, Autrup H, Loft S, Knudsen LE Urinary 1-hydroxypyrene and mutagenicity in bus drivers and mail carriers exposed to urban air pollution in Denmark. Mutat Res. 2004 Jan 10;557(1):7-17.

Hays SM, Aylward LL, Kirman CR, Krishnan K, Nong A. Biomonitoring equivalents for di-isononyl phthalate (DINP). Regul Toxicol Pharmacol. 2011 Jul;60(2):181-8. Epub 2011 Apr 3.

Hukkelhoven MW, Bronkhorst AM, Vermorken AJ. Covalent binding of BP-metabolites to DNA of cultured human hair follicle keratinocytes. Arch Toxicol. 1985 Apr;57(1):6-12.

IUPAC (1997) Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford, United Kingdom

Joas R, Casteleyn L, Biot P, Kolossa-Gehring M, Castano A, Angerer J, Schoeters G, Sepai O, Knudsen LE, Joas A, Horvat M, Bloemen L. Harmonised human biomonitoring in Europe: activities towards an EU HBM framework.

Int J Hyg Environ Health. 2012 Feb;215(2):172-5. Epub 2011 Sep 21.

Kirman CR, Aylward LL, Blount BC, Pyatt DW, Hays SM.Evaluation of NHANES biomonitoring data for volatile organic chemicals in blood: application of chemical-specific screening criteria. J Expo Sci Environ Epidemiol. 2012 Jan-Feb;22(1):24-34.

Krishnan K, Gagné M, Nong A, Aylward LL, Hays SM. Biomonitoring Equivalents for triclosan. Regul Toxicol Pharmacol. 2010 Oct;58(1):10-7. Epub 2010 Jun 10. Review.

LaKind JS, Aylward LL, Brunk C, DiZio S, Dourson M, Goldstein DA, Kilpatrick ME, Krewski D, Bartels MJ, Barton HA, Boogaard PJ, Lipscomb J, Krishnan K, Nordberg M, Okino M, Tan YM, Viau C, Yager JW, Hays SM; Biomonitoring Equivalents Expert Workshop. Guidelines for the communication of Biomonitoring Equivalents: report from the Biomonitoring Equivalents Expert Workshop. Regul Toxicol Pharmacol. 2008 Aug;51(3 Suppl):S16-26. Epub 2008 May 22.

Latini, G, 2005. Monitoring phthalate exposure in humans. Clin. Chim. Acta 361, 20–29.

Manno M, Viau C. ISBM-7: Biological Monitoring in a Globalized World. Preface. Toxicol Lett. 2010 Jan 15;192(1):1-2. Epub 2009 Aug 13.

Manno M, Viau C; in collaboration with, Cocker J, Colosio C, Lowry L, Mutti A, Nordberg M, Wang S. Biomonitoring for occupational health risk assessment (BOHRA). Toxicol Lett. 2010 Jan 15;192(1):3-16. Epub 2009 May 13. Review.

Manini, P., De Palma, G., Mutti, A., 2007. Exposure assessment at the workplace: implications of biological variability. Toxicol. Lett. 168, 210–218.

Marsh DO, Clarkson TW, Cox C, Myers GJ, Amin-Zaki L, Al-Tikriti S. Fetal methylmercury poisoning. Relationship between concentration in single strands of maternal hair and child effects. Arch Neurol. 1987 Oct;44(10):1017-22.

Mercadante R, Polledri E, Giavini E, Menegola E, Bertazzi PA, Fustinoni S. Terbuthylazine in hair as a biomarker of exposure. Toxicol Lett. 2012 Apr 25;210(2):169-73. Epub 2011 Nov 28.

Müller M, Schmiechen K (2012) Humanbiomonitoring im Bevölkerungsschutz. Band 16. Bundesamt für Bevölkerungsschutz und Katasprophenhilfe, Bonn.

Mutti A, Corradi M. (2006) Recent developments in human biomonitoring: non-invasive assessment of target tissue dose and effects of pneumotoxic metals. Med Lav. 2006 Mar-Apr;97(2):199-206. Review.

Pocklington WD (1990) Harmonized protocols for the adoption of standardized analytical methods and for the presentation of their performance characteristics. Pure & Appl Chemi 62:149-162.

Polyzois I, Nikolopoulos D, Michos I, Patsouris E, Theocharis S. Local and systemic toxicity of nanoscale debris particles in total hip arthroplasty. J Appl Toxicol. 2012 Apr;32(4):255-69. doi: 10.1002/jat.2729. Epub 2012 Feb 10.

Scheepers PTJ and Heussen GAH (2002) Assessing health risk of toxic substances by analysis of body fluids and exhaled air. Trends Anal Chem 21:11-15.

Scheepers PTJ, Heussen GAH (2005) New and improved biomarkers ready to be used in health-risk oriented exposure and susceptibility assessments: report of the 6th International Symposium on Biological Monitoring in Occupational and Environmental Health. Biomarkers, 10:80-94.

Scheepers PTJ and Heussen GAH (2008) New applications of biological monitoring for environmental exposure and susceptibility monitoring. Report of the 7th International

Symposium on Biological Monitoring in Occupational and Environmental Health Biomarkers 13:133-144.

Scheepers PTJ (2008) The use of biomarkers for improved retrospective exposure assessment in epidemiological studies: summary of an ECETOC workshop. Biomarkers, 13:734-748.

Scheepers PTJ (2009) Biomarkers of Exposure to Carcinogens. In: Ballantyne B, Marrs T, Syversen T (eds) General and Applied Toxicology, 3rd edition, John Wiley and Sons, Chisester, UK., pp 1841-1855.

Scheepers PTJ (2011) The role of biomarkers in chemicals management. Trends Anal Chem 30:3, 415-421.

Scheepers PT, Bos PM, Konings J, Janssen NA, Grievink L. (2011) Application of biological monitoring for exposure assessment following chemical incidents: a procedure for decision making. J Expo Sci Environ Epidemiol. 2011 May-Jun;21(3):247-61. Epub 2010 Mar 24.

Scheepers PTJ, Beckmann G, Biesterbos J (2013) Biomarkers of environmental risk factors for prevention and research. Trends in Analytical Chemistry 52:275–281

Scheepers PTJ, Van Brederode NE, Bos PMJ, Nijhuis NJ, Van de Weerdt, Van der Woude I, Eggens ML (2014a) Human biological monitoring for exposure assessment in response to an incident involving hazardous materials. Toxicol. Lett. (accepted).

Scheepers, PTJ (2014b) Chemical disaster management and public health In: Armon R and Hänninen O Environmental indicators. Springer Verlag, Berlin (In press).

Scherer G, Renner T, Meger M (1998) Analysis and evaluation of trans,trans-muconic acid as a biomarker for benzene exposure. J Chromatogr 717:179-199.

Schulz C, Conrad A, Becker K, Kolossa-Gehring M, Seiwert M, Seifert B. Twenty years of the German Environmental Survey (GerES): human biomonitoring--temporal and spatial (West Germany/East Germany) differences in population exposure. Int J Hyg Environ Health. 2007 May;210(3-4):271-97. Epub 2007 Mar 7.

Talhout R, Schulz T, Florek E, van Benthem J, Wester P, Opperhuizen A. Hazardous compounds in tobacco smoke. Int J Environ Res Public Health. 2011 Feb;8(2):613-28. Epub 2011 Feb 23.

Van Rooij JGM, Veeger MMS, Bodelier Bade MM, Scheepers PTJ, Jongeneelen FJ (1994) Smoking and dietary intake of polycyclic aromatic hydrocarbons as sources of interindividual variability in the base line excretion of 1 hydroxypyrene in urine. Int Arch Occup Environ Hyg 66:55-65.

Watson WP, Mutti A. Role of biomarkers in monitoring exposures to chemicals: present position, future prospects. Biomarkers. 2004 May-Jun;9(3):211-42.

Zielhuis, RL, Henderson, PT, 1986. Definitions of monitoring activities and their relevance for the practice of occupational health. Int. Arch. Occup. Environ. Health 57, 249–257.

II-2. Volunteer study

II-2.1 Introduction

The aim of the volunteer study is to collect data regarding dermal exposure to octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5) after application of two different cosmetic and personal care products (C&PCPs) containing D4 and D5. The second aim is to investigate the population baseline monitoring levels from the normal use of C&PCPs containing D4 and D5 by measuring concentrations of both substances in end-exhaled air.

II-2.2 Methods

II-2.2.1 *Ethical approval*

The ethics committee CMO Regio Arnhem-Nijmegen has approved this study (registration number: 2011/131).

II-2.2.2 *Chemicals and test substances*

Octamethylcyclotetrasiloxane (98% D4; CAS 556-67-2) and decamethylcyclopentasiloxane (97% D5; CAS 541-02-6) were obtained from Sigma-Aldrich (St. Louis MO, United States). A commercially available night cream (50 mL) and a deodorant (40 mL) were purchased from an online pharmacy (*www.drogisterij.nl*). The night cream contains approximately 25% D5 and 0.3% D4. The deodorant contains approximately 30% D5 and 0.3% D4. Figure II: 2-1 shows the ingredient lists of both products. ^{13}C-labelled D4 and ^{13}C-labelled D5, used as an internal standard, were purchased from Dow Corning (Midland MI, United States).

Figure II: 2-1. Ingredients list of the used deodorant (A) and night cream (B).

II-2.2.3 *Study subjects*

We recruited 15 healthy volunteers via advertisements on bulletin boards. Ten female and five male volunteers were included. The participants were asked to refrain from the use of personal care products 24 hours before the start of each experiment. However, they were allowed to brush their teeth using toothpaste (Elmex anti-caries, 75 mL) provided by us. According to the ingredients list, this toothpaste was free of D4 and D5.

II-2.2.4 *Exposure protocol*

II-2.2.4.1 Baseline measurements

After recruitment and before the start of the exposure experiments, the volunteers completed a questionnaire and a 24-hour diary, which were used to assess their C&PCP usage pattern. During the first visit, a spot sample of end-exhaled air was collected to study their baseline excretion of D4 and D5.

II-2.2.4.2 Exposure experiments

Next, a series of five exposure experiments started in which the volunteers were dermally exposed to D4 and/or D5 in different media (Table II: 2-1). The experimental setup is described below. During the exposure experiments the setup remained the same. The only thing that changed was the vehicle of the applied substance.

Table II: 2-1. Overview of the exposure experiments and the applied substances and vehicles.

Experiment:	**Applied substance and vehicle:**
Baseline	-
1	D5 (pure substance)
2	Cream containing D4 and D5
3	Deodorant containing D4 and D5
4	Cream and deodorant (simultaneously)
5	D4 (pure substance)

The total administration period was one hour. Every ten minutes a dose of 2.5 mg D5 per cm^2 was applied to the forearm, leading to an intended total accumulated exposure of 15 mg D5 per cm^2 for each experiment. The exposed forearm areas of each volunteer are reported in Table 2.7. In order to prevent inhalation during exposure, the participant was sitting with

his or her forearm inside a flow cabinet (Figure II: 2-2 A). To monitor the ambient air concentration and possible inhalation during exposure, the subject carried a head-set (Fenix Environmental, Umeå, Sweden) with two sampling heads that were placed in the breathing zone slightly above the nose. The sampling heads were equipped with mini ATD tubes loaded with Tenax TA (Fenix Environmental, Umeå, Sweden). The measurements with the mini ATD tubes provided a time weighted average concentration of D5 in ambient air during the exposure and post exposure periods, respectively. After one hour, the exposure was terminated by removing the substance and washing the arm with water and soap inside the flow cabinet. To prevent inhalation of cyclosiloxanes from the ambient air after the end of exposure, a fume hood was placed over the head of the participant (Figure II: 2-2 B), which supplied a constant downstream flow of filtered air. The ‘fume hood’ was custom made, using a 3M Jupiter air stream device connected to a 3M Versaflo Headtop and equipped with two 3M A2BEKP R (organic gases & vapours, inorganic, acid gases, ammonia and particulates) filters (Biesheuvel Techniek, Wijchen, The Netherlands).

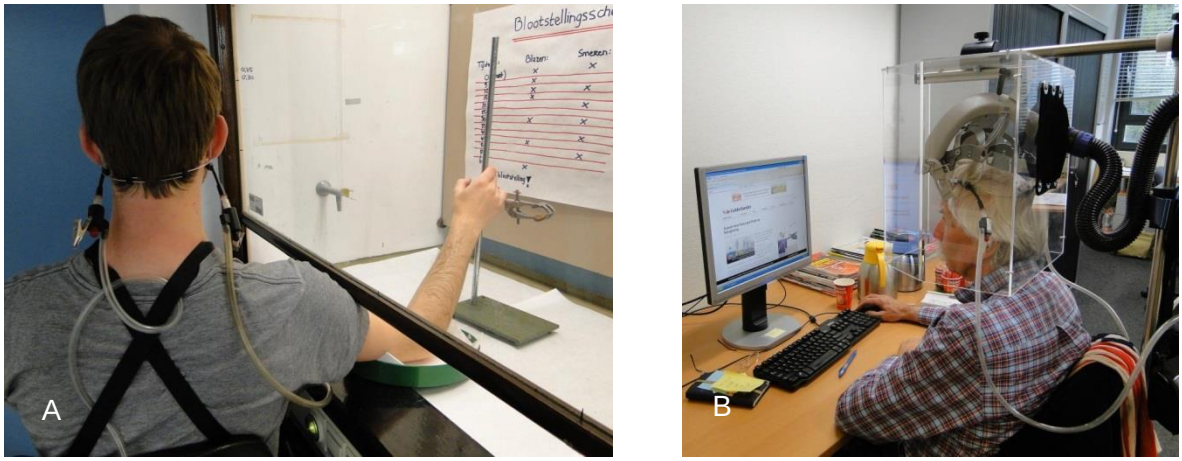


Figure II: 2-2. A: A participant with his lower arm inside the flow cabinet during administration. B: A participant after cessation of exposure with the fume hood placed over his head.

II-2.2.4.3 Control experiments

Before administering cyclosiloxanes or products to the skin of the study participants we performed three control experiments to study the contributions of background exposure. The experiments were performed as described above, but no substance was administered to the arm of the volunteer. Instead, D4 or D5 was applied on a ‘dummy’ arm, placed next to the arm of the volunteer (Figure II: 2-3).

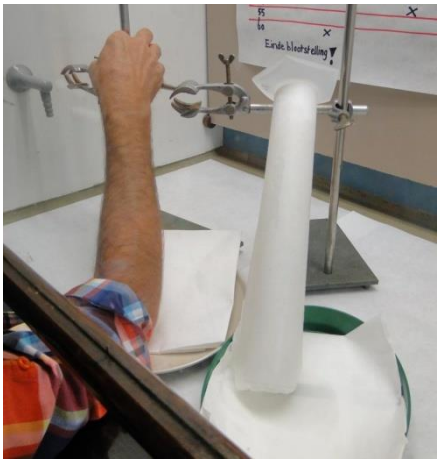


Figure II: 2-3. Set-up of the control experiment with the untreated forearm of the volunteer (L) and the dummy treated with an amount of D5 equivalent to the amount used during the exposures (R).

II-2.2.4.4 Exposure experiments without the prevention of inhalation

Finally we conducted three exposure experiments without the prevention of inhalation, as the results of the previous experiments showed that inhalation instead of dermal uptake was the most important route of exposure. A volunteer was seated inside a toilet area of approximately 9 m^3 (Figure II: 2-4). Four grams of night cream were applied to the forearm of the volunteer. After five minutes the cream was removed and the arm washed with water and soap. The volunteers remained seated in the toilet area for another ten minutes. At the end of these ten minutes inhalation exposure was terminated by having the volunteer exit the toilet area. The volunteer was then placed underneath the fume hood and seated behind a desk.

Figure II: 2-4. A participant seated inside the toilet area.

II-2.2.5 *Sample collection*

Before, during and after exposure end-exhaled air was collected at predetermined intervals (Figure II: 2-5).

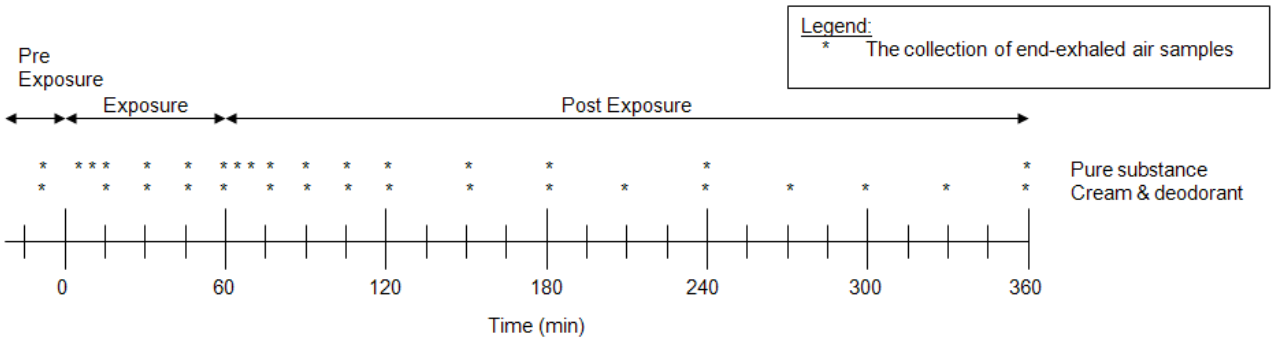


Figure II: 2-5. Overview of the time points used for the collection of end-exhaled air samples.

The participants were asked to exhale completely in a disposable cardboard mouthpiece that was fitted to a 141.5 mL Bio-VOC container (Markes International, Llantrisant, United Kingdom). In total, 17 end-exhaled air samples were collected in duplicate, resulting in a total of 34 samples per person per experiment. Immediately after collection of the sample the organic compounds were transferred to a 1/4" x 3.5" Stainless Steel tube filled with Carbograph 2TD 60/80 and Carbograph 1 TD 60/80 (CAMSCO, Houston TX, United States).

II-2.2.6 *Sample analysis*

We prepared an internal standard solution of 5 ng/µL ^{13}C-labelled D4/D5 in methanol. Prior to analysis, 2.5 ng ^{13}C-labelled D4 /D5 (0.5 µL) was loaded on the ATD tubes using a loading rig (Markes International, Llantrisant, United Kingdom). The ATD tube was connected to the loading rig, the internal standard solution injected by a syringe and the tube finally flushed with helium 5.0 (Linde Gas, Schiedam, The Netherlands) at a flow of 50 mL/min for three minutes to remove the methanol.

The samples were analysed using thermal desorption gas chromatography mass spectrometry (TD-GC-MS). The analytical instrument consisted of a thermal desorption unit and an auto sampler (Unity 2 and Ultra 2, Markes) coupled to a gas chromatograph mass spectrometer (Focus and ISQ, Thermo) using electron ionization (EI). The ATD tubes were

positioned in the auto sampler and subsequently desorbed at 275 °C for 15 minutes. The analytical column was a 30 m Rxi-5 MS, (0.25 mm i.d., 0.5 µm film thickness, Restek). The carrier gas was helium 5.0. The GC oven temperature was 50 °C; hold 5 min; 10 °C/min to 150 °C; 30 °C/min to 250 °C, hold 2 min. The transfer line was kept at 250 °C and the ion source at 250 °C. The ions monitored were *m/z* 281 for D4, 355 for D5, 285 for ^{13}C-labelled D4 and 360 for ^{13}C-labelled D5, respectively. The dwell time was 0.4 sec.

The limit of quantification (LOQ) was determined using a cut-off point, which was defined as the point at which the repeatability has a coefficient of variation of ≤25%. The LOQ was 2.1 ng/L and 1.4 ng/L in end-exhaled air for D4 and D5, respectively. End-exhaled air samples were quantified using ^{13}C-labelled D4/D5 as an internal standard. The calibration curve included seven standard solutions with a concentration range of 0-10 ng/µL.

II-2.3 Results

II-2.3.1 *Baseline results*

Ten female and five male participants were included. Some characteristics of the participants are presented in Table II: 2-2.

Table II: 2-2. Characteristics of the included female and male participants.

Volunteer ID	Sex	Age (years)	Body weight (kg)
1	F	23	60
2	F	26	71
3	F	64	65
4	M	56	70
5	M	64	75
6	M	21	75
7	M	55	86
8	F	70	64
9	F	55	60
10	F	22	69
11	M	42	76
12	F	25	46
13	F	36	71
14	F	43	83
15	F	21	73

Table II: 2-3 provides an overview of the concentrations of D4 and D5 in end-exhaled air measured after regular use of personal care products by our volunteers. Information on regular use during a period of 24 hours prior to the baseline measurement was collected in a diary (Appendix A5-1). Table II: 2-3 also presents the median D4 and D5 concentration (ng/L) in end-exhaled air for the total number of volunteers and male and female volunteers separately.

Table II: 2-3. The baseline concentrations of D4 and D5 in end-exhaled air after normal use of personal care products for all participants.

Gender	Volunteer	D4 (ng/L)	D5 (ng/L)	Ratio D4/D5
Male (N=5)	4	6.7	1.6	4.3
	5	3.2	1.9	1.7
	6	2.7	2.8	1.0
	7	4.3	27.1	0.2
	11	11.8	2.3	5.2
	Median (min-max)	*4.3 (2.7 – 11.8)*	*2.3 (1.6 – 27.1)*	
Female (N=10)	1	3.2	3.1	1.0
	2	7.0	6.6	1.1
	3	14.5	18.2	0.8
	8	1.9	2.8	0.7
	9	9.8	44.4	0.2
	10	ND*	4.7	ND
	12	27.4	33.2	0.8
	13	6.5	2.1	3.1
	14	2.8	4.4	0.6
	15	44.8	17.9	2.5
	Median (min-max)	*7.0 (1.9 – 44.8)*	*5.7 (2.1 – 44.4)*	
All (N=15)	*Median (min-max)*	*6.6 (1.9 – 44.8)*	*4.4 (1.6 – 44.4)*	

* ND = due to a technical problem no value is available.

When adjusted for partitioning, the end-exhaled air concentration is a proxy for the free blood concentration of D5. For these volunteers, the (free) blood concentration-time curve is simulated using the full PBK model (Reddy et al., 2007), and compared to the baseline measurement.

The PBK model was applied as reported by Reddy et al. (2007). Volunteer specific parameter values were adjusted for the parameters sex, age, body weight (Table 2.2), time of application of a D5 containing product, the concentration in that product, amount used, and treated area (Table II: 2-4).

Table II: 2-4. Use of D5 containing products reported by individual volunteers.

Volunteer ID	Product	Time	Concentration (mg D5/g product)		Applied amount (g)	Treated area (cm^2)
			low	High		
4	Eyeliner	7:47	1	300	0.0023	9.09
5	Shampoo	19:30	10	150	7.7	883.44
	Hair gel	19:30	1	250	3.8	883.44
	Body lotion	19:30	3.9	48.1	8.9	17668.80
	Hair gel	7:00	1	250	3.8	883.44
6	Shampoo	15:45	10	150	5.2	8.78.67
8	Night cream	22:30	16.3	214.1	0.9	777.69
	Hand cream	22:30	1.6	19.1	0.9	691.28
	Day cream	8:00	16.3	214.1	0.7	1468.97
	Mascara	8:00	1	200	0.01193	8.641
	Lipstick	8:00	10	650	0.0065	8.64
	Lip pencil	8:00	1	500	0.005	8.64
	Eyebrow pencil	8:00	1	500	0.00033	8.64
9	Lipstick	14:00	10	650	0.0065	16.48
	Lipstick	9:05	10	650	0.0065	16.48
	Mascara	9:40	1	200	0.01193	8.241
10	Face cream	7:40	16.3	214.1	0.2	817.07
	Hand cream	8:25	1.6	19.1	0.4	726.28
11	Feet care	21:10	1	300	0.2	1198.50
13	Hair conditioner	23:12	1	16.2	2.7	824
	Night cream	23:20	1	214.1	0.3	824
	Night cream	7:15	1	214.1	0.3	824
15	Day cream	12:00	16.3	214.1	0.4	840.42
	Day cream	24:00	16.3	214.1	0.4	840.42

The volunteers used more C&PCPs than listed in Table II: 2-4, but only the C&PCPs listed in Table II: 2-4 contain D5 according to their label. For this reason, only for the volunteers mentioned in Table II: 2-4 PBK modelling was performed. The D5 concentrations in the C&PCPs are based on a concentration dataset provided by Dudzina et al., 2014. The amount used is obtained from the diaries filled out by the participants, using pictures as presented by Biesterbos et al., 2013. Information about the treated area is derived from the diaries and recalculated into an exposed surface area.

Several volunteers are not listed in Table II: 2-4, because they used D5 containing (deo) sprays. The information available on the use of D5 containing spray was not sufficient to estimate the inhalation exposure to D5 from spraying, therefore these volunteers were omitted from the analysis.

The D5 baselines (Table II: 2-3) are measured in end-exhaled air, by taking a 142 mL sample of end-exhaled air. The amount of D5 in this sample (two samples per volunteer) is reported in Table II: 2-5. The free D5 concentration in blood is obtained by dividing this amount by the sample volume and multiplying by the blood:air partition coefficient (0.41, Reddy et al., 2008).

Table II: 2-5. Baseline blood concentration derived from end-exhaled air.

Volunteer ID	D5 per sampling tube (ng)		Blood concentration (ng/L)	
	1st sample	2nd sample	1st sample	2nd sample
1	0.42	0.49	1.20	1.41
2	1.31	0.56	3.78	1.62
3	3.30	1.88	9.52	5.43
4	0.19	0.25	0.55	0.72
5	0.28	0.24	0.82	0.70
6	0.38	0.42	1.09	1.22
7	2.41	5.29	6.95	15.28
8	0.52	0.26	1.50	0.76
9	0.70	11.89	2.03	34.34
10	-	0.66	-	1.91
11	0.46	0.17	1.32	0.50
12	1.47	7.93	4.25	22.90
13	0.42	0.19	1.22	0.54
14	0.97	0.30	2.80	0.86
15	4.85	0.23	13.99	0.67

In Figure II: 2-6 and Figure II: 2-7 the modelled blood concentration of D5 is plotted against time. It starts at the first application of a D5 containing product. The lower curve is based on the lowest D5 product concentration and the upper curve is based on the highest D5 concentration determined by Dudzina et al., 2014 (both corrected for recovery). The black points indicate the obtained baseline values for the free D5 concentration in blood.

Volunteer 5 is given as an example: The concentration time curve starts at 19:30 when he uses shampoo, hair gel and body lotion. At 7:00 he uses hair gel again, which results in an increase in blood concentration at that time. At 14:00 two end-exhaled air samples are taken: they indicate a free blood concentration of 820 and 700 pg/L.

At 14:00 the simulated blood concentration between 1240 and 47000 pg/L based on the low and high concentrations of D5 in the product, respectively. This latter information is, for all volunteers, comprised in Table II: 2-6 to compare the simulated and experimental D5 blood concentrations (at the same time). Altogether, ten out of the seventeen measurements assessed here fall between the lower and upper boundary of simulated D5 concentrations.

The PBK model used is based on the application of pure D5, while here formulated D5 is applied. This probably does not influence the simulations, because formulation is not expected to considerably alter the absorption and evaporation kinetics of D5 (Jovanovic et al., 2008).

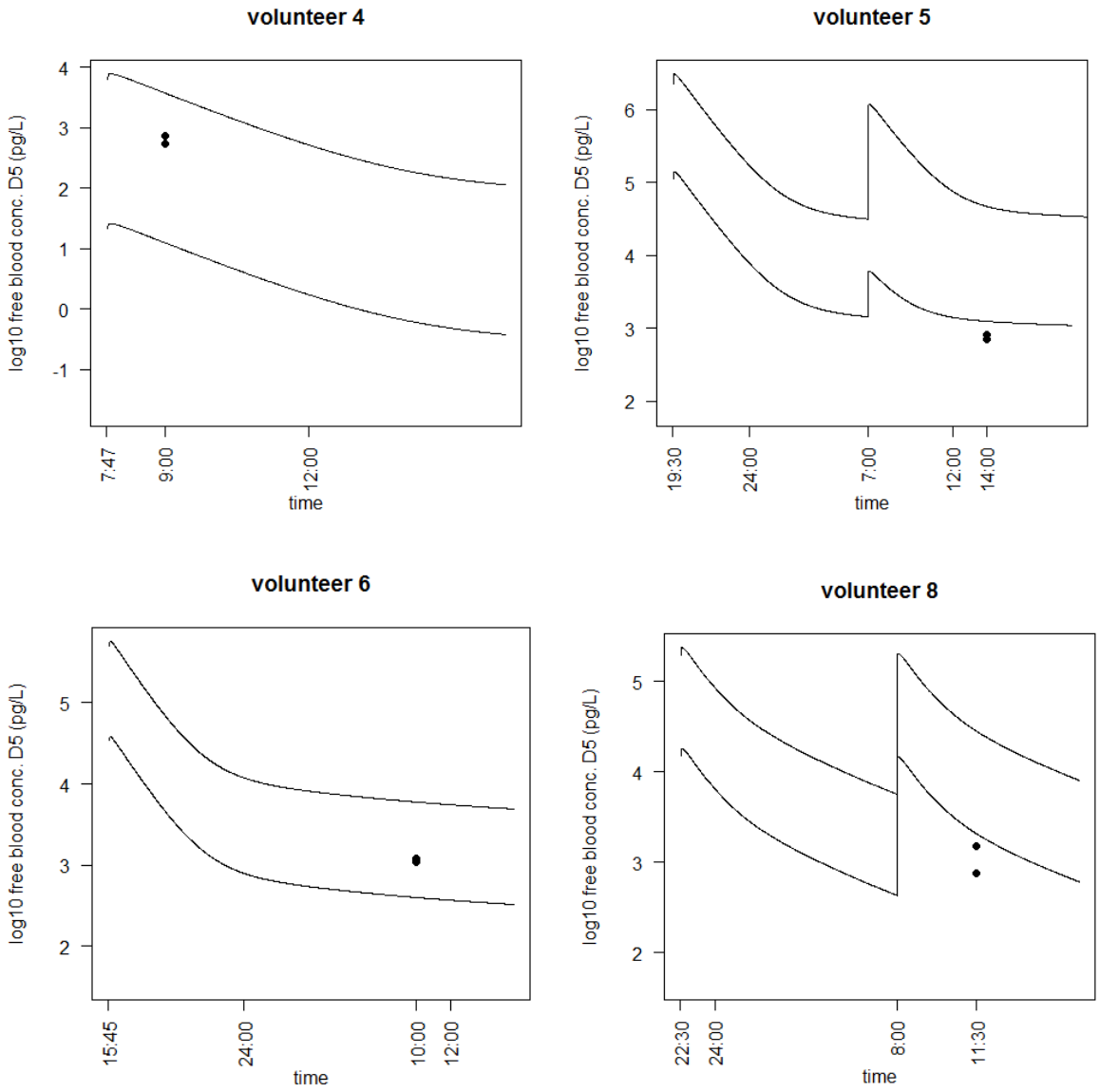


Figure II: 2-6. Modelled D5 blood concentration plotted against time for volunteers 4,5, 6 and 8. Dots represent the experimental values.

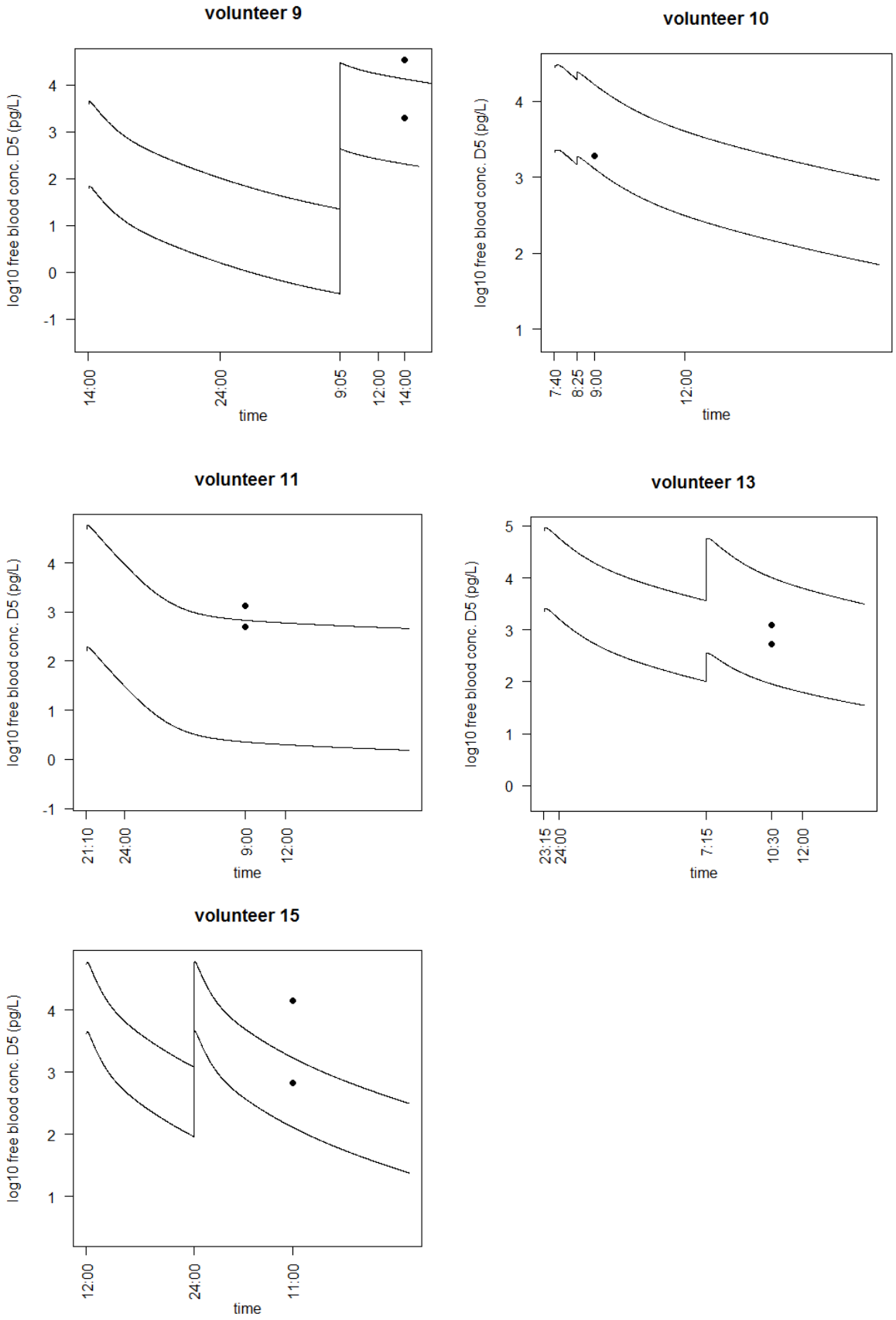


Figure II: 2-7. Modelled D5 blood concentration plotted against time for volunteers 9, 10, 11, 13, 15. Dots represent the experimental values.

Table II: 2-6. Simulated vs. experimentally derived D5 blood concentration. Measured samples in bold are between the two simulated concentrations based on low and high product concentrations.

Volunteer ID	Simulated blood concentration (ng/L) based on low / high product concentrations		Blood concentration (ng/L)	
	Low	High	1st sample	2nd sample
4	0.012	3.7	**0.55**	**0.72**
5	1.2	47	0.82	0.70
6	0.40	6.0	**1.09**	**1.22**
8	2.1	28	1.50	0.76
9	0.21	14	**2.03**	34.34
10	1.3	17	-	**1.91**
11	0.0023	0.68	1.32	**0.50**
13	0.090	10	**1.22**	**0.54**
15	0.13	1.7	13.99	**0.67**

II-2.3.2 *Control experiments*

These experiments provided information on the contribution of inhalation to the total uptake. The mean D4 and D5 concentrations in end-exhaled air measured during the control experiments are presented in Figure II: 2-8 and Figure II: 2-9. The results for all volunteers separately are presented in Appendices A5-2 and A5-3. In the control experiments the measured concentrations in end-exhaled air ranged between approximately 0.8 - 3.5 and 0.8 - 4.0 ng/L, for D4 and D5, respectively.

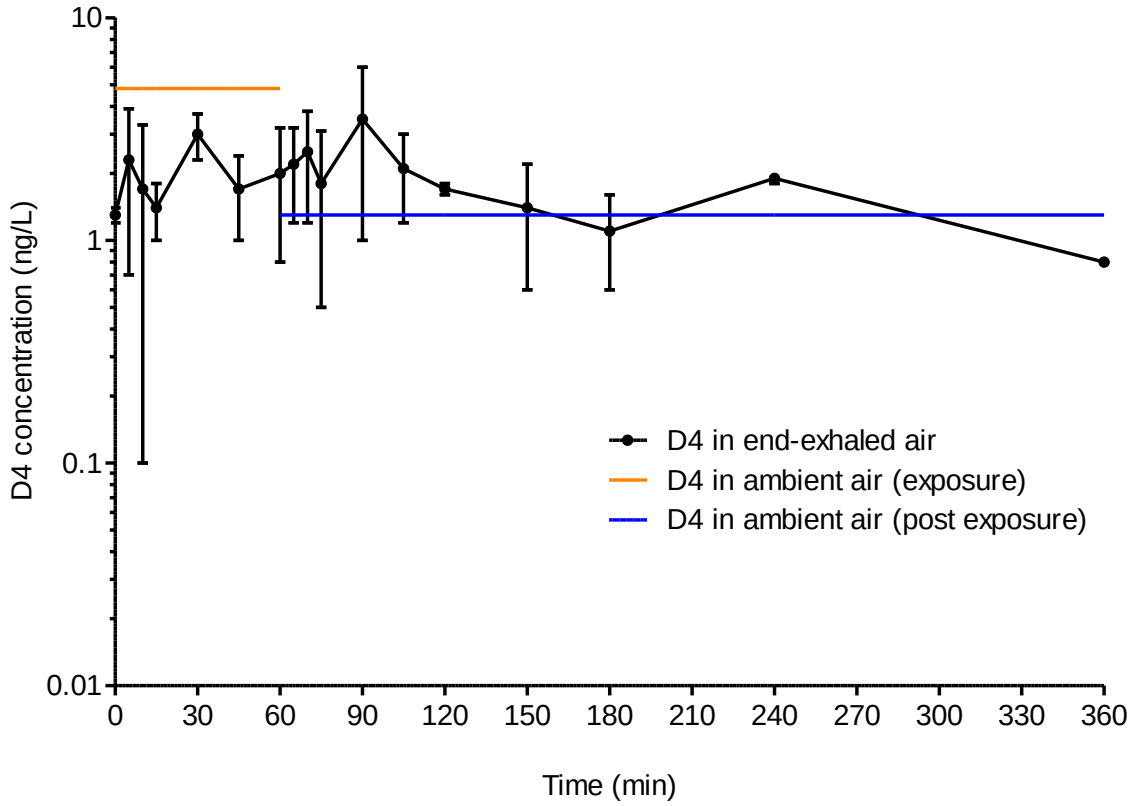


Figure II: 2-8. The mean (±sd) D4 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D4 concentration in ambient air (ng/L) during control experiments (N=3).

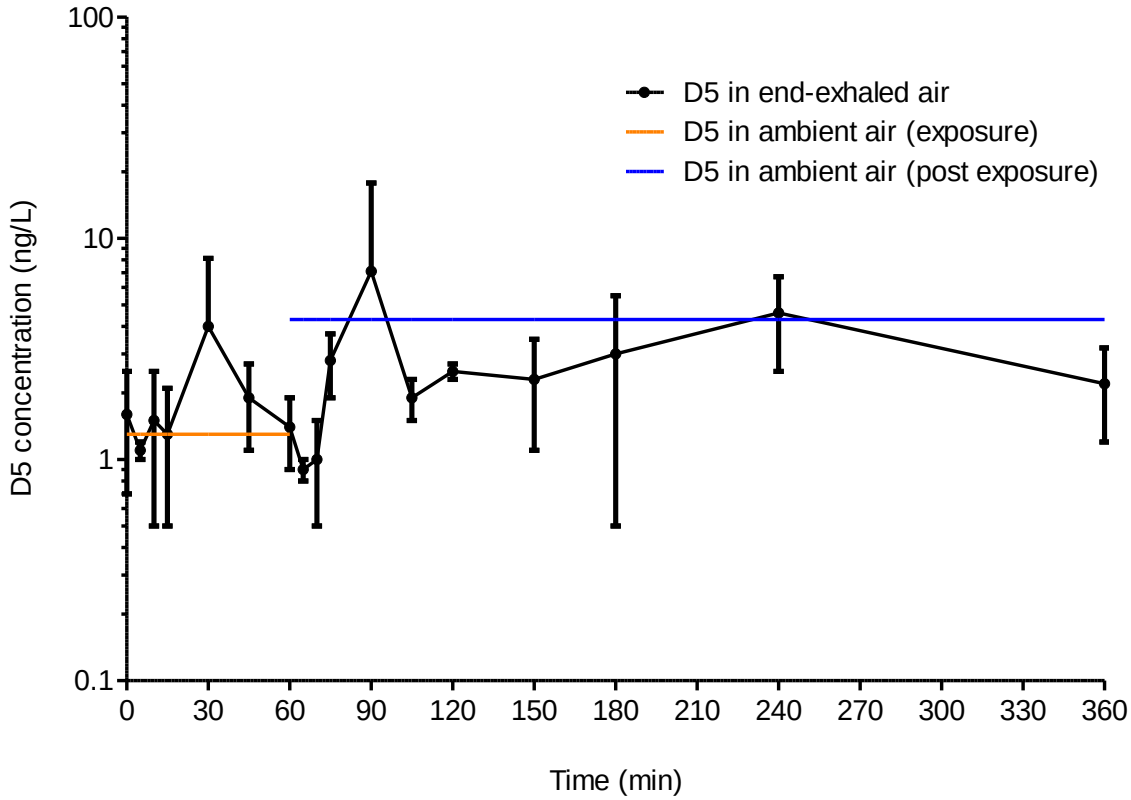


Figure II: 2-9. The mean (±sd) D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) during control experiments (N=3).

II-2.3.3 *Exposure experiments*

In total we performed 29 exposure experiments. Fifteen volunteers were exposed to D5 as a pure substance, four volunteers to night cream, one volunteer to deodorant, two volunteers to a combination of night cream and deodorant and six volunteers were exposed to D4 as a pure substance. Figure II: 2-10 to Figure II: 2-14 provide examples of registered pattern D4/D5 present in end-exhaled air after exposure to different media. All results are presented in Appendices A5-4 to A5-9.

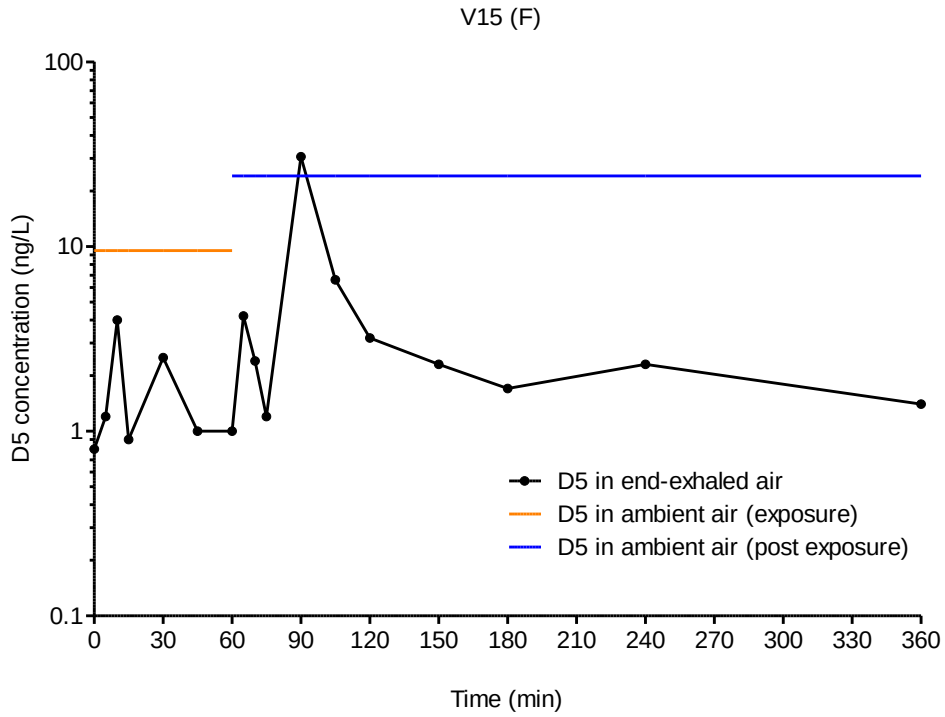


Figure II: 2-10. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 as a pure substance.

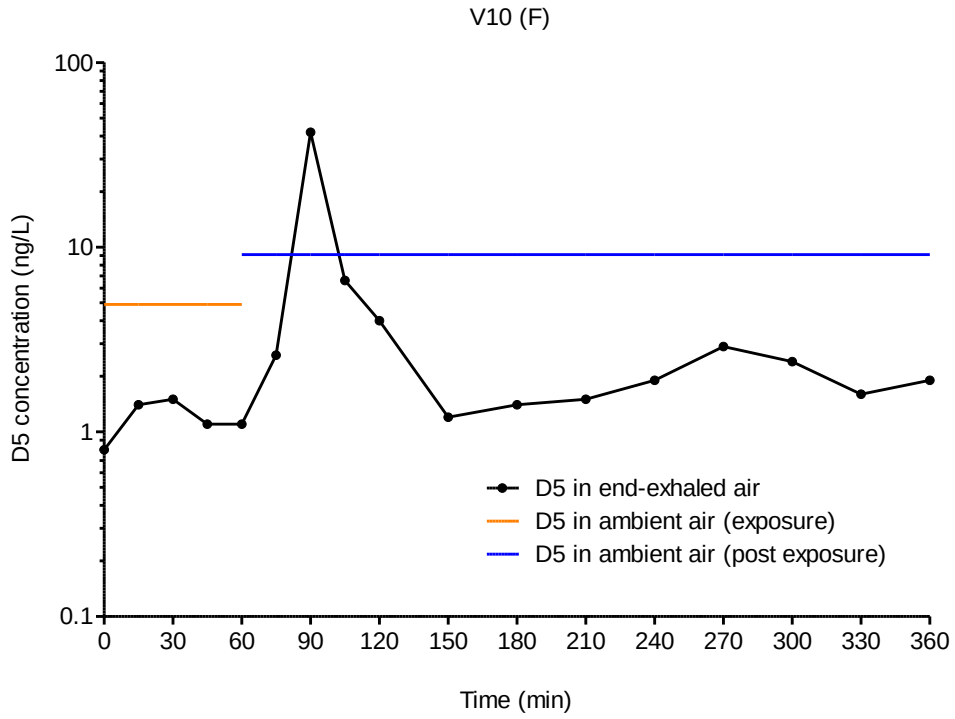


Figure II: 2-11. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to night cream.

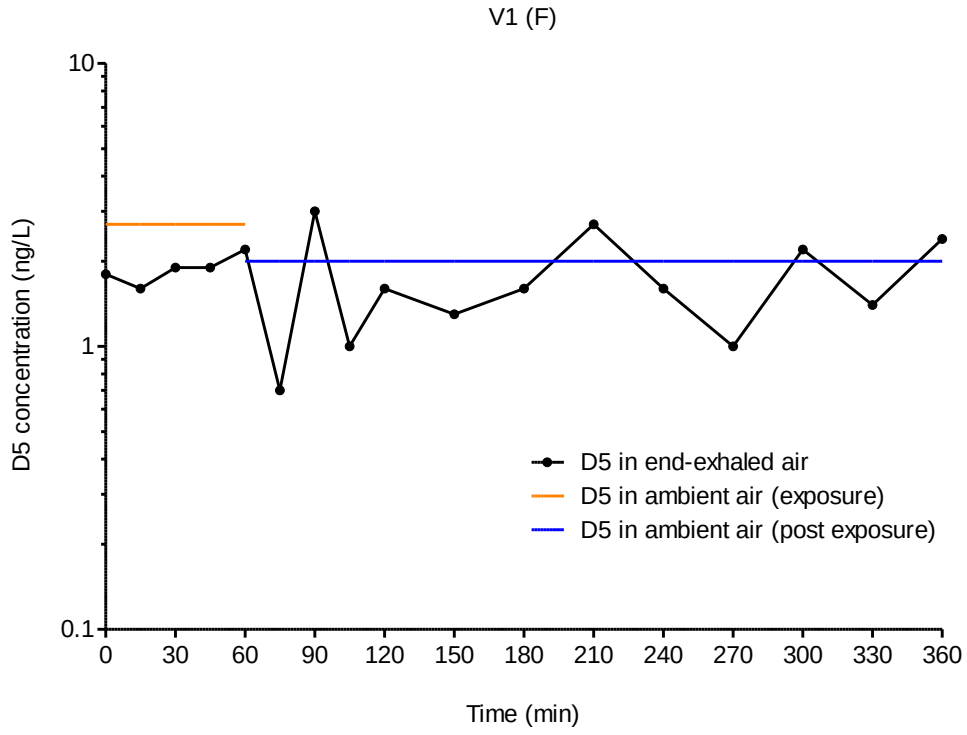


Figure II: 2-12. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to deodorant.

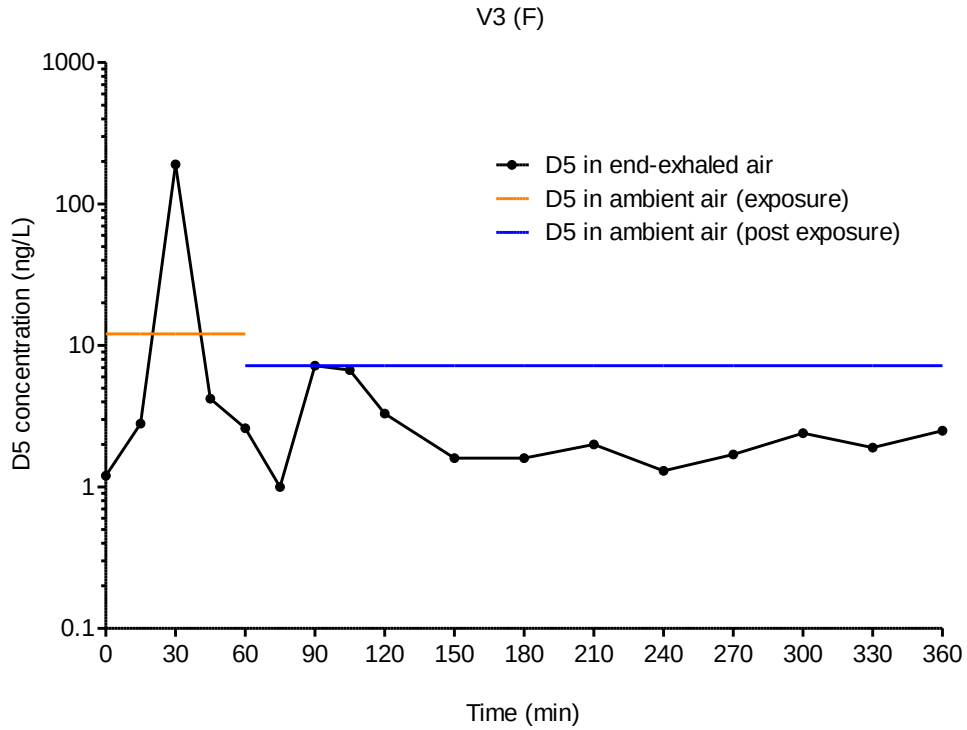


Figure II: 2-13. The means D5 concentration in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to a combination of night cream and deodorant.

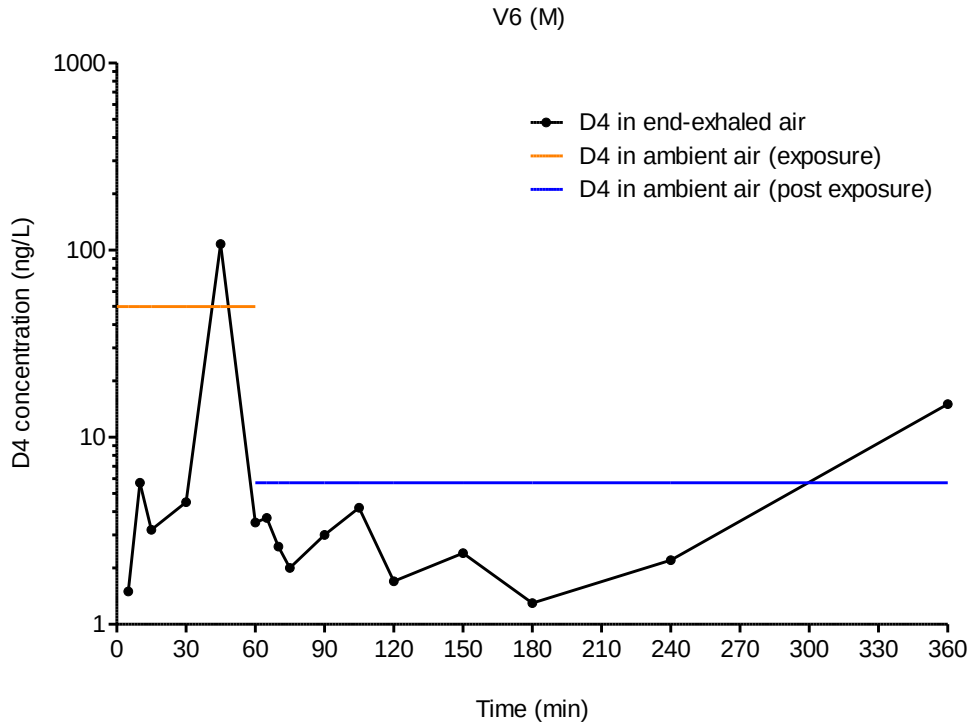


Figure II: 2-14. The mean D4 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D4 concentration in ambient air (ng/L) after dermal exposure to D4 as a pure substance.

The actually applied amount and the resulting applied dose for all experiments are presented in Table II: 2-7 to Table II: 2-9. Regarding D5, the intended dose was 15 mg/cm^2. This dose was not actually applied because the applied substance runs from the arm (D5/D4 pure substance) or sticks to the glove (cream/deodorant), and a residue is left in the jar.

Table II: 2-7. Overview of the applied amount of substance (D5 pure substance, cream and deodorant) and the resulting applied dose D5.

Applied substance	Volunteer	Exposed surface forearm (cm^2)	Amount (g)	Dose of D5 (mg/cm^2)
D5 pure substance	1	689	4.85	7.0
	2	870	4.33	5.0
	3	771	3.01	3.9
	4	819	2.65	3.2
	5	934	5.02	5.4
	6	922	5.37	5.8
	7	949	5.25	5.5
	8	730	6.24	8.5
	9	749	3.96	5.3
	10	747	4.25	5.7
	13	937	4.46	5.8
	14	581	4.99	6.5
	15	763	7.33	9.6
D5 pure substance (no toilet visit at t=90 min)	7	949	5.85	6.2
	11	937	7.43	7.9
	12	581	4.90	8.4
Cream	3	771	6.27	2.0
	4	819	15.98	4.9
	5	934	18.78	5.1
	10	747	16.36	5.5
Deodorant	1	689	5.27	2.3

Table II: 2-8. Overview of the applied amount of substance (cream and deodorant) and the resulting applied dose D5.

Applied substance	Volunteer	Exposed surface forearm (cm^2)		Amount (g)		Dose of D5 (mg/cm^2)		
		Deodorant	Cream	Deodorant	Cream	Deodorant	Cream	Total
Cream & deodorant	3	771	761	13.82	8.42	4.5	3.3	7.8
	4	819	800	19.42	9.48	6.0	3.5	9.5

Table II: 2-9. Overview of the applied amount of D4 pure substance and the resulting applied dose D4.

Applied substance	Volunteer	Exposed surface forearm (cm^2)	Amount (g)	Dose of D4 (mg/cm^2)
D4 pure substance	2	870	7.21	8.3
	6	922	10.0	10.8
	7	949	9.73	10.3
	8	730	9.76	13.4
	11	937	8.09	8.6
	14	581	6.92	9.0

II-2.3.4 *Exposure experiments without the prevention of inhalation*

The mean D5 concentration in end-exhaled air measured during the inhalation experiments is presented in Figure II: 2-15. The results for all volunteers separately are presented in Appendix A5-10. The highest concentration of D5 in end-exhaled air was measured during the stay at the toilet area, between five and ten minutes after the application of night cream. This concentration ranged from 1000 to 1500 ng/L. When the same experiment was performed inside the toilet area but without the application of night cream, the D5 concentration in end-exhaled air was approximately 4 ng/L and the D5 concentration in ambient air was approximately 16 ng/L.

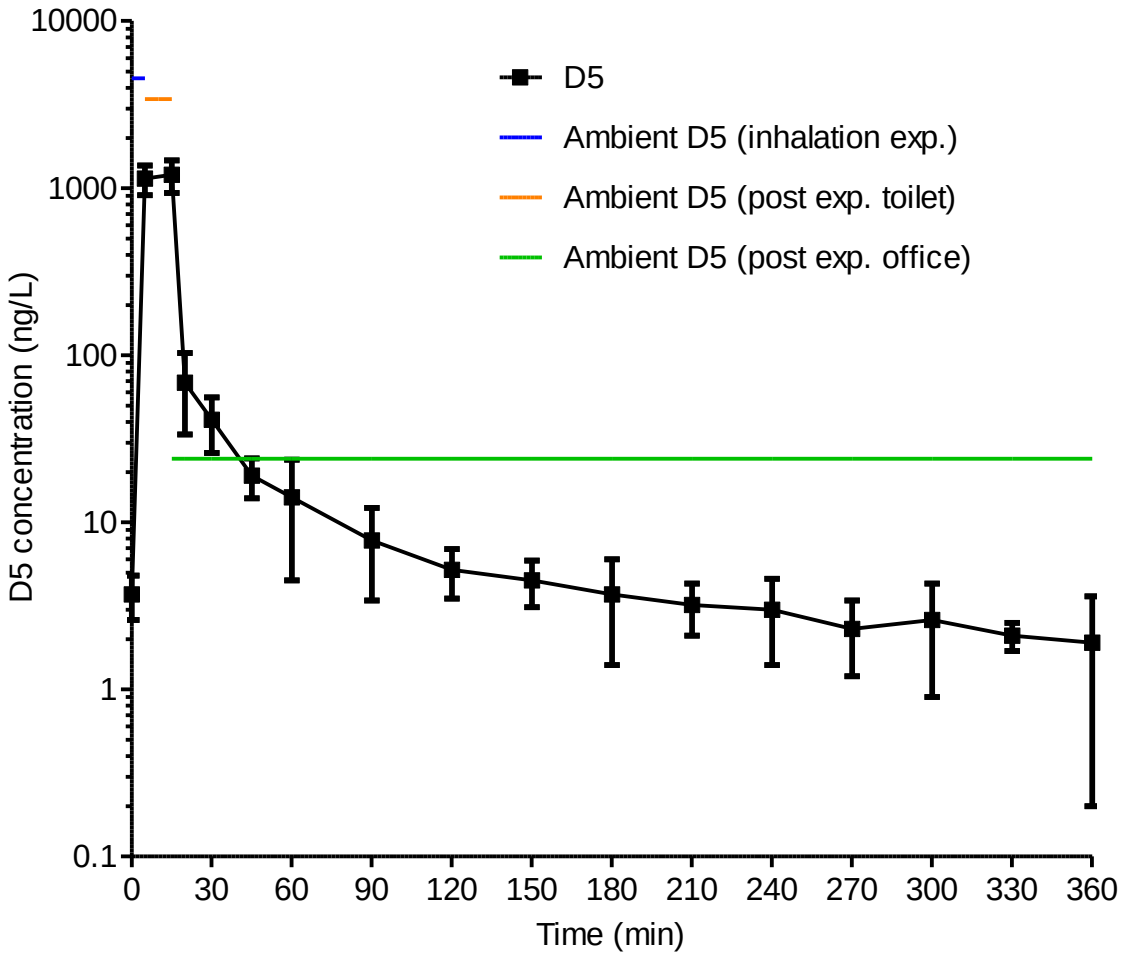


Figure II: 2-15. The mean (±sd) D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) during inhalation experiments (N=3).

II-2.4 Discussion

The results of the baseline measurements showed that some volunteers (i.e. volunteer 2, 4, 5, 11, 13 and 15) had a ratio of D4/D5 that exceeded unity. This is remarkable, since nowadays D5 is the primary siloxane ingredient used in personal care products. Similar findings were reported in a recent biomonitoring study in Norway. Hanssen and co-workers analyzed blood samples from 94 postmenopausal women and 17 pregnant women (Hanssen et al., 2013) and found that D4 was the dominant compound in plasma of both cohorts.

A PBK model was applied to simulate the baseline D5 measurements. Altogether, ten out of the seventeen measurements fall between the lower and upper simulated D5 concentrations. The uncertainty of the simulated concentrations is rather large. This emphasizes the need to use accurate product concentrations when internal concentrations are estimated from product use patterns. It should be noted that the simulated concentration range reflects the uncertainty in the product concentration only. Other (quantifiable) uncertainties, e.g. about the amount of product used and the surface area, are not included. Also, the influence of inhalation on the volunteer's D5 blood concentration is unknown. From their diaries it is known that the assessed volunteers did not use C&PCPs that resulted in direct inhalation of D5, such as deodorant, 24 hours prior to taking the baseline sample. However, it is not known if and how much the volunteers were exposed to D5 present in ambient air.

The concentration of D4 in end-exhaled air in the control experiments ranged between approximately 0.8 and 3.5 ng/L. The results in the control experiment with D5 show similar results (range 0.8 – 4.0 ng/L). This is considered the background level. It is clear from the graphical representation of the results in Appendices A5-2 and A5-3 that the majority of the observed results did not or hardly exceeded the aforementioned range of background noise.

After 60 minutes the exposure was ended by removal of D5 using water and soap (with no D4/D5 on the ingredient list). The volunteer provided three end-exhaled air samples shortly after the end of exposure (t=65, t=70 and t=75 min). During these actions the forearm was kept inside the flow cabinet. The fume hood was placed over the head of the volunteer and he/she walked via the toilet to the desk where he/she was sitting for the rest of the observation period, before the collection of the next end-exhaled air sample (t=90 min). The volunteer was not using the fume hood during the toilet visit. Several graphs showed a sharp increase of the percentage D5 in end-exhaled air at this time point (t=90 min). The mean D5 concentration in end-exhaled air at t=90 minutes was 64.7 ng/L with the toilet visit and 5.7 ng/L without the toilet visit. The sharp increase in D5 concentration at t=90 minutes is most likely caused by inhalation of the substance. The source could be evaporation of a residue from the treated skin surface (i.e. not completely removed or back-diffusion from the skin to

the air). We also observed similar sharp increases at other time points during exposure. As the pattern showed similarities with the peak at t=90 minutes, we also believe that inhalation is of influence despite the fact that the volunteers were placed with their forearm inside a flow cabinet (exposure) and underneath a fume hood (post exposure).

The peak levels of D5 in end-exhaled air of different individuals occurred during exposure and post exposure, and ranged between 3.8 and 605 ng/L. These levels are well within the range of a study by Plotzke and colleagues (Plotzke et al., 2002). The authors observed peak levels of D5 in exhaled air between 15 and 60 minutes after the application of 1.0 or 1.4 g C^{13}-labelled D5 to the axillae, ranging from 347 to 2,315 ng/L. The peak levels of D4 in end-exhaled air of different individuals occurred during exposure and ranged between 7.5 and 280 ng/L. These levels are well within the range of an earlier study by Plotzke and colleagues (Plotzke et al., 2000). The authors observed peak levels of D4 in exhaled air 60 minutes after the application of 1.0 or 1.4 g of ^{13}C-labelled D4 to the axillae, ranging from 30 to 111 ng/L.

Plotzke and co-workers did not report measures to prevent inhalation during dermal application of C^{13}-labelled $D4^{3}$. During the application of ^{13}C-labelled D5 volunteers were instructed to breathe from a clean air source (Plotzke et al., 2002). The exact time point and duration of usage of the clean air source was not specified, nor did they measure the ambient air level of ^{13}C-labelled D5. Due to this supposedly limited prevention of inhalation exposure and the fact that the peak concentrations D4 and D5 in end-exhaled air in both studies are similar to our findings, the results reported by Plotzke and colleagues may not exclusively represent dermal absorption, but include some inhalation.

In order to assess inhalation exposure, we performed three additional experiments in which we simulated a realistic exposure scenario of a consumer who used a C&PCP in the bathroom. The highest D5 concentrations in end-exhaled air were measured between five and ten minutes after dermal application of a cream (range 1000 – 1500 ng/L). These levels are in the same order of magnitude as D5 peak levels in exhaled air observed by Plotze and co-workers after dermal absorption of labelled D5 (Plotzke et al., 2002). When the exposure was ended (the volunteer left the toilet area), the D5 concentration in end-exhaled air decreased to approximately 70 ng/L within five minutes.

Overall, the results of our exposure experiments using D5 (as a pure substance), D4 (as a pure substance), a cream, a deodorant and a combination of the latter two indicate that dermal absorption of D4 and D5 cannot be discriminated from the background. Conclusively, when applying C&PCPs containing cyclic siloxanes (D4/D5), inhalation and not dermal exposure is the major pathway of uptake. Therefore, it is important to account also for

inhalation exposure when performing aggregate exposure assessments to dermally applied substances with physicochemical properties similar to those of D4 and D5.

II-2.5 References

Biesterbos J., et al., Usage patterns of personal care products: important factors for exposure assessment. Food Chem Toxicol, 2013. 55: p. 8-17.

Dudzina T., et al., Concentrations of cyclic volatile methylsiloxanes in European cosmetics and personal care products: Prerequisite for human and environmental exposure assessment. Environ Int, 2014, 62: p. 86-94.

Hanssen, L., et al., Plasma concentrations of cyclic volatile methylsiloxanes (cVMS) in pregnant and postmenopausal Norwegian women and self-reported use of personal care products (PCPs). Environ Int, 2013. 51: p. 82-7.

Horii, Y. and K. Kannan, Survey of organosilicone compounds, including cyclic and linear siloxanes, in personal-care and household products. Arch Environ Contam Toxicol, 2008. 55(4): p. 701-710.

Lu, Y., et al., Concentrations and assessment of exposure to siloxanes and synthetic musks in personal care products from China. Environ Pollut, 2011.

Plotzke, K.P., M.J. Utell, and J.R. Looney, Absorption, Distribution and Elimination of 13C-D4 in Humans After Dermal Administration, 2000. EPA document number 86010000007.

Plotzke, K.P., M.J. Utell, and J.R. Looney, Absorption, Distribution and Elimination of 13C-D5 in Humans After Dermal Administration, 2002. EPA document number 84030000008.

Reddy, M.B. et al., Modeling of human dermal absorption of octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5). Toxicological Sciences, 2007. 99(2): p. 422-431.

Reddy, M.B., et al., Inhalation dosimetry modeling with decamethylcyclopentasiloxane in rats and humans. Toxicological Sciences, 2008. 105(2): p. 275-285.

Wang, R., et al., Low molecular weight cyclic volatile methylsiloxanes in cosmetic products sold in Canada: implication for dermal exposure. Environ Int, 2009. 35(6): p. 900-904.

Conclusions for the project

- The guidance for aggregate exposure assessment was followed for the two case studies and revised during the process, resulting in guidance generally suitable for performing aggregate exposure assessments of substances in consumer products.
- The performance of the tiered approach to modelling (realistic) aggregate consumer exposure was demonstrated: for both case substances the 95th percentiles of chronic population exposure modelled in the tier 2 assessment were almost two orders of magnitude lower than the tier 1 estimates, indicating that for aggregate exposure assessment the probabilistic assessment versus worst case assessment is a valuable means for refinement.
- Advancing from a tier 1 to a tier 2 aggregate exposure estimate the key data are those on product use and co-use profiles. The percentage of product users, and prevalence of a substance in a product category) are important as well.
- For exposure factors like human body characteristics and product use patterns some publicly available databases exist, but most of these databases are not designed for exposure estimation and therefore often lack important data for the aggregation of exposure like e.g. co-use data. Further data gaps include substance-specific data like the prevalence in products and market share of substance-containing products
- For the Dutch adult population high-quality product use data for C&PCP (including co-use on a chronic basis) were successfully obtained and linked with the PACEM model.
- The probabilistic aggregate exposure model PACEM developed within this project is suitable to be used for tier 2 assessments of substances that occur in cosmetic and personal care products (C&PCPs). The required model input consists of the exposure fractions (depending on the physico-chemical properties of a substance and the product application scenario) and the concentrations and occurrence of the substance in the products.
- Validation of exposure models with biomonitoring seems to be possible as long as toxicokinetic data are available to develop a PBK model or a PBK model is already available. For our case studies on D5 and TCS both the tier 1 and the tier 2 models proved to be reasonably conservative: the modelled exposure was higher compared to the baseline levels, with the probabilistic results nearly approaching the realistic exposure values observed in higher percentiles of the population.

- Regarding validation of the aggregation of two dermally applied products, the project did not provide conclusive answers, since for the volatile ingredients dermal exposure turned out to be negligible compared to inhalation exposure. Hence aggregation of two dermally applied products did not induce significant differences in exposure if compared to the single source applications.
- Concerning a possible role for human biological monitoring in the characterization of aggregate exposure there are three areas where well-informed choices need to be made: (1) model compound, (2) biological medium for sample collection and (3) the choice for the biomarker.
    - (1) For dermal absorption a model compound should be selected based on physico-chemical properties (Log P_{ow} preferably between 0 and 6) and limited volatility to avoid overwhelming contribution from inhalation exposure (i.e. vapor pressure < 10 Pa at 20°C).
    - (2) Non-invasive sample collection (biological media: urine, exhaled air) is preferred: to limit the burden and risk of infection for the study subjects repeated puncture of veins should be avoided. Therefore, in the case of repeated sample collection blood samples are only a last resort. If there is no good alternative to blood collection, volunteers should be invited to a clinical trial center and a peripheral venous catheter should be installed for repeated blood collection.
    - (3) For aggregate exposure assessment the parent substance is the preferred biomarker. Only if biotransformation in humans is extensive a metabolite should be considered as a possible alternative biomarker.

Recommendations for future research

The probabilistic aggregate exposure model PACEM to date is only available as R code, which prevents the use by a larger community not necessarily knowledgeable in R. The development of a graphical user interface (GUI) for PACEM would enable dissemination to a much larger community. The PACEM model itself could further be enhanced e.g. by increasing the time-resolution for exposure events (i.e. mornings, afternoons, evenings instead of days), accommodating exposure fractions calculations into the PACEM framework and by including further product types like e.g. textiles.

End-exhaled air analysis was used to characterize aggregate exposures to personal care products in volunteers in a laboratory setting. The next challenge is to validate the use of end-exhaled air analysis of consumers in real life exposures. A self-assessment procedure could be developed to collect exhaled air samples from consumers in residential settings. To verify that such samples contain (only) end-exhaled fractions, an electronic device can be used to monitor clock time and temperature pattern or pattern of carbon dioxide levels during the sample collection procedure.

With a self-assessment procedure a personal baseline can be established in the early morning (before the use of any products). Subsequent samples during the same day can be collected to reflect exposures from use of C&PCPs. Information on the use of different products can be collected using questionnaires similar to those used in the current project. The interpretation of the levels of the substance of interest in end-exhaled air can be aided by information from the questionnaire and by toxicokinetic models.

Appendix 1

Suggested tier 1 model equations

In this section model equations are suggested that can be used in low (i.e. first) tier aggregate exposure evaluations. Other equations may be equally well suited.

A1-1 Equations for inhalation exposure

Inhalation exposure E_{inh} is defined as the amount of substance inhaled in a specified timeframe (e.g. day, hour) per unit of body mass.
It is evaluated from the air concentration in the breathing zone of the exposed person C_{air}, the inhaled volume of air $Q_{inhalation}$, the exposure duration T_{exp}, and the body weight W_{body}.

$$E_{inhal} = \frac{C_{air} \times Q_{inhal} \times T_{\exp}}{W_{body}}$$

Internal exposure (absorbed dose) D_{inhal} follows from the external exposure E_{inhal} by multiplication with the absorption fraction f_{abs}

$$D_{inhal} = \frac{C_{air} \times Q_{inhal} \times T_{\exp}}{W_{body}} \times f_{abs}$$

The air concentration C_{air} has units of mass per unit of volume and can be estimated in a number of ways, depending on the situation. For example, for small amounts of volatile substances the air concentration can be obtained as the weight fraction of the substance in the product w_f times the fraction of release $f_{release}$ times the amount of the product A_{prod} divided by the room volume V:

$$C_{air} = \frac{w_f \times f_{release} \times A_{prod}}{V}$$

For tier 1 assessments the fraction of substance released should be assumed as 1 (complete release of substance), unless good, science-based evidence exists that the release may be only partial even under worst-case conditions.
For low volatility substances or high amounts of substances that are inhaled as a gas (i.e. not as an aerosol), C_{air} may be calculated by assuming saturation of the air:

$$C_{air} = \frac{p}{RT} \times MW$$

Where p is the vapour pressure, R is the molar gas constant, T is temperature (in Kelvin) and MW is the molecular weight of the substance.

Finally, if a reasonable, conservative estimate of the release rate of the substance can be made, C_{air} may be estimated by multiplying the release rate $R_{release}$ (mass per time) by the release duration $T_{release}$ and dividing by the room volume V:

$$C_{air} = \frac{R_{release} \times T_{release}}{V}$$

A1-2 Equations for dermal exposure

Dermal external exposure E_{dermal} may be estimated as the amount loaded onto the skin A_{load} divided by the body weight W_{body}. The internal exposure (absorbed dose) D_{dermal} follows from this by multiplication with the absorption fraction f_{abs}.

$$D_{dermal} = \frac{A_{load}}{W_{body}} \times f_{abs}$$

The amount of substance released onto the skin may be estimated by

$$A_{load} = w_f \times f_{release} \times A_{prod}$$

with w_f the weight fraction in the product and A_{prod} the amount of product used. Again, $f_{release}$ should usually be assumed to be 1 if no science-based evidence (e.g. extraction/migration experiments) exists that a smaller fraction can be applied.
In cases that migration data are available or can be estimated $A_{release}$ may be estimated by:

$$A_{release} = R_{release} \times T_{\exp}$$

with $R_{release}$ the release rate and T_{exp} the study duration.

A1-3 Equations for oral exposure

External oral exposure E_{oral} is the amount ingested after oral contact with a consumer product. It can be estimated as $A_{release}$ divided by body weight W_{body}. Internal exposure (absorbed dose) D_{oral} follows from this by multiplication with the absorption fraction f_{abs}.

$$D_{oral} = \frac{A_{release}}{W_{body}} \times f_{abs}$$

The method to estimate the amount that is released into saliva depends on the conditions of exposure. For a product that is swallowed, it may be estimated as:

$$A_{release} = w_f \times f_{release} \times A_{ingested}$$

Here, $f_{release}$ is the fraction of the substance that becomes bio-accessible in the gastro-intestinal tract. In tier 1 applications, this should usually be assumed to be equal to 1.
For a product being mouthed (e.g. toys), for which a reasonable estimate of the release (migration) rate $R_{release}$ (amount per unit time per unit surface area) can be made, it is given by

$$A_{release} = R_{release} \times S \times T_{\exp}$$

with S as the surface of the product being mouthed and T_{exp} as the exposure duration.

For hand-to-mouth transfer after dermal contact with a treated surface, $A_{release}$ is the result of a more complicated relation between the residue on contacted surface areas, transfer to the skin of the hands, and the frequency, duration and effectiveness of hand-mouth contact. Depending on the scenario and data availability, special purpose model equations have to be derived.

Appendix 2
The framework for tier 2 in detail

This section provides the details of an aggregate exposure framework: a method to model aggregate exposure to substances in consumer products, intended for a tier 2 probabilistic exposure assessment.

The core of the framework consists of data on product use within a population. These use data include information on the frequency of product use and the amount of product used per event.

These data are used to evaluate aggregate exposure for a population, using a person-oriented approach. This approach involves the following steps:

1) define the population for which to aggregate
2) develop the scenarios according to which the members of the population are exposed
3) select a person from the population
4) construct a contact profile for this person using information on products and uses (i.e. list all use events of this person with specified products over a specified duration)
5) evaluate exposure for all events in the contact profile
6) determine the aggregate exposure by appropriately adding the event exposures
7) repeat steps 2-6 until a representative number of individuals from the population is sampled
8) repeat steps 1-7 for all relevant subpopulations

The corresponding subsections of Appendix 2 describe in more detail the steps outlined above and provide the following information:

A2-1 Description of the dataflow in the tier 2 aggregate exposure model

Population definition

As exposure usually is not homogeneously distributed within a population, it is often practical to consider different subpopulations separately. Such subpopulations may be, for example, children in different age strata, men, women, etc. In general, individuals with distinct exposures (e.g. exposure due to use of a product versus exposure as a bystander) could be chosen to form separate subgroups.

Scenario development

An exposure scenario is a complete description of the manner in which exposure to a product may take place. As such, the exposure scenario forms the basis of the quantitative exposure evaluation.

Exposure to a product may occur in many ways. For example, a person may be exposed to a substance in a cleaning product during preparation of suds, during use of the suds, and after application of the product by re-entering the room where the cleaning agent was used. These examples constitute three different scenarios describing distinct modes of exposure. Other examples of exposure scenarios are: indoor exposure of an adult to an active ingredient of a biocidal product, a person being present when a product is being used (bystander exposure), a child entering a room after application of a biocide and contacting treated surfaces.

In an aggregate exposure assessment, all distinct exposure scenarios have to be identified and described. The scenario description should be specific and include assumptions on parameters and processes that are essential to quantify the exposure in the scenario. The calculation of exposure in the scenario should follow directly from the scenario description by implementing the scenario assumptions in a mathematical model (or a representative experiment, if such is possible).

Select person from population

In a person-oriented approach, exposure is evaluated from the perspective of a person. For this particular person exposure scenarios are constructed (Figure A2 - 1.1). This approach guarantees consistency of the exposure profiles and avoids combinations of incompatible exposure scenarios (e.g. exposure due to use of a spray and exposure of a child crawling on the floor, contacting contaminated surfaces). In this approach, in addition to direct exposure

originating from the use of a product, the post-application exposure can be estimated as well as the bystander exposure, which is the exposure from product use by another individual.

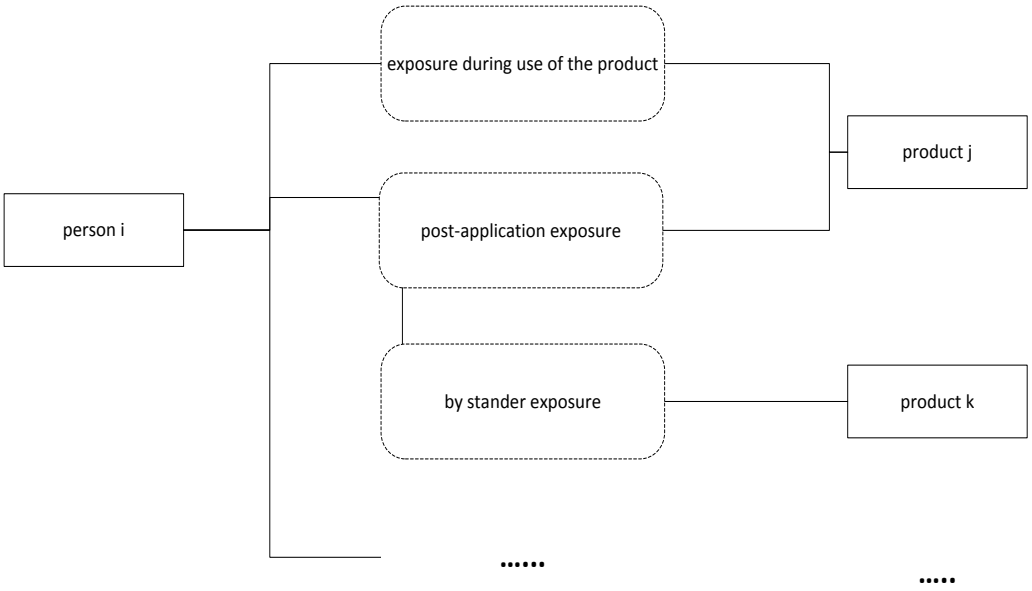


Figure A2 - 1.1. Schematic representation of the specification of exposure scenarios in a person-oriented approach. For each person the scenarios are developed that describe how this person is exposed to different products containing the substance of interest. In this example, the person i contacts product j in two settings: during use of the product and after use of the product (for example by repeated re-entering the room where the product was applied). These two contacts will lead to different exposure events and need to be described in distinct exposure scenarios. In addition, the person in the example will also contact the product k, but only while another person is using this product (that is, person i has contact as a bystander). Quantification of the aggregate exposure for a population involves the specification of all scenarios that describe how exposure occurs to the plethora of different products that contain the substance.

Construction of contact profiles

Contact profiles are constructed from product use information. From the use data, contact profiles are constructed using data from diaries kept by individual users in the population. In a diary it is specified for each day which product was used and how often (specification of potential exposure sources). The contact profiles are constructed by random sampling: for each person, on a specific day, it is determined from data on the frequency of use whether

the person has used this product on this particular day (and if yes, how many times) and whether he or she is potentially exposed by using this product. This process is repeated for all days in the required time interval (e.g. one week, one year, a persons entire life) and all products. This is schematically represented in Figure A2 - 1. 2.

In constructing an exposure profile, ideally a distinction should be made between week days and weekend days, as product use is expected to be different on these days (not implemented here).

Here, it may also be noted that contact profiles may not always completely be constructed from information in a database on product use alone. For example, exposure of a person as a bystander requires additional information or assumptions such as time present at the exposure event, not available in such a database.

Exposure can also be calculated on the basis of frequency information alone, thus skipping the step of constructing contact diaries. An advantage of the use of diaries is that they enable to study variability in day-to-day exposure, and provide different averaging options such as running averages (for example for weekly averages: from Monday to Monday, Tuesday to Tuesday). Which method is most appropriate should be decided on a case-by-case basis.

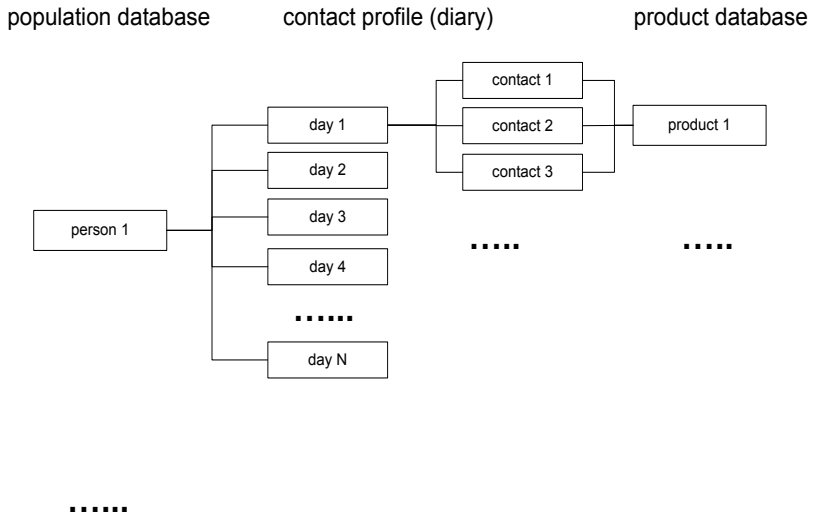


Figure A2 - 1. 2. Schematic representation of the construction of contact profiles. For each day in the considered time interval and for each product to which a person may potentially be exposed it is determined whether for this particular day, contact with the product occurs.

Exposure evaluation

In order to separate the calculation-intensive aggregation of exposure from the event-exposure calculation, so-called exposure fractions will be used in the framework. An exposure fraction is a single quantity that describes exposure as a fraction of the amount of substance used. Once exposure fractions are given, exposure follows by direct multiplication from the used amount in each event. Exposure fractions are developed outside the framework and introduced directly in the equations for calculation of route exposures (see A2 – 3). In order to account for variability (or uncertainty) in the exposure factors that determine the exposure, the exposure fractions have been developed as a frequency distribution rather than a single number. Assuming that there is no correlation between product use information and anthropometric information, exposure then can be determined by random sampling from these exposure fraction distributions[1]. The concept of exposure fractions, the feasibility of their use and how to develop them is described in more detail below.

Aggregating event exposures

For the calculation of aggregate exposure, exposures from different events have to be added. The procedure of adding event exposures depends on the timescale of the health endpoint to which the exposure evaluation is eventually compared. For acute effects, only the exposure events that are simultaneous with respect to the time scale of the effect should be added up. Whether events can be considered simultaneous is largely determined by the toxico-kinetics of a substance. Evaluating acute exposures involves assessing the likelihood of simultaneity of exposure events. This means that the time resolution of the data on product use should be similar to that of the acute timescale.

To aggregate exposures that may contribute to chronic effects average exposures are summed up. The time interval for averaging depends again on the substance, but typically one year or the entire lifetime of a person is used.

[1] This assumption may not always be correct. In those cases that a correlation between anthropometric and use data exists and is known, a more complicated method of correlated sampling will have to be employed. See section Exposure fractions.

A2-2 Description of the input data required for tier 2 aggregate exposure model

Data needs

The framework requires various types of data. Data on the substance, the product formulation and the exposure fractions are substance-specific input and are therefore not included in the framework. The data on the population, products and the use of products are to be part of the framework. The required information on each of these database entities/relations is described below.

Population

Information on each individual enables identification of covariates and stratification of individuals in subpopulations (age, gender). Furthermore, biometric information on body weight and length is required to express the exposure per body weight or body surface area and estimate inhalation rates of exposed individuals.

Product

In principle, the framework requires information on all consumer products that may contribute to exposure for all substances that may be evaluated with the framework. A classification of consumer products in categories will be made. The selected categories should be diverse enough to cover most consumer products. The categorization will be used to collect and store data on products. Each product in the database should be described by brand and category on several levels (e.g. see Table A2 - 2.1). A detailed description of the product is needed construct a link to a model product, for which the composition is known (the input data on formulation). Physical phase (liquid, solid, gaseous) and packaging (bottle, spray, tube) are needed in the exposure evaluation.

The specific product is a specification of a generic product (e.g. products in category 3 in Table A2 - 2.1). The generic product refers to generalized default values (i.e. default formulation) that can be used in absence of more case specific values. The specific product refers to a particular brand and product line that can be used if this type of specific information is available.

Table A2 - 2.1. Examples of products with the required information on product category, brand appearance and application type

Id.	Category 1	Categ ory 2	Category 3	Brand 1	Brand 2	Phase	Packaging
1	Cosmetic s	Hair care	Shampoo	Andrelo n	Every day shampoo	Liquid	Bottle
2	Do-it-yourself	Glues	Carpet glue	Bison	Vloerbedek-kingslijm	Liquid	Tube
3	…						-
…							

Use

For each individual product, information is required on the conditions of use for the product. For all products at least the frequency of use, amount used and the exposure duration should be available to derive the relevant route(s) of exposure and to estimate the exposure. Additional information on use may be needed in specific cases, depending on product, user and use of the product. Such information includes data on the (intentionally and unintentionally) treated parts of the body or objects[2] and the surface area thereof, information on the dilution of the product, room volume, ventilation, protective measures[3] etc. Ideally, these data are available for all persons and use events in the database on population, product and use. In case the collection of these (additional) data proves impossible or unpractical, defaults or surrogates can be obtained from other sources (e.g. ConsExpo fact sheets (Bremmer et al., (2006a, 2006b), (Prud'homme de Lodder et al., 2006)).

[2] E.g. object that is painted/cleaned/etc. with product: wall, floor, window, table, silver dishes, etc.
[3] E.g. gloves

A2-3 Concept of exposure fractions

Exposure fractions express exposure as a fraction of the amount in the source or amount released from a source. The use of exposure fractions allows compression of the exposure calculation to a single (product and substance specific) quantity. The amount of substance to which a person is exposed is calculated as:

$$A_{exp} = eF \times w_f \times A_{product}$$

A_{exp}	amount of substance to which a person is exposed
eF	exposure fraction
w_f	fraction of the substance in the product
$A_{product}$	amount of product used

Exposure fractions depend on the exposure factors that describe the exposure conditions such as room dimensions and ventilation, transfer of residue from touched surfaces et cetera. To account for variability (or uncertainty) in these exposure factors, a distribution of exposure fractions can be determined, derived from distributions in exposure factors. Exposure is determined in the framework by random sampling from the exposure fraction distribution, assuming, for example, that exposure fractions and other model parameters are not correlated

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Usage patterns of personal care products: Important factors for exposure assessment

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ABSTRACT

Complete information regarding the use of personal care products (PCPs) by consumers is limited, but such information is crucial for realistic consumer exposure assessment. To fill this gap, a database was created with person-oriented information regarding usage patterns and circumstances of use for 32 different PCPs. Out of 2700 potential participants from the Netherlands, 516 men and women completed a digital questionnaire. The prevalence of use varied by gender, age, level of education and skin type. A high frequency of use was observed for some products (e.g. lip care products), while toothpaste, deodorant and day cream were generally used once or twice a day. The frequency of use for other PCPs varied over a wide range. The amounts of use varied largely between and within different product groups. Body lotion, sunscreen and after sun lotion were often applied on adjacent body parts. The majority of PCPs were applied in the morning, but some products, such as night cream and after sun, were predominantly applied in the evening or night. As expected, the participants used several PCPs simultaneously. The database yields important personalized exposure factors which can be used in aggregate consumer exposure assessment for substances that are components of PCPs.

1. Introduction

In daily life, many people use numerous personal care products (PCPs), such as deodorant, facial moisturizer or night cream on a regular basis (Wu et al., 2010). PCPs are carefully prepared using intricate recipes and a variety of substances with diverse functions. These substances include active ingredients, but also solvents, preservatives and additives, some of which are suspected to affect the health of the consumer, e.g. phthalates, parabens or antimicrobials (triclosan/triclocarban), which may have endocrine disrupting properties (Chen et al., 2008; Lyche et al., 2009; Witorsch and Thomas, 2010). UV absorbers in sunscreens, such as dibenzoylmethanes and benzophenones, as well as fragrances and preservative agents in cosmetics, may initiate allergic or photo-allergic contact dermatitis (Goossens, 2011; Schauder and Ippen, 1997). Other PCPs contain heavy metals, such as mercury or cadmium that may lead to neurotoxicity (CDC, 2012; Ayenimo et al., 2010; Chan, 2011). Consumers are exposed to these substances in small amounts through various PCPs, via multiple routes including inhalation, dermal absorption and ingestion.

In order to assess potential health risks for consumers, it is necessary to conduct aggregate exposure assessments considering the simultaneous exposure to a substance from all possible sources and routes (Lorenz et al., 2011; von Goetz et al., 2010). A common approach is to aggregate deterministic worst-case assessments for all sources and routes, which results in highly unrealistic, but conservative, exposure levels. Therefore, refinement of these unrealistic exposure levels will often be needed. For aggregate exposure, the most effective refinement is to take into account co-use and non-use of products in a person-oriented approach (Cowan-Ellsberry and Robison, 2009). In order to do so, individual exposure factors, such as frequency and amount of use of single products, as well as specific information about the circumstances of use are needed (Van Engelen et al., 2007). In a series of three studies, Loretz and co-workers investigated the distribution of the frequency and amount of use of several cosmetics in a US female population of regular users (Loretz et al., 2005, 2006, 2008).

Abbreviation: PCP, personal care product.

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Wu and colleagues collected information on the usage patterns of 30 types of PCPs in Californian households (Wu et al., 2010). Special attention was paid to the distribution of the frequency of use of the investigated products. Hall and co-workers also provided distributions of daily amounts of use for several cosmetic products in Europe, including body lotion, facial moisturiser, hair styling products, hand cream, liquid foundation, mouthwash, shampoo, shower gel and toothpaste (Hall et al., 2007, 2011). The Scientific Committee on Consumer Safety used the data collected by Hall and co-workers to provide exposure data for some cosmetic products in their 7th notes of guidance (Scientific Committee on Consumer Safety (SCCS), 2010). All of these studies mainly focused on the frequency and amount of PCP use, but none addressed both the circumstances and patterns of individual product use. Circumstances of use are for example the presence of ventilation or the location of application (indoors/outdoors). Inhalation exposure will be relatively low when a product is used in a ventilated area. Therefore, the aim of the current study was to create a database containing information regarding the circumstances and patterns of individual PCP use. It provides important information on product use for different age and gender groups and can be used to calculate aggregate consumer exposure to various substances in PCPs, by incorporating the information on both product co-use and the circumstances of use.

2. Methods

2.1. Study population

We randomly selected one large (>100,000 inhabitants) and one small (<20,000 inhabitants) municipality in every province of the Netherlands for a total of 24 municipalities. These were requested to draw a random sample of inhabitants between 18 and 70 years of age from their population administration. Each large municipality provided 150 addresses and each small municipality 75 addresses, leading to a total of 2700 addresses of potential participants. We sent invitation letters for the study to all of these addresses, including an internet address linking to a digital questionnaire in November 2011. In early January 2012, a reminder was sent. We also offered the opportunity to complete the questionnaire on paper instead of through the internet.

2.2. Data collection

We developed a web-based questionnaire to assess the use patterns and circumstances of PCPs. This questionnaire contained general questions regarding demographics, lifestyle and skin type. The detailed usage patterns of 32 types of PCPs were assessed using questions regarding the frequency of use and the amount of product used per application. We used photographs to visualize the amount of product used in the following product categories: general hygiene (e.g. deodorant), shaving products, hair care, skin care and tanning products. The photographs contained three images displaying an increasing amount of product (Fig. 1). We recorded the weight of the amount of product shown in each of the images. This information was used to transform the categorical data provided by the respondents (e.g. an amount equal to picture A or an amount between pictures A and B) into numerical values (e.g. 2.5 g) for actual exposure calculation.

For the following PCPs the visual display of amounts was not meaningful: deodorant spray, perfume or eau de toilette, aftershave spray, hair spray, eye shadow, mascara, eye pencil, eyebrow pencil, lip pencil, lipstick, lip balm and nail polish. For these products, we developed alternative questions to describe the amounts used such as: "how often did you spray?" (spray products), "where exactly did you apply the product?" (eye shadow, eye pencil and lip pencil), "how many layers did you apply?" (mascara, eyebrow pencil, lip pencil, lipstick, lip balm and nail polish). A small experimental study was performed and the mean amounts used were calculated by weighing before and after application of the product.

In addition, the questionnaire contained questions regarding the type and brand of the product, the application area on the body, the time of day a product was used (e.g. morning or evening), the location of use (indoors or outdoors) and the presence of ventilation. All of the questions concerned use within the past 6 months, except for the questions regarding tanning products, which covered the past year to minimize seasonal influences.

2.3. Data analysis

Frequency tables were used to describe the prevalence of PCP use. This variable was analyzed by gender (male, female), age group (18–39, 40–54, 55–71), level of education (low, intermediate, high), skin type (dry/sensitive skin, oily/combined skin, normal skin), skin colour (Northern European, Southern European) and lifestyle (non-smoking/no use of alcohol, smoking/use of alcohol) using Chi-square tests. The frequency of use, amount of use, application area on the body, time of application, location of use and the presence of ventilation were also analyzed by gender, age group and level of education using Chi-square tests. In addition, the co-use of products was analyzed using Cohen's kappa, which reflects the level of agreement corrected for agreement by chance between the use of two products. The brand loyalty of the respondents was described by the proportion of respondents using a specific brand per product. Data were analyzed using SPSS version 18.0. Differences with a p-value of less than 0.05 were considered to be statistically significant unless noted otherwise.

3. Results

The results presented below give a general overview; more detailed information is available as Supplementary material.

3.1. Demographics

In total, 516 out of the 2700 potential participants completed the questionnaire and 27 invitation letters were returned to sender. Therefore, the minimum adjusted response rate was 19.3%. A small proportion of the respondents did not provide information on the demographic variables. Among the ones who did, 210 respondents (41.0%) were male and 302 respondents (59.0%) were female. We constructed three age groups: young (18–39), middle aged (40–54) and senior (55–71). These groups contained 21.6%, 36.9% and 41.5% of the respondents, respectively. Furthermore, the respondents were divided into three groups based on the level of education: low (24.2%), intermediate (38.6%) and high (37.2%), defined as the completion of 6–10 years, 11–14 years and 15 years or more of education. Additionally, the parameter skin type was divided into three groups: dry/sensitive skin, oily/combined skin and normal skin for future detailed exposure assessment. Male respondents mostly reported to have normal skin (68.0%), whereas 21.5% and 10.5% had a dry/sensitive or oily/combined skin, respectively. The proportion of women in the three groups was evenly distributed, being 32.6%, 35.5%, 31.9% in the dry/sensitive skin, oily/combined skin and normal skin group, respectively. Only eight respondents had an Asian skin colour and no respondents had a Negroid skin. Therefore, the parameter skin colour was divided into two groups: Northern European (69.3%) versus Southern European (30.7%).

3.2. Prevalence of use

The prevalence of use was defined as the proportion of users that reported the use of a PCP at least once in the past 6 months. Table 1 shows an overview of the percentages of users per product. Although the percentages of users for most general hygiene products were high, approximately 10% of the respondents reported not to have used deodorant or toothpaste in the last 6 months. Of the hair care products, shampoo was used by 96.7% of the respondents while conditioner was used by 33.5%. The majority of the respondents who used conditioner used a rinse off product (84.4%), while others used a leave on product (6.4%) or a combination of both (9.2%). The percentages of female users were higher ($p < 0.05$) compared to the percentages of male users for all PCPs studied, except for shaving products (Fig. 2). For most products, the percentage of users in the age group 18–39 (young) was higher compared to the percentages of users in the older age groups (data not shown). However, hair dye was most often used by middle aged and low/intermediately educated respondents. In addition, the level of education influenced the use of several other PCPs. More users with a high level of education used aftershave (32.8%) compared to users with an intermediate or low level of education (25.1% and 16.0%, respectively; $p < 0.05$). These figures were 42.2%, 41.2% and 17.6%

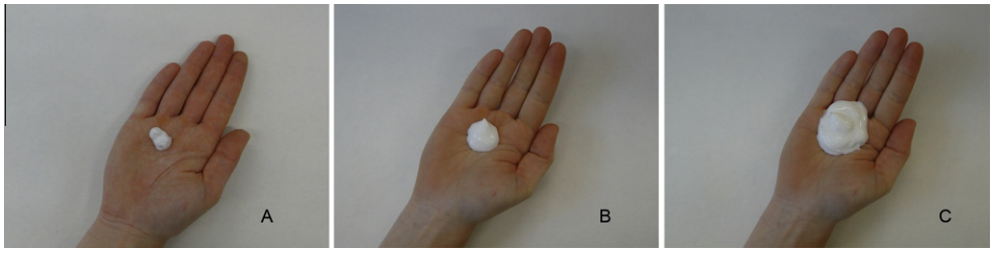

Fig. 1. Example of a photograph used to assess the amount of product (e.g. make-up remover) used per application.

for shaving foam/gel/oil/soap and 81.3%, 69.3% and 59.2% for sunscreen products.

3.3. Frequency of use

The frequency of use of the products with a similar range (<1 time per week, 1–2 times per week, 3–4 times per week, 5–6 times per week, 1 time per day, ⩾2–3 times per day) is summarized in Fig. 3. The distributions of the frequency of use for all PCPs studied are provided in Supplementary material S1. The majority of users (>50%) clearly indicated to use deodorant, day cream, night cream, make-up remover, mascara, eye pencil and eye brow pencil once a day. The frequency of use of the other products was much more diverse and a predominant frequency of use could not be assessed. Toothpaste (not shown in Fig. 3), was generally used once (22.9%) or twice (67.1%) per day, with women belonging slightly more often to the latter category. Hair dye was mostly used every 5–10 weeks (76.7%), while the majority of users (64.7%) applied nail polish less than once a month (data not shown). We observed a higher frequency of use for all skin care products, except for body lotion, among women (1 time per day) compared to men (<1 time per week, $p < 0.05$). The young age group used shaving foam/gel/oil/soap less frequently compared to the senior age group, i.e. 1 time per week and 1 time per day, respectively. This difference in frequency of use was statistically significant. Table 2 shows the frequency of use for tanning products. We observed a large variability in the use of bronzers, sunscreen and after sun ranging from only one to more than 100 days in the past year.

Table 1
General overview of the percentages of users by product and gender based on all respondents ($N = 516$).

Product	Number of users ($N = 516$)	% of users	% of male users ($N = 210$)	% of female users ($N = 302$)
General hygiene				
Deodorant	470	91.1	86.7	94.7
Perfume or Eau de toilette	326	63.2	34.3	83.8
Shower gel	411	79.7	71.0	85.8
Bathing foam/oil	121	23.4	18.1	27.2
Toothpaste	461	89.3	77.6	97.7
Shaving products				
Shaving foam/gel/oil/soap	185	35.9	53.3	23.5
Aftershave	133	25.8	61.0	1.0
Hair care				
Shampoo	499	96.7	92.9	99.7
Conditioner	173	33.5	9.5	50.7
Hairspray	159	30.8	3.3	50.0
Other (gel, lotion, foam, wax)	258	50.0	28.1	65.9
Hair dye	175	33.9	3.3	55.6
Skin care				
Body lotion	264	51.2	21.4	72.2
Hand cream	273	52.9	28.6	69.5
Day cream	268	51.9	11.9	80.5
Night cream	147	28.5	3.3	46.0
Facial cleaning lotion or tonic	140	27.1	2.9	44.4
Cosmetics				
Foundation	99	19.2	0.5	32.5
Make-up remover	130	25.2	0.5	42.7
Powder or rouge	105	20.3	0.5	34.4
Eye shadow	154	29.8	0	50.7
Mascara	187	36.2	0	61.6
Eye pencil	160	31.0	0	52.6
Eyebrow pencil	80	15.5	0	26.5
Lip pencil	24	4.7	0	7.9
Lipstick or lip gloss	170	32.9	0.5	55.6
Lip balm	173	33.5	10.5	50.0
Nail care				
Nail polish	155	30.0	0	51.0
Nail polish remover	145	28.1	0	47.7
Tanning products				
Bronzers	32	6.2	0.5	10.3
Sunscreen	368	71.3	60.5	79.1
After sun	228	44.2	37.6	49.3

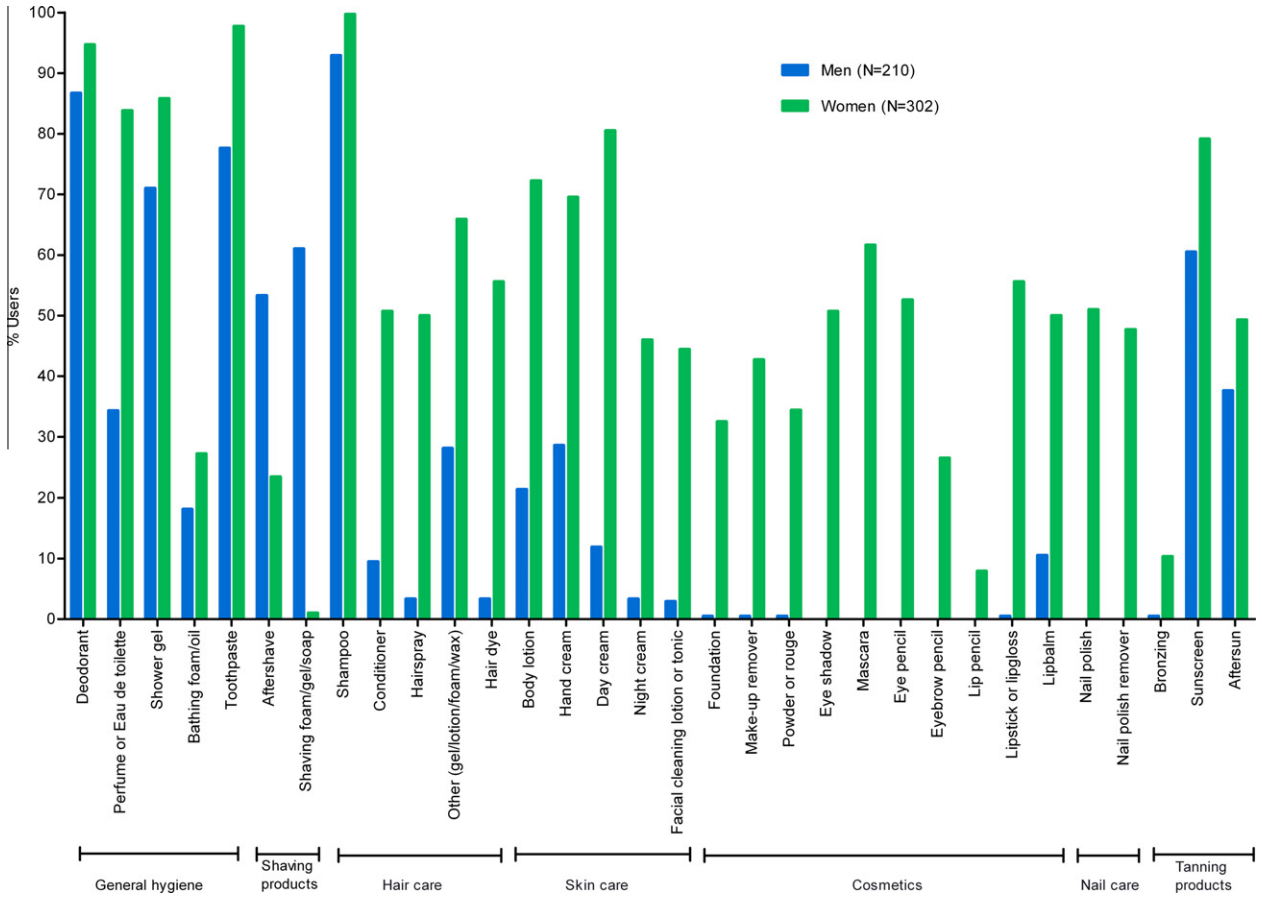

Fig. 2. Percentages of users by gender for all PCPs studied.

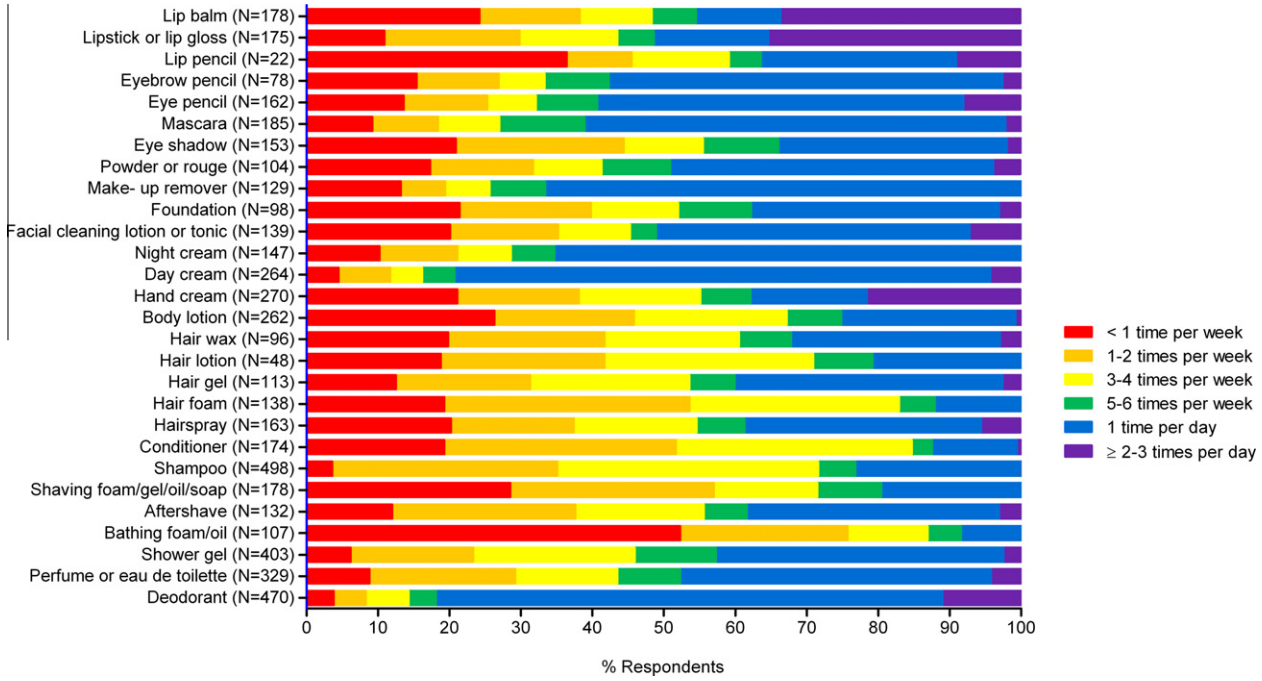

Fig. 3. Frequency of use among respondents ($n = 516$) for the majority of PCPs studied.

3.4. Amount of use

Table 3 shows the mean amounts of use of the PCPs studied per application and per day. For some products, we were unable to determine the amount applied by weighing before and after application due to very small differences (e.g. for eye shadow). The distributions of the amount of use for all PCPs studied are provided in Supplementary material S2. In general, the amounts used differed

Table 2
Frequency of use for bronzers, sunscreen and after sun.

Product	Number of days of use in the past year % of users								
	1 day	2–4 days	5–7 days	8–14 days	15–21 days	22–30 days	31–60 days	61–100 days	>100 days
Tanning products									
Bronzers ($N = 32$)	0	18.8	21.9	15.6	15.6	12.5	15.6	0	0
Sunscreen ($N = 364$)	2.2	12.9	18.7	21.4	17.9	14.6	7.7	2.2	2.5
After sun ($N = 226$)	5.3	15.9	20.4	22.1	17.3	10.6	5.3	2.2	0.9

Table 3
Amount of use per application for all PCPs studied.

Product	Mean amount per application	Mean amount per day	Range of amount per day
General hygiene			
Deodorant			
Cream (g)	1.0	1.0	0.8–8.9
Roller (g)	0.2	0.2	0.1–0.2
Stick (g)	0.1	0.1	0.04–0.1
Spray (g)	0.4	0.4	0.06–0.1
Perfume or Eau de toilette (g)	0.1	0.1	0.04–0.07
Shower gel (g)	6.3	4.5	0.7–10.7
Bathing foam (g)	8.1	1.2	0.1–2.1
Bathing oil (ml)	3.3	0.5	0.1–0.9
Toothpaste (g)	1.1	2.2	0.8–4.0
Shaving products			
Shaving foam (g)	3.1	1.3	0.3–3.4
Shaving gel (g)	4.0	1.7	0.3–3.8
Shaving oil (ml)	1.0	0.4	0.3–2.6
Shaving soap	ND[a]	ND	ND
Aftershave			
Lotion/balm/gel (ml)	1.3	0.6	0.3–2.6
Spray (g)	0.08	0.03	0.03–0.04
Hair care			
Shampoo (g)	4.8	2.4	0.5–7.5
Conditioner (g)	4.9	2.1	0.4–6.4
Hairspray (g)	0.9	0.4	0.3–0.6
Other			
Hair foam (g)	3.5	1.5	0.3–3.4
Hair gel (g)	1.7	1.0	0.3–4.3
Hair lotion (ml)	1.8	1.0	0.4–3.4
Hair wax (g)	1.3	0.6	0.3–3.2
Hair dye	ND	ND	ND
Skin care			
Body lotion (g)	8.5	3.6	0.4–21.4
Hand cream (g)	0.5	0.4	0.08–0.9
Day cream (g)	0.4	0.4	0.1–1.1
Night cream (g)	0.4	0.3	0.09–0.9
Facial cleaning lotion or tonic (ml)	1.6	1.1	0.5–4.3
Cosmetics			
Foundation (g)	0.3	0.2	0.06–0.6
Make-up remover (g)	1.8	1.5	0.7–7.6
Powder or rouge (mg)	5.9	4.2	2.1–21.4
Eye shadow	ND	ND	ND
Mascara (mg)	9.6	8.2	5.1–15.3
Eye pencil (mg)	0.3	0.3	0.2–0.3
Eyebrow pencil (mg)	0.3	0.3	0.2–0.4
Lip pencil (mg)	0.8	0.4	0.3–0.6
Lipstick or lip gloss (mg)	5.2	4.1	1.7–5.1
Lip balm (mg)	12.0	8.6	3.6–10.7
Nail care			
Nail polish (g)	0.3	0.04	0.03–0.1
Nail polish remover (ml)	2.0	0.3	0.1–0.9
Tanning products			
Bronzers (g)	5.8	0.3	0.06–2.9
Sunscreen (g)	9.2	0.4	0.04–1.9
After sun (g)	8.8	0.3	0.04–1.9

[a] ND = not determined. We were unable to determine the amounts used by weighing the products.

between and within the product groups. Some products were used in a wide range of amounts, especially products that are usually applied in large quantities, such as body lotion or sunscreen. In general, men used smaller amounts of skin care products (i.e. body lotion, night cream and hand cream) and tanning products (i.e. sunscreen and after sun) per application compared to women.

Female users applied more shaving foam compared to men, presumably because the shaving area for women is usually larger than for men. These differences were statistically significant. Almost no differences in product amounts used were found between the age groups. Only the amount of eye shadow applied by younger and middle aged users was higher compared to senior users ($p < 0.05$). We hardly observed an effect of educational level on the amount of use, except that users with a high level of education applied more eye pencil compared to users with an intermediate or low level of education.

3.5. Application area

Some PCPs were applied on a single part of the body, whereas others were applied on multiple body parts. The determination of the total exposure to PCPs is influenced by skin permeability, which differs between anatomical sites. The scrotum, forehead, axilla, scalp, back and extremities are sites in general order of decreasing permeability (Klaassen, 2001). Therefore, the most frequently exposed parts of the body were examined regarding the use of body lotion, sunscreen and after sun of which relatively large amounts were used (Fig. 4). The application of these products was not restricted to one body part. Approximately 70–80% of the users applied sunscreen and 65–80% of the users applied after sun on all parts of their body exposed to sunlight on a summer day. Moreover, most users (75–90%) applied body lotion on the upper and lower arms and legs. The percentage of male users applying body lotion on their head and face was higher compared to the percentage of female users. The majority of users applied body lotion, sunscreen and after sun on adjacent body parts. For example, 95.2% of the users who applied body lotion on their lower arms also applied body lotion on their upper arms, while 90.0% of the users that applied sunscreen on their neck also applied sunscreen on their shoulders. Furthermore, most male users applied shaving foam on their head and face (93.5%), whereas most female users applied this product on their axillae (78.3%), pubic area (68.1%) and lower legs (84.1%). More young users compared to middle aged and senior users used shaving foam on their axillae, pubic area, upper legs and lower legs ($p < 0.05$).

3.6. Time of application

Only a small proportion of users reported to use PCPs after midnight. We assumed that these users go to sleep after twelve o'clock in the evening. Therefore, we combined the users applying a product in the evening and the users applying a product at night into a single group. Fig. 5 shows a summary of the application time of the PCPs studied. This figure indicates that the majority of products were predominantly applied in the morning. However, some specific products, such as bathing foam/oil, night cream, facial cleaning lotion or tonic, make-up remover, nail polish remover and after sun were mostly used during the evening or night. Other products, such as hand cream, lip balm and lip stick, did not have a restricted time of application, but were used during the entire day.

3.7. Location of use and the presence of ventilation

Most users (between 89.7% and 99.7%) applied deodorant spray, hair spray, nail polish and nail polish remover indoors. Of these users, approximately 65–75% applied the products in a ventilated area, which was defined as the presence of natural or mechanical ventilation. No meaningful differences were observed for gender, age groups, level of education and skin type.

3.8. Co-use

The usage patterns of all 32 different PCPs were also investigated. Overall, the respondents used an average number of thirteen products (range 0–28). The average number of products used was seventeen (range 3–28) among women and seven (range 2–20) among men. The respondents in the young age group used 16 products on average, whereas 14 and 11 products were used by respondents in the middle age group and the senior age group, respectively. Table 4 shows the Cohen's kappa values with a $p < 0.05$ for co-use of the PCPs studied, with the moderately to highly positive (kappa > 0.40) and negative (kappa < −0.40) values presented in bold. The table shows that the respondents used several products at the same time. For example, 93.5% of all users who applied nail polish

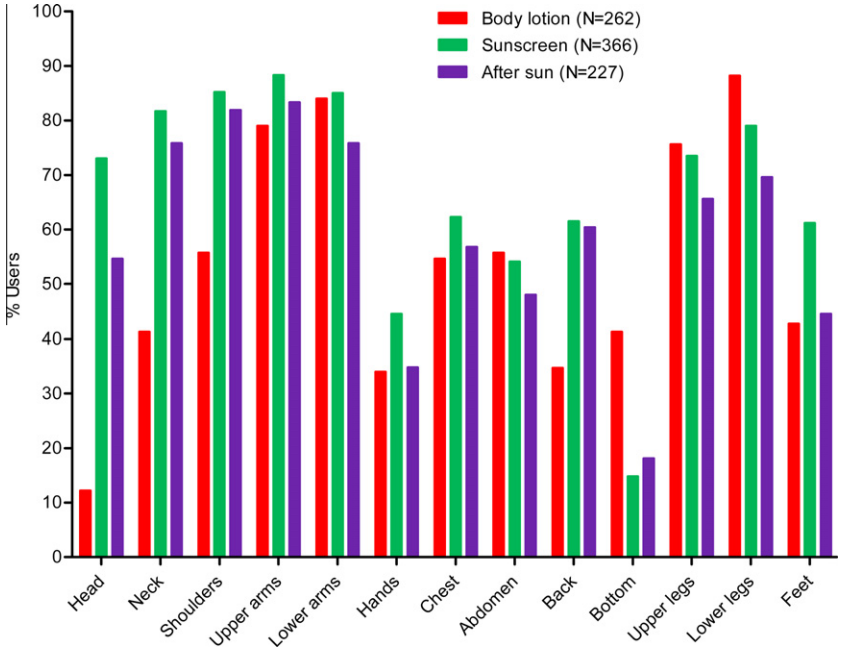

Fig. 4. Application of body lotion, sunscreen and after sun on different parts of the body.

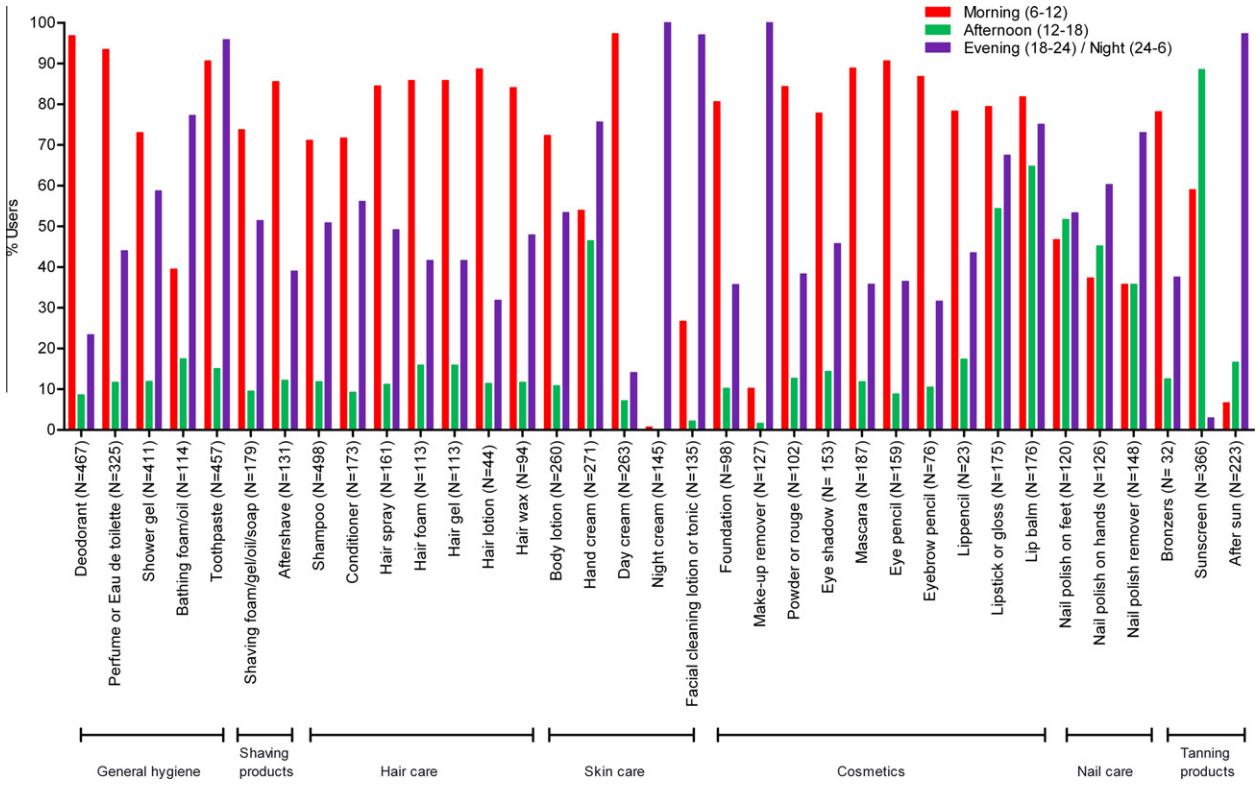

Fig. 5. Frequency of use by time of application (morning, afternoon, evening/night) for all PCPs studied.

also used nail polish remover (kappa = 0.95), and 82.5% of all users who applied eye shadow also used mascara (kappa = 0.62). Being a predominantly male product, the use of aftershave was negatively associated with the use of day cream (kappa = −0.40), night cream (kappa = −0.30), mascara (kappa = −0.40) and several other hair care, skin care, nail care and cosmetic products. The use of most products within the hair care, skin care or cosmetic products groups was correlated. For instance, day cream was quite often used by the same people that used night cream (kappa = 0.49) and the use of powder was highly likely among people who used foundation (kappa = 0.67). However, not all products that seem to be associated were used simultaneously. Out of 499 respondents using shampoo, only 173 (34.7%) used conditioner as well (kappa = 0.03).

4. Discussion

In this study, we created a database containing specific information regarding the usage patterns and circumstances of use of 32 personal care products (PCPs). This database includes the prevalence of use, frequency of use, amount of use, application area on the body, time of application (i.e. time of day), the presence or absence of room ventilation, the co-use of PCPs and the brand loyalty of the users. To the best of our knowledge, no similar studies that include circumstances of use have been published previously. This is the first comprehensive study providing this information for a single population on an individual level.

4.1. Strength and weaknesses

4.1.1. Response rate

Web-based questionnaires are easy to administer and have several advantages, such as immediate checks for incomplete or implausible answers and hiding of non-relevant follow-up questions. In contrast, the response rates in web-based questionnaires are generally lower compared to postal questionnaires, as safety and confidentially issues may play a role (van Gelder et al., 2010). The overall response rate to our web-based questionnaire was 19.3%, which is similar to some population-based studies (Chen and Goodson, 2010; Russell et al., 2010), but relatively low compared to others (Balter et al., 2005; Kongsved et al., 2007; Seguin et al., 2004). Nearly immediately after sending the invitations for this study to potential participants, we were contacted by some people who were unable to access the questionnaire via the URL that was provided in the printed invitation letter. Therefore, we sent these respondents an email with a direct link to the website that hosted the questionnaire. However, this issue may have had a negative impact on the response rate, as it is unlikely that all respondents who experienced difficulties contacted us.

4.1.2. Representativeness

We believe that the usage patterns and circumstances of use of PCPs collected in this study are fairly representative for the Dutch adult population, as we started with a random sample of Dutch citizens living throughout the entire country and we have no indications for selective non-response. In addition, most results seem to be logic and are generally as expected. However, the highly educated respondents (37.2%) may be slightly overrepresented compared to the Dutch general population. In 2010, the Dutch adult population (age 24–64) consisted for 33% of highly educated people (Harbers, 2011). Consumer behaviour (i.e. usage of PCPs) is influenced by personal, socio-cultural and marketing variables (Souiden and Diagne, 2009; Weber and Capitant de Villebonne, 2002). The latter two issues make it hard to generalize our results to other populations, such as in Southern Europe or other continents. However, the format of our web-based questionnaire is universal. After translation, the questionnaire could be implemented in other European countries or elsewhere in order to assess usage patterns and circumstances of PCPs use.

Table 4
Kappa coefficients for co-use of all PCPs studied among all respondents ($N = 516$).

	General hygiene					Shaving products		Hair care					Skin care					Cosmetics										Nail care		Tanning products		
	Deodorant	Perfume or Eau de toilette	Shower gel	Bathing foam/oil	Toothpaste	Shaving foam/gel/oil/ soap	Aftershave	Shampoo	Conditioner	Hairspray	Other (gel, lotion, foam, wax)	Hair dye	Body lotion	Hand cream	Day cream	Night cream	Facial cleaning lotion or tonic	Foundation	Make-up remover	Powder or rouge	Eye shadow	Mascara	Eye pencil	Eyebrow pencil	Lip pencil	Lipstick or lip gloss	Lip balm	Nail polish	Nail polish remover	Bronzers	Sunscreen	After sun
General hygiene																															
Deodorant																															
Perfume or Eau de toilette	0.12																														
Shower gel	0.13	0.19																													
Bathing foam/ oil		0.11																													
Toothpaste	0.09	0.14	0.10	0.04																											
Shaving products																															
Shaving foam/ gel/oil/ soap			0.06																												
Aftershave		−0.31		−0.11	−0.09	0.24																									
Hair care																															
Shampoo	0.08	0.08			0.18																										
Conditioner		0.26	0.09	0.14	0.06		−0.28	0.03																							
Hairspray	0.04	0.31	0.12	0.11	0.10		−0.36	0.03	0.33																						
Other (gel, lotion, foam, wax)	0.09	0.34	0.18		0.14		−0.24	0.07	0.19	0.28																					
Hair dye	0.06	0.31	0.10		0.09	−0.18	−0.38	0.03	0.37	0.30	0.27																				
Skin care																															
Body lotion	0.10	0.38	0.24	0.15	0.14		−0.28	0.05	0.30	0.31	0.30	0.30																			
Hand cream	0.06	0.26	0.14	0.12	0.16		−0.18	0.03	0.17	0.23	0.19	0.20	0.39																		
Day cream	0.09	**0.40**	0.12	0.11	0.19	−0.22	**−0.40**	0.07	0.34	0.36	0.34	0.39	**0.49**	0.39																	
Night cream		0.25	0.10	0.18	0.08	−0.17	−0.30	0.03	0.35	0.27	0.22	0.33	**0.41**	0.34	**0.49**																
Facial cleaning lotion or tonic	0.04	0.24	0.11	0.10	0.08		−0.29	0.03	0.29	0.32	0.23	0.35	0.33	0.23	**0.42**	**0.45**															
Cosmetics																															
Foundation	0.03	0.20	0.08	0.18	0.05		−0.26	0.02	0.31	0.39	0.19	0.29	0.26	0.17	0.32	**0.44**	**0.41**														
Make-up remover	0.04	0.25	0.13	0.11	0.07		−0.31	0.02	0.30	**0.40**	0.24	0.33	0.35	0.25	0.36	**0.43**	**0.44**	**0.47**													
Powder or rouge		0.21	0.07	0.12	0.05		−0.27	0.02	0.32	**0.40**	0.22	0.33	0.24	0.18	0.35	**0.42**	0.38	**0.67**	**0.45**												
Eye shadow		0.31	0.10	0.12	0.10	−0.10	−0.35	0.03	0.35	**0.45**	0.26	0.33	0.39	0.28	**0.47**	**0.46**	**0.45**	**0.50**	**0.55**	**0.53**											
Mascara	0.04	0.38	0.14		0.11		**−0.40**	0.03	0.38	**0.43**	0.31	**0.43**	**0.43**	0.28	**0.50**	**0.44**	**0.51**	**0.46**	**0.63**	**0.49**	**0.62**										
Eye pencil	0.04	0.29	0.11	0.14	0.09		−0.36		0.37	**0.42**	0.30	0.39	0.35	0.25	**0.44**	**0.41**	**0.47**	**0.44**	**0.54**	**0.46**	**0.55**	**0.63**									
Eyebrow pencil		0.15	0.06		0.04		−0.23		0.15	0.27	0.12	0.24	0.21	0.13	0.25	0.26	0.29	0.39	0.36	**0.44**	0.36	0.34	0.34								
Lip pencil		0.03		0.10			−0.07		0.07	0.06		0.09	0.04	0.06	0.08	0.18	0.11	0.22	0.14	0.20	0.16	0.10	0.14	0.25							
Lipstick or lip gloss	0.04	0.30	0.10	0.14	0.10	−0.14	−0.39	0.03	0.34	**0.44**	0.25	**0.41**	**0.42**	0.34	**0.52**	**0.49**	**0.45**	**0.46**	**0.50**	**0.47**	**0.61**	**0.60**	**0.52**	0.34	0.16						
Lip balm	0.05	0.23	0.12	0.15	0.10		−0.26	0.03	0.30	0.29	0.27	0.25	0.34	0.34	0.32	0.23	0.31	0.28	0.38	0.25	0.31	**0.40**	0.32	0.11	0.06	0.29					
Nail care																															
Nail polish		0.26	0.12	0.14	0.09		−0.37	0.03	**0.40**	**0.42**	0.24	**0.43**	**0.41**	0.27	**0.42**	0.35	0.38	0.38	**0.51**	0.39	**0.44**	**0.57**	**0.48**	0.28	0.12	**0.57**	0.35				
Nail polish remover	0.03	0.23	0.11	0.12	0.09		−0.35	0.03	0.38	0.39	0.23	**0.43**	0.37	0.25	0.39	0.31	0.38	0.36	**0.51**	0.37	**0.42**	**0.53**	**0.42**	0.26	0.12	**0.53**	0.34	**0.95**			
Tanning products																															
Bronzers		0.05	0.02		0.02		−0.11		0.10	0.11	0.05	0.08	0.08	0.07	0.09	0.10	0.12	0.12	0.11	0.12	0.17	0.13	0.13	0.18	0.10	0.17	0.11	0.14	0.13		
Sunscreen	0.09	0.21	0.20		0.14		−0.08		0.14	0.12	0.16	0.11	0.17	0.16	0.24	0.13	0.12	0.06	0.12	0.10	0.12	0.17	0.13	0.06		0.13	0.13	0.14	0.13		
After sun	0.07	0.15	0.10		0.12		−0.06		0.18	0.16	0.17	0.14	0.15	0.13	0.21	0.18	0.19	0.12	0.18	0.16	0.15	0.22	0.12	0.10		0.16	0.16	0.18	0.20	0.06	**0.42**

Cohen's kappa. Only values with $p < 0.05$ are shown.

4.1.3. Recall issues

The respondents were asked to recall their use of most PCPs during the previous 6 months, and their use of tanning products during the previous year. These relatively long time periods made it difficult for the respondents to recall their use exactly, but take into account variability in use of PCPs. Furthermore, by using a questionnaire alone, it was difficult to assess precise amounts of the products that were used per application. Weighing a PCP before and after application is a more accurate method to assess the precise amount of product used (Bennett et al., 2011), but this is impractical with large survey-based studies and puts an additional burden on the respondents. In nutritional research, photographs are often used to assess the amount of food consumed (Boon et al., 2009). This method results in a representative assessment (Ovaskainen et al., 2008; Turconi et al., 2005). Therefore, a similar strategy with photographic aids was used to assess the amount of product used per application.

We assumed that the usage patterns of consumers are influenced by skin type. For example, someone with dry/sensitive skin would likely apply more body lotion than someone with normal or oily/combined skin. However, the question related to this topic was not formulated specific enough in the questionnaire. The questionnaire referred to general skin type, but this should have been divided into specific parts of the body. For example, in one individual, facial skin might be classified as sensitive skin, whereas the rest of the body might be classified as normal skin. Therefore, the results by skin type should be interpreted with caution.

4.1.4. Exposure assessment

The distributions of the frequency of use and the amount of use per product and by gender presented in the Supplementary material provide an excellent basis for exposure assessment to PCPs. In addition, extra exposure information regarding level of education, skin type or skin colour could be beneficial when a specific population requires attention. Also, the circumstances of use, such as the time of application, the location of use or the presence of ventilation could provide additional useful information. Because we assessed product use over the past 6 months, no information was given about peak exposures. In general, however, time-weighted averages make for more balanced exposure assessment.

4.2. Reflection on the literature

4.2.1. Prevalence of use

The prevalence of PCPs use was influenced by demographic factors, such as gender and age. Within all product categories (with the exception of shaving products), the percentage of female respondents was higher than that of male respondents. Recently, Wu et al. (2010) collected information regarding usage patterns of personal care products in California households and reported similar results. However, the prevalence of use of shaving foam/gel/oil was not investigated. Furthermore, only female participants received questions regarding the use of cosmetics (i.e. make-up products), and only male participants were questioned regarding the use of aftershave. In the current study, we did not make such a predefined assumption that only women use cosmetic products and only men use aftershave. Such an assumption can cause information to be missed, as men may use cosmetics professionally (e.g. actors) and male cosmetic use is also becoming more accepted in society. Indeed, some of our male respondents (0.5%) reported using make-up products (foundation, make-up remover and powder or rouge).

4.2.2. Frequency of use

In general, the frequency of use of the PCPs studied varied widely. This variation was also observed by Wu et al. (2010). In a series of studies reported by Loretz et al. (2005, 2006, 2008) exposure data were collected for cosmetic products and the daily use rates of several PCPs were reported, including facial cleanser, hair conditioner and eye shadow. However, for these studies only female respondents who regularly used two or more test products were recruited. As a random population sample was included in the current study, it was not possible to compare our results with these previous reports.

4.2.3. Amount of use

The European cosmetics manufacturers, acting within the trade organisation Colipa, modelled the exposure of European consumers to several cosmetics products (Hall et al., 2007, 2011). In these studies, Hall et al. assessed the amount applied per day, whereas Loretz et al. (2005, 2006, 2008) reported on the amount applied per application. Table 5 gives an overview of the amount of use per application or per day for the current study and the studies described by Loretz and Hall. In the current study, the mean amounts of shampoo and conditioner applied *per application* were 4.8 and 4.9 g, respectively. The corresponding mean amounts applied *per day* were 2.4 and 2.1 g. In contrast, Loretz et al. (2006, 2008) reported values that were more than twice these amounts (11.8 and 13.1 g *per application* for shampoo and conditioner, respectively). Hall et al. also reported at least a twofold higher amount for the application of shampoo (application *per day* being 6.0 g) (Hall et al., 2011). Similar differences were observed with respect

Table 5
Overview of the amount of use for some PCPs presented in the current study and in the literature.

Product	Loretz et al.[a] (amount of use per application)	Current study (amount of use per application)	Hall et al.[b] (amount of use per day)	Current study (amount of use per day)
Perfume spray	0.5 g	0.1 g	ND[c]	0.1 g
Shower gel	ND	6.3 g	11.3 g	4.5 g
Toothpaste	ND	1.1 g	2.1 g	2.2 g
Shampoo	12.8 g	4.8 g	6.0 g	2.4 g
Conditioner	13.1 g	4.9 g	ND	2.1 g
Hair spray	3.6 g	0.9 g	ND	0.4 g
Body lotion	4.4 g	8.5 g	4.5 g	3.6 g
Hand cream	ND	0.5 g	1.1 g	0.4 g
Day cream	1.2 g	0.4 g	ND	0.4 g
Foundation	0.7 g	0.3 g	0.2 g	0.2 g
Lip stick	0.01 g	5.2 mg	24.6 mg	4.2 mg

[a] Loretz et al. (2005, 2006, 2008).
[b] Hall et al. (2007, 2011).
[c] ND = No data available.

to the amounts of shower gel, hand cream, day cream and lip stick used. On the other hand, the amount of body lotion *per application* was 8.5 g in the current study, whereas Loretz et al. (2005) reported only 4.4 g. *Per day*, the amount of body lotion applied was 4.5 g in the study by Hall and colleagues, which is more or less similar to our findings (3.6 g). The reported amounts of foundation and toothpaste in the current study were equal to the amounts presented in the Colipa study (Hall et al., 2007, 2011).

4.2.4. Co-use

In contrast to Wu et al. (2010), Cohen's kappa values were calculated to evaluate the combined use of several PCPs. In addition, the percentages of respondents using one product and a second product were calculated. A high percentage of respondents (70–95%) used a combination of two skin care products, for example, day cream and night cream. A similar usage pattern was observed by Wu et al., who reported a moderate correlation between the amounts of shampoo and hair conditioner used ($R = 0.43$). In our study, however, only 34.7% of the respondents who used shampoo also used conditioner, which led to a kappa coefficient of 0.03.

The differences regarding prevalence of use, frequency of use, amount of use and co-use between our study and the studies described in the literature may be explained by the different populations studied. However, the literature was not sufficiently detailed on age, gender or level of education to properly assess the differences and similarities. Another explanation may be the variability in the methods of data collection. Telephone interviews were used by Wu et al. (2010), whereas Hall et al. (2007, 2011) used existing databases, such as the ETCD (European Toiletries and Cosmetics Database). The information in that database is provided by volunteers via a postal survey. Volunteers included in the study by Loretz et al. (2005, 2006, 2008) used products of which the weight was recorded at the beginning and at the end of the study. In addition, these volunteers recorded daily use information in a diary.

In conclusion, the current study provides valuable information on the individual usage patterns and circumstances of PCP use by Dutch adults that may partly be extrapolated to other populations. A database was created that will guide the next step in consumer exposure modelling of PCPs as well as aggregate exposure assessment for substances that are components of PCPs.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.fct.2012.11.014.

References

Ayenimo, J.G., Yusuf, A.M., Adekunle, A.S., Makinde, O.W., 2010. Heavy metal exposure from personal care products. Bull. Environ. Contam. Toxicol. 84, 8–14.

Balter, K.A., Balter, O., Fondell, E., Lagerros, Y.T., 2005. Web-based and mailed questionnaires: a comparison of response rates and compliance. Epidemiology 16, 577–579.

Bennett, D.H., Wu, X.M., Teague, C.H., Lee, K., Cassady, D.L., Ritz, B., Hertz-Picciotto, I., 2011. Passive sampling methods to determine household and personal care product use. J. Expo. Sci. Environ. Epidemiol. 22, 148–160.

Boon, P.E., Bakker, M.I., van Klaveren, J.D., van Rossum, C.T.M., 2009. Risk Assessment of the Dietary Exposure to Contaminants and Pesticide Residues in Young Children in the Netherlands. National Institute for Public Health and the Environment, Bilthoven.

Centers for Disease Control and Prevention (CDC), 2012. Mercury exposure among household users and nonusers of skin-lightening creams produced in Mexico – California and Virginia, 2010. MMWR Morb. Mortal. Wkly. Rep. 61, 33–36.

Chan, T.Y., 2011. Inorganic mercury poisoning associated with skin-lightening cosmetic products. Clin. Toxicol. 49, 886–891.

Chen, L.S., Goodson, P., 2010. Web-based survey of US health educators: challenges and lessons. Am. J. Health Behav. 34, 3–11.

Chen, J., Ahn, K.C., Gee, N.A., Ahmed, M.I., Duleba, A.J., Zhao, L., Gee, S.J., Hammock, B.D., Lasley, B.L., 2008. Triclocarban enhances testosterone action: a new type of endocrine disruptor? Endocrinology 149, 1173–1179.

Cowan-Ellsberry, C.E., Robison, S.H., 2009. Refining aggregate exposure: example using parabens. Regul. Toxicol. Pharmacol. 55, 321–329.

Goossens, A., 2011. Contact-allergic reactions to cosmetics. J. Allergy, 6 p. (Article ID 467071).

Hall, B., Tozer, S., Safford, B., Coroama, M., Steiling, W., Leneveu-Duchemin, M.C., McNamara, C., Gibney, M., 2007. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments. Food Chem. Toxicol. 45, 2097–2108.

Hall, B., Steiling, W., Safford, B., Coroama, M., Tozer, S., Firmani, C., McNamara, C., Gibney, M., 2011. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments. Part 2. Food Chem. Toxicol. 49, 408–422.

Harbers, M.M., 2011. Scholing en opleiding: Zijn er verschillen tussen Nederland en andere landen? In: RIVM (Ed.), Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. National Institute for Public Health and the Environment, Bilthoven.

Klaassen, C.D., 2001. Casarett and Doull's Toxicology: The Basic Science of Poisons, sixth ed. McGraw-Hill, New York.

Kongsved, S.M., Basnov, M., Holm-Christensen, K., Hjollund, N.H., 2007. Response rate and completeness of questionnaires: a randomized study of Internet versus paper-and-pencil versions. J. Med. Internet Res. 9, e25.

Lorenz, C., Von Goetz, N., Scheringer, M., Wormuth, M., Hungerbuhler, K., 2011. Potential exposure of German consumers to engineered nanoparticles in cosmetics and personal care products. Nanotoxicology 5, 12–29.

Loretz, L.J., Api, A.M., Barraj, L.M., Burdick, J., Dressler, W.E., Gettings, S.D., Han, H.H., Pan, Y.H., Re, T.A., Renskers, K.J., Rothenstein, A., Scrafford, C.G., Sewall, C., 2005. Exposure data for cosmetic products: lipstick, body lotion, and face cream. Food Chem. Toxicol. 43, 279–291.

Loretz, L., Api, A.M., Barraj, L., Burdick, J., Davis, d.A., Dressler, W., Gilberti, E., Jarrett, G., Mann, S., Laurie Pan, Y.H., Re, T., Renskers, K., Scrafford, C., Vater, S., 2006. Exposure data for personal care products: hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. Food Chem. Toxicol. 44, 2008–2018.

Loretz, L.J., Api, A.M., Babcock, L., Barraj, L.M., Burdick, J., Cater, K.C., Jarrett, G., Mann, S., Pan, Y.H., Re, T.A., Renskers, K.J., Scrafford, C.G., 2008. Exposure data for cosmetic products: facial cleanser, hair conditioner, and eye shadow. Food Chem. Toxicol. 46, 1516–1524.

Lyche, J.L., Gutleb, A.C., Bergman, A., Eriksen, G.S., Murk, A.J., Ropstad, E., Saunders, M., Skaare, J.U., 2009. Reproductive and developmental toxicity of phthalates. J. Toxicol. Environ. Health B: Crit. Rev. 12, 225–249.

Ovaskainen, M.L., Paturi, M., Reinivuo, H., Hannila, M.L., Sinkko, H., Lehtisalo, J., Pynnonen-Polari, O., Mannisto, S., 2008. Accuracy in the estimation of food servings against the portions in food photographs. Eur. J. Clin. Nutr. 62, 674–681.

Russell, C.W., Boggs, D.A., Palmer, J.R., Rosenberg, L., 2010. Use of a web-based questionnaire in the Black Women's Health Study. Am. J. Epidemiol. 172, 1286–1291.

Schauder, S., Ippen, H., 1997. Contact and photocontact sensitivity to sunscreens. Review of a 15-year experience and of the literature. Contact Dermatitis 37, 221–232.

Scientific Committee on Consumer Safety (SCCS), 2010. The SCCS'S Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation, 7th revision. Directorate-General for Health & Consumers, Brussels.

Seguin, R., Godwin, M., MacDonald, S., McCall, M., 2004. E-mail or snail mail? Randomized controlled trial on which works better for surveys. Can. Fam. Physician 50, 414–419.

Souiden, N., Diagne, M., 2009. Canadian and French men's consumption of cosmetics: a comparison of their attitudes and motivations. J. Consum. Mark. 26, 97–109.

Turconi, G., Guarcello, M., Berzolari, F.G., Carolei, A., Bazzano, R., Roggi, C., 2005. An evaluation of a colour food photography atlas as a tool for quantifying food portion size in epidemiological dietary surveys. Eur. J. Clin. Nutr. 59, 923–931.

Van Engelen, J.G., Heinemeyer, G., Rodriguez, C., 2007. Consumer exposure scenarios: development, challenges and possible solutions. J. Expo. Sci. Environ. Epidemiol. 17 (Suppl. 1), S26–33.

van Gelder, M.M., Bretveld, R.W., Roeleveld, N., 2010. Web-based questionnaires: the future in epidemiology? Am. J. Epidemiol. 172, 1292–1298.

von Goetz, N., Wormuth, M., Scheringer, M., Hungerbuhler, K., 2010. Bisphenol a: how the most relevant exposure sources contribute to total consumer exposure. Risk Anal. 30, 473–487.

Weber, J.M., Capitant de Villebonne, J., 2002. Differences in purchase behavior between France and the USA: the cosmetic industry. JFMM 6, 396–407.

Witorsch, R.J., Thomas, J.A., 2010. Personal care products and endocrine disruption: a critical review of the literature. Crit. Rev. Toxicol. 40 (Suppl. 3), 1–30.

Wu, X.M., Bennett, D.H., Ritz, B., Cassady, D.L., Lee, K., Hertz-Picciotto, I., 2010. Usage pattern of personal care products in California households. Food Chem. Toxicol. 48, 3109–3119.

Appendix 4

The corresponding subsections of Appendix 4 contain the following information:

A4-1 General equations and the default input parameters used for the exposure calculations in tier 1 assessment

Inhalation:

$$C_{inh} = \frac{Q_{prod} \cdot Fc_{prod}}{V_{room}}$$

$$D_{inh} = \frac{F_{resp} \cdot C_{inh} \cdot IH \cdot T_{contact} \cdot FQ}{BW}$$

Input Parameter	Description	Unit	Default
Q_{prod}	Amount of product used	[mg]	
Fc_{prod}	Weight fraction of D5 in a product	[g/g$_{prod}$]	
V_{room}	Room volume	[m^3]	2
F_{resp}	Respirable fraction of inhaled D5	[-]	1
IH	Inhalation rate of a person	[m^3/day]	26
$T_{contact}$	Duration of contact per event	[day]	
FQ	Frequency of use	[1/day]	
BW	Body weight of a person	[kg]	60
Output Parameter	**Description**	**Unit**	
C_{inh}	Concentration of D5 in room air	[mg/m^3]	
D_{inh}	Inhalatory dose	[mg/kg bw/day]	

Dermal:

$$D_{der} = \frac{Q_{prod} \cdot Fc_{prod} \cdot A_{abs} \cdot FQ \cdot Rf}{BW}$$

Input Parameter	Description	Unit	Default
Q_{prod}	Amount of product used	[mg]	
Fc_{prod}	Weight fraction of D5 in a product	[g/g$_{prod}$]	
A_{abs}	Dermal absorption fraction	[-]	1
FQ	Frequency of use	[1/day]	
Rf	Retention factor	[-]	
BW	Body weight of a person	[kg]	60
Output Parameter	**Description**	**Unit**	
D_{der}	Dermal dose	[mg/kg bw/day]	

Oral:

$$D_{oral} = \frac{V \cdot D \cdot Fc_{prod} \cdot FQ}{BW}$$

Input Parameter	Description	Unit	Default
V	Volume of product swallowed	[cm^3]	
D	Density of product	[mg/cm^3]	1
Fc_{prod}	Weight fraction of D5 in a product	[-]	
FQ	Frequency of use	[1/day]	
BW	Body weight of a person	[kg]	60

Output Parameter	Description	Unit
D_{oral}	Oral dose	[mg/kg bw/day]

A4-2 Physicochemical properties of D5 and TCS

Table A4 - 2.1. Physicochemical properties and thermodynamic characteristics of D5 (source: modified from Health Canada, 2008)

Parameter	Type	Units	Temperature (°C)	Value	Reference
Molar Mass	-	g/mol	-	370.78	
Melting point	Experimental	°C	-	-38	PhysProp 2006
	Modelled	°C	-	-5.19	MPBPWIN 2000
Boiling point	Experimental	°C	-	210	PhysProp 2006
	Modelled	°C	-	196.78	MPBPWIN 2000
Density	Experimental	kg/m^3	-	959	GDL, 2011
Vapour Pressure	Experimental	Pa	25	26.66	Flaningam 1986
	Experimental	Pa	25	33.2	SEHSC 2005a
	Modelled	Pa	25	29.06	MPBPWIN 2000
Henry's Law constant	Modelled	$Pa*m^3/mol$	-	3,350,000	Calculated from Kaw value of Xu and Kropscott 2007
	Experimental	$Pa*m^3/mol$	23	13,444	David et al., 2000
	Experimental	$Pa*m^3/mol$	26	32,317	Kochetkov et al., 2001
	Experimental	$Pa*m^3/mol$	26	29,831	Kochetkov et al., 2001
	Modelled	$Pa*m^3/mol$	25	12,159	HENRY WIN 2000
$LogK_{aw}$	Experimental		24.6	3.13	Xu and Kropscott 2007
$LogK_{ow}$	Experimental		-	5.2	Bruggeman et al., 1984
	Experimental		25.3	8.03	Kozerski 2007
	Experimental		22.4	4.76	Sible 2006
	Modelled		-	5.71	KOWWIN 2000
$LogK_{oc}$	Experimental		-	5.17	SEHSC 2005a
	Modelled		-	5.16	PCKOCWIN 2000
$LogK_{oa}$	Experimental		24	5.06	Xu 2006
Blood:Air Partitioning Coefficient	Modelled		-	0.4	Andersen et al., 2001 Reddy et al., 2008
Water Solubility	Experimental	mg/L	23	0.017	Varaprath et al., 1996
	Modelled	mg/L	25	0.05	WSKOWWIN 2000
Heat of Evaporation	not stated	kJ/mol	-	51.4	CES, 2013

Table A4 - 2.2. Physicochemical properties and thermodynamic characteristics of TCS (sources: modified from NICNAS, 2009 and Health Canada, 2012)

Parameter	Type	Units	Temperature (°C)	Value	Reference
Molar Mass	-	g/mol	-	289.54	
Melting point	Experimental	°C	-	54-57	Sax and Lewis, 2000
	Experimental	°C	-	54-57.3	O'Neil, 2001
Boiling point	Modelled	°C	-	374	MPBPWIN 2008
Density	Experimental	kg/m^3	22	1550	Fiege et al., 2000
Vapour Pressure	Experimental	Pa	20	$5.33x10^{-4}$	O'Neil, 2001
	Experimental	Pa	100	2.6	Fiege et al., 2000
Henry's Law constant	Modelled	$Pa*m^3/mol$	25	$5.05x10^{-4}$	HENRYWIN 2008
	Experimental	$Pa*m^3/mol$	25	$1.54x10^{-2}$	O'Neil, 2001; Yalkowsky and He, 2003
LogKow	Experimental		-	4.76	NITE 2006
LogKoa	Modelled		-	9.97	KOAWIN 2008
LogKoc	Experimental		-	3.34-4.67	Singer et al., 2002; Wu et al., 2009; Xu et al., 2009; Karnjanapiboonwong et al., 2010
Solubility	in water	mg/L	20	10	Ciba Specialty Chemicals, 2001
	in *n*-hexane	mg/L	25	85,000	
	in acetone	mg/L	25	>1,000,000	

A4-3 Results of the tier 1 assessment for D5 and TCS

Table A4 - 3.1. Tier 1 worst-case scenario assessment of aggregate consumer exposure to D5 from application of C&PCPs (evaporation scenario not included)

Product category	Product subcategory	Acute exposure (i.e. on the day of use), mg/kg_bw/day						Chronic exposure, mg/kg_bw/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
Hair Care	Shampoo			2.6E-01	4.4E-04					9.3E-02	1.6E-04		
	Conditioner (rinse-off)			1.3E-01	2.2E-04					3.7E-02	6.3E-05		
	Conditioner (leave-on) [d]			6.5E+00	1.1E-02					1.8E+00	3.1E-03		
	Hair mask			3.3E-01	5.6E-04					9.3E-02	1.6E-04		
	Hair styling (wax, mousse, gel)			1.3E+01	2.2E-02					6.5E+00	1.1E-02		
	Fixative spray	9.2E+00	1.8E-01	1.0E+00	1.7E-03			5.5E+00	1.1E-01	6.0E-01	1.0E-03		
	Detangle spray	4.6E+00	9.2E-02	5.0E-01	8.5E-04			1.3E+00	2.6E-02	1.4E-01	2.4E-04		
	Semi-permanent dye			7.5E-01	1.3E-03					2.7E-02	4.5E-05		
	Permanent dye (oxidative)			2.5E+00	4.3E-03					6.8E-02	1.2E-04		
	Hair bleach [d]			3.3E+00	5.7E-03					9.1E-02	1.6E-04		
	Permanent wave			1.9E+00	3.2E-03					2.0E-02	3.5E-05		
Bath and Shower	Body wash (gel, cream, scrub)			3.1E-02	5.3E-05					1.4E-02	2.4E-05		

Product category	Product subcategory	Acute exposure (i.e. on the day of use), mg/kg_bw/day						Chronic exposure, mg/kg_bw/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
Sun Care	Bronzer, sun-tan			1.3E+01	2.2E-02					1.4E+00	2.4E-03		
	Sun screen (cream, lotion)			2.4E+02	4.1E-01					2.5E+01	4.2E-02		
	Sun screen (spray) [d]	2.3E+01	4.6E-01	2.4E+02	4.1E-01			2.4E+00	4.7E-02	2.5E+01	4.2E-02		
Skin Care	Face cream (day, night)			2.3E+01	3.9E-02					2.3E+01	3.9E-02		
	Face whitening cream			1.2E+01	2.0E-02					2.9E+00	4.9E-03		
	Hand cream			3.2E+01	5.5E-02					3.2E+01	5.5E-02		
	Eye cream			2.0E+00	3.5E-03					2.0E+00	3.5E-03		
	Facial cleanser (peeling, scrub)			1.3E-03	2.3E-06					3.8E-04	6.5E-07		
	Facial cleanser (tissues)			1.7E-01	2.9E-04					4.8E-02	8.2E-05		
	Face pack (peel-off mask)			6.7E+01	1.1E-01					1.9E+01	3.2E-02		
Oral Care	Toothpaste					3.0E-02	3.0E-02					3.0E-02	3.0E-02
	Mouthwash					3.6E+00	3.6E+00					3.6E+00	3.6E+00
Foot Care	Antiperspirant (gel, cream)			1.2E+01	2.0E-02					1.2E+01	2.0E-02		
	Antifungal gel, cream			3.3E-01	5.6E-04					8.1E-02	1.4E-04		
Deodorant	Spray [d]	1.7E+00	3.3E-02	1.7E+01	2.9E-02			1.7E+00	3.3E-02	1.7E+01	2.9E-02		
	Stick and roll-on			1.3E+01	2.1E-02					6.3E+00	1.1E-02		
Shaving	Gel, foam			3.0E-02	5.1E-05					3.0E-02	5.1E-05		
	Balm, balsam			4.0E+00	6.8E-03					4.0E+00	6.8E-03		
Make-up	Mascara			3.3E-01	5.6E-04					3.3E-01	5.6E-04		
	Eye shadow (liquid and powder)			2.3E-01	3.9E-04					2.3E-01	3.9E-04		
	Eye liner			4.2E-02	7.1E-05					4.2E-02	7.1E-05		

Product category	Product subcategory	Acute exposure (i.e. on the day of use), mg/kg_bw/day						Chronic exposure, mg/kg_bw/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
	Liquid foundation			3.4E+00	5.8E-03					3.4E+00	5.8E-03		
	Compact powder			7.1E+00	1.2E-02					7.1E+00	1.2E-02		
	Remover			4.2E-01	7.1E-04					4.2E-01	7.1E-04		
	Lipstick, lip balm			4.3E-01	7.3E-04	4.3E-01	4.3E-01			4.3E-01	7.3E-04	4.3E-01	4.3E-01
Nail Care	Polish enamel, top and base coat			8.8E-03	1.5E-05					3.7E-03	6.4E-06		
	Polish remover			4.0E-02	6.8E-05					1.7E-02	2.9E-05		
Baby Care	Diaper cream			2.6E+01	4.4E-02					2.6E+01	4.4E-02		
	Talc			8.0E-01	1.4E-03					8.0E-01	1.4E-03		
	Tissues			2.5E+00	4.3E-03					2.5E+00	4.3E-03		
Fragrance	Eau de toilette (spray) [d]	2.9E-02	5.9E-04	3.1E-01	5.3E-04			2.9E-02	5.9E-04	3.1E-01	5.3E-04		
	Eau de perfume (spray)	6.2E-03	1.2E-04	7.0E-02	1.2E-04			2.0E-03	4.0E-05	2.3E-02	3.9E-05		
Miscellaneous	Depilatory Cream			3.0E-02	5.1E-05					1.4E-03	2.4E-06		
	Massage Essential Oil			2.0E+01	3.3E-02					1.3E+00	2.2E-03		
	Bath Essential Oil			4.0E-02	6.8E-05					5.7E-03	9.7E-06		
Antifoam agent (in food packaging)	-					1.7E-03	1.7E-03					1.7E-03	1.7E-03
Pharmacy: OTC drugs	-					1.7E-03	1.7E-03					1.7E-03	1.7E-03
Aggregate Exposure:		**38.4**	**0.77**	**614**	**1.04**	**4.06**	**4.06**	**10.8**	**0.22**	**307**	**0.52**	**4.06**	**4.06**
Aggregate Exposure excluding sun care products:		**15.4**	**0.31**	**374**	**0.64**	**4.06**	**4.06**	**8.5**	**0.17**	**282**	**0.48**	**4.06**	**4.06**

[d] - this product subcategory was selected amongst similarly shaded ones to calculate aggregate daily exposure

Table A4 - 3.2. Tier 1 worst-case scenario assessment of aggregate consumer exposure to D5 from application of C&PCPs (evaporation scenario included)

Product category	Product subcategory	Acute exposure (i.e. on the day of use), mg/kg_bw/day						Chronic exposure, mg/kg_bw/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
Hair Care	Shampoo	1.8E-05	3.6E-07	2.1E-01	3.6E-04			6.5E-06	1.3E-07	7.5E-02	1.3E-04		
	Conditioner (rinse-off)	9.1E-06	1.8E-07	1.0E-01	1.8E-04			2.6E-06	5.2E-08	3.0E-02	5.1E-05		
	Conditioner (leave-on) [d]	2.2E-02	4.5E-04	5.2E+00	8.8E-03			6.4E-03	1.3E-04	1.5E+00	2.5E-03		
	Hair mask	5.7E-05	1.1E-06	2.6E-01	4.4E-04			1.6E-05	3.2E-07	7.4E-02	1.3E-04		
	Hair styling (wax, mousse, gel)	4.6E-02	9.3E-04	1.1E+01	1.8E-02			2.3E-02	4.6E-04	5.2E+00	8.8E-03		
	Fixative spray	9.2E+00	1.8E-01	8.0E-01	1.4E-03			5.5E+00	1.1E-01	4.8E-01	8.2E-04		
	Detangle spray	4.6E+00	9.2E-02	4.0E-01	6.8E-04			1.3E+00	2.6E-02	1.1E-01	1.9E-04		
	Semi-permanent dye	3.0E-04	6.0E-06	6.0E-01	1.0E-03			1.1E-05	2.1E-07	2.1E-02	3.6E-05		
	Permanent dye (oxidative)	3.3E-03	6.7E-05	2.0E+00	3.4E-03			9.1E-05	1.8E-06	5.5E-02	9.3E-05		
	Hair bleach [d]	5.9E-03	1.2E-04	2.7E+00	4.5E-03			1.6E-04	3.2E-06	7.3E-02	1.2E-04		
	Permanent wave	1.9E-03	3.8E-05	1.5E+00	2.5E-03			2.1E-05	4.2E-07	1.6E-02	2.8E-05		
Bath and Shower	Body wash (gel, cream, scrub)	8.6E-09	1.7E-10	2.5E-02	4.2E-05			3.9E-09	7.7E-11	1.1E-02	1.9E-05		
	Hand soap (liquid and solid)	8.0E-08	1.6E-09	2.7E-02	4.5E-05			8.0E-08	1.6E-09	2.7E-02	4.5E-05		
	Bath foam, oil, salt	8.2E-07	1.6E-08	1.7E-01	2.9E-04			2.3E-07	4.7E-09	4.8E-02	8.2E-05		
Body Care	Body lotion (cream, oil, milk)	1.3E-01	2.6E-03	9.4E+01	1.6E-01			1.3E-01	2.6E-03	9.4E+01	1.6E-01		
	Body pack (mud mask)	9.1E-06	1.8E-07	5.5E-01	9.4E-04			1.0E-07	2.0E-09	6.0E-03	1.0E-05		
Sun Care	Bronzer, sun-tan	3.2E-03	6.4E-05	1.0E+01	1.8E-02			3.4E-04	6.9E-06	1.1E+00	1.9E-03		
	Sun screen (cream, lotion)	5.1E-01	1.0E-02	1.9E+02	3.3E-01			5.2E-02	1.0E-03	2.0E+01	3.4E-02		
	Sun screen (spray) [d]	2.3E+01	4.6E-01	1.9E+02	3.3E-01			2.4E+00	4.7E-02	2.0E+01	3.4E-02		

Product category	Product subcategory	Acute exposure (i.e. on the day of use), mg/kg_bw/day						Chronic exposure, mg/kg_bw/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
Skin Care	Face cream (day, night)	1.5E-01	2.9E-03	1.8E+01	3.1E-02			1.5E-01	2.9E-03	1.8E+01	3.1E-02		
	Face whitening cream	7.3E-02	1.5E-03	9.2E+00	1.6E-02			1.8E-02	3.6E-04	2.3E+00	3.9E-03		
	Hand cream	1.9E-01	3.8E-03	2.6E+01	4.4E-02			1.9E-01	3.8E-03	2.6E+01	4.4E-02		
	Eye cream	1.3E-02	2.6E-04	1.6E+00	2.8E-03			1.3E-02	2.6E-04	1.6E+00	2.8E-03		
	Facial cleanser (peeling, scrub)	9.7E-10	1.9E-11	1.1E-03	1.8E-06			2.8E-10	5.6E-12	3.0E-04	5.2E-07		
	Facial cleanser (tissues)	1.5E-05	3.0E-07	1.3E-01	2.2E-04			4.3E-06	8.7E-08	3.7E-02	6.3E-05		
	Face pack (peel-off mask)	2.4E+00	4.9E-02	5.3E+01	9.1E-02			6.9E-01	1.4E-02	1.5E+01	2.6E-02		
Oral Care	Toothpaste					3.0E-02	3.0E-02					3.0E-02	3.0E-02
	Mouthwash					3.6E+00	3.6E+00					3.6E+00	3.6E+00
Foot Care	Antiperspirant (gel, cream)	1.9E-02	3.8E-04	9.6E+00	1.6E-02			1.9E-02	3.8E-04	9.6E+00	1.6E-02		
	Antifungal gel, cream	3.4E-04	6.9E-06	2.7E-01	4.6E-04			8.5E-05	1.7E-06	6.7E-02	1.1E-04		
Deodorant	Spray [d]	1.8E+00	3.5E-02	1.4E+01	2.4E-02			1.8E+00	3.5E-02	1.4E+01	2.4E-02		
	Stick and roll-on	2.5E-01	4.9E-03	1.0E+01	1.7E-02			1.2E-01	2.5E-03	5.0E+00	8.6E-03		
Shaving	Gel, foam	1.2E-06	2.4E-08	3.0E-02	5.1E-05			1.2E-06	2.4E-08	3.0E-02	5.1E-05		
	Balm, balsam	1.7E-02	3.4E-04	3.2E+00	5.4E-03			1.7E-02	3.4E-04	3.2E+00	5.4E-03		
Make-up	Mascara	2.1E-02	4.3E-04	2.7E-01	4.6E-04			2.1E-02	4.3E-04	2.7E-01	4.6E-04		
	Eye shadow (liquid and powder)	3.5E-04	7.0E-06	1.9E-01	3.2E-04			3.5E-04	7.0E-06	1.9E-01	3.2E-04		
	Eye liner	1.7E-04	3.4E-06	3.3E-02	5.7E-05			1.7E-04	3.4E-06	3.3E-02	5.7E-05		
	Liquid foundation	6.3E-03	1.3E-04	2.7E+00	4.6E-03			6.3E-03	1.3E-04	2.7E+00	4.6E-03		
	Compact powder	6.8E-03	1.4E-04	5.7E+00	9.6E-03			6.8E-03	1.4E-04	5.7E+00	9.6E-03		
	Remover	4.8E-05	9.5E-07	3.3E-01	5.6E-04			4.8E-05	9.5E-07	3.3E-01	5.6E-04		

Product category	Product subcategory	Acute exposure (i.e. on the day of use), mg/kg_bw/day						Chronic exposure, mg/kg_bw/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
	Lipstick, lip balm	1.5E-03	2.9E-05	3.5E-01	6.0E-04	4.3E-01	4.3E-01	1.5E-03	2.9E-05	3.5E-01	6.0E-04	4.3E-01	4.3E-01
Nail Care	Polish enamel, top and base coat	6.0E-06	1.2E-07	7.0E-03	1.2E-05			2.5E-06	5.1E-08	3.0E-03	5.1E-06		
	Polish remover	3.5E-05	7.0E-07	3.0E-02	5.1E-05			1.5E-05	3.0E-07	1.3E-02	2.2E-05		
Baby Care	Diaper cream	4.1E-02	8.1E-04	2.1E+01	3.5E-02			4.1E-02	8.1E-04	2.1E+01	3.5E-02		
	Talc	3.9E-05	7.7E-07	6.4E-01	1.1E-03			3.9E-05	7.7E-07	6.4E-01	1.1E-03		
	Tissues	4.5E-04	9.0E-06	2.0E+00	3.4E-03			4.5E-04	9.0E-06	2.0E+00	3.4E-03		
Fragrance	Eau de toilette (spray) [d]	2.9E-02	5.9E-04	2.4E-01	4.1E-04			2.9E-02	5.9E-04	2.4E-01	4.1E-04		
	Eau de perfume (spray)	6.2E-03	1.2E-04	5.0E-02	8.5E-05			2.0E-03	4.0E-05	1.6E-02	2.8E-05		
Miscellaneous	Depilatory Cream	4.2E-08	8.5E-10	2.0E-02	3.4E-05			2.0E-09	3.9E-11	9.3E-04	1.6E-06		
	Massage Essential Oil	7.2E-03	1.4E-04	1.6E+01	2.7E-02			4.8E-04	9.5E-06	1.0E+00	1.7E-03		
	Bath Essential Oil	3.0E-08	6.1E-10	3.0E-02	5.1E-05			4.3E-09	8.6E-11	4.3E-03	7.3E-06		
Antifoam agent (in food packaging)	-					1.7E-03	1.7E-03					1.7E-03	1.7E-03
Pharmacy: OTC drugs	-					1.7E-03	1.7E-03					1.7E-03	1.7E-03
Aggregate Exposure:		**42.6**	**0.85**	**491**	**0.84**	**4.06**	**4.06**	**12.5**	**0.25**	**246**	**0.42**	**4.06**	**4.06**
Aggregate Exposure excluding sun care products:		**19.0**	**0.38**	**299**	**0.51**	**4.06**	**4.06**	**10.1**	**0.20**	**226**	**0.38**	**4.06**	**4.06**

[d] - this product subcategory was selected amongst similarly shaded ones to calculate aggregate daily exposure

Table A4 - 3.3. Tier 1 worst-case scenario assessment of aggregate consumer exposure to TCS from application of selected C&PCPs

Product category	Product subcategory	Acute exposure (i.e. on the day of use), mg/kg_bw/day						Chronic exposure, mg/kg_bw/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
Hair Care	Shampoo			5.2E-03	5.2E-03					1.9E-03	1.9E-03		
	Conditioner (rinse-off)												
	Conditioner (leave-on) [d]			2.0E-02	2.0E-02					5.6E-03	5.6E-03		
	Hair mask			2.0E-03	2.0E-03					5.6E-04	5.6E-04		
	Hair styling (wax, mousse, gel)			4.0E-02	4.0E-02					2.0E-02	2.0E-02		
	Fixative spray	5.5E-02	5.5E-02	6.0E-03	6.0E-03			3.3E-02	3.3E-02	3.6E-03	3.6E-03		
	Detangle spray	2.7E-02	2.7E-02	3.0E-03	3.0E-03			7.8E-03	7.8E-03	8.5E-04	8.5E-04		
	Semi-permanent dye												
	Permanent dye (oxidative)												
	Hair bleach [d]			1.0E-01	1.0E-01					2.7E-03	2.7E-03		
	Permanent wave												
Bath and Shower	Body wash (gel, cream, scrub)			9.3E-03	9.3E-03					4.2E-03	4.2E-03		
	Hand soap (liquid and solid)			1.0E-02	1.0E-02					1.0E-02	1.0E-02		
	Bath foam, oil, salt			1.3E-02	1.3E-02					3.6E-03	3.6E-03		
Body Care	Body lotion (cream, oil, milk)			3.9E-01	3.9E-01					3.9E-01	3.9E-01		
	Body pack (mud mask)			2.1E-01	2.1E-01					2.3E-03	2.3E-03		
Sun Care	Bronzer, sun-tan												
	Sun screen (cream, lotion)												
	Sun screen (spray) [d]	1.7E-01	1.7E-01	1.8E+00	1.8E+00			1.8E-02	1.8E-02	1.8E-01	1.8E-01		
Skin Care	Face cream (day, night)			7.7E-02	7.7E-02					7.7E-02	7.7E-02		

Product category	Product subcategory	Acute exposure (i.e. on the day of use), mg/kg_bw/day						Chronic exposure, mg/kg_bw/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
	Face whitening cream			3.9E-02	3.9E-02					9.6E-03	9.6E-03		
	Hand cream			1.1E-01	1.1E-01					1.1E-01	1.1E-01		
	Eye cream			6.8E-03	6.8E-03					6.8E-03	6.8E-03		
	Facial cleanser (peeling, scrub)			4.0E-04	4.0E-04					1.1E-04	1.1E-04		
	Facial cleanser (tissues)			5.0E-02	5.0E-02					1.4E-02	1.4E-02		
	Face pack (peel-off mask)			1.0E+00	1.0E+00					2.8E-01	2.8E-01		
Oral Care	Toothpaste					1.2E-02	4.8E-03					8.0E-03	3.2E-03
	Mouthwash					1.1E+00	4.3E-01					1.1E+00	4.3E-01
Foot Care	Antiperspirant (gel, cream)			1.2E-01	1.2E-01					1.2E-01	1.2E-01		
	Antifungal gel, cream			5.0E-03	5.0E-03					1.2E-03	1.2E-03		
Deodorant	Spray [d]	2.5E-02	2.5E-02	2.6E-01	2.6E-01			2.5E-02	2.5E-02	2.6E-01	2.6E-01		
	Stick and roll-on			7.6E-02	7.6E-02					3.8E-02	3.8E-02		
Shaving	Gel, foam			1.0E-03	1.0E-03					1.0E-03	1.0E-03		
	Balm, balsam			6.0E-02	6.0E-02					6.0E-02	6.0E-02		
Make-up	Mascara			1.3E-03	1.3E-03					1.3E-03	1.3E-03		
	Eye shadow (liquid and powder)			1.0E-03	1.0E-03					1.0E-03	1.0E-03		
	Eye liner			2.5E-04	2.5E-04					2.5E-04	2.5E-04		
	Liquid foundation			2.6E-02	2.6E-02					2.6E-02	2.6E-02		
	Compact powder			4.7E-02	4.7E-02					4.7E-02	4.7E-02		
	Remover			2.5E-03	2.5E-03					2.5E-03	2.5E-03		
	Lipstick, lip balm			2.0E-03	2.0E-03	2.0E-03	8.0E-04			2.0E-03	2.0E-03	2.0E-03	8.0E-04

Product category	Product subcategory	Acute exposure (i.e. on the day of use), mg/kg_bw/day						Chronic exposure, mg/kg_bw/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
Nail Care	Polish enamel, top and base coat			2.6E-03	2.6E-03					1.1E-03	1.1E-03		
	Polish remover			1.1E-02	1.1E-02					4.5E-03	4.5E-03		
Baby Care	Diaper cream			3.9E-01	3.9E-01					3.9E-01	3.9E-01		
	Talc			2.4E-01	2.4E-01					2.4E-01	2.4E-01		
	Tissues			2.5E-01	2.5E-01					2.5E-01	2.5E-01		
Fragrance	Eau de toilette (spray) [d]	8.8E-03	8.8E-03	9.2E-02	9.2E-02			8.8E-03	8.8E-03	9.2E-02	9.2E-02		
	Eau de perfume (spray)												
Miscellaneous	Depilatory Cream			2.8E-03	2.8E-03					1.3E-04	1.3E-04		
	Massage Essential Oil			2.0E-01	2.0E-01					1.3E-02	1.3E-02		
	Bath Essential Oil			4.0E-04	4.0E-04					5.7E-05	5.7E-05		
Antifoam agent (in food packaging)	-												
Pharmacy: OTC drugs	-												
Aggregate Exposure:		**2.9E-01**	**2.9E-01**	**5.7E+00**	**5.7E+00**	**1.1E+00**	**4.4E-01**	**9.2E-02**	**9.2E-02**	**2.7E+00**	**2.7E+00**	**1.1E+00**	**4.4E-01**
Aggregate Exposure excluding sun care products:		**1.2E-01**	**1.2E-01**	**3.9E+00**	**3.9E+00**	**1.1E+00**	**4.4E-01**	**7.4E-02**	**7.4E-02**	**2.5E+00**	**2.5E+00**	**1.1E+00**	**4.4E-01**

[d] - this product subcategory was selected amongst similarly shaded ones to calculate aggregate daily exposure

Table A4 - 3.4. Tier 1 worst-case scenario assessment of consumer exposure to TCS from application of household care products

AISE Product category	AISE Product subcategory	Acute exposure, mg/kg_day/day						Chronic exposure mg/kg_day/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
LAUNDRY REGULAR (AISE C1, PC35)	LAUNDRY REGULAR												
	Powder	-	-	1.6E-01	1.6E-01	-	-	-	-	1.4E-01	1.4E-01	-	-
	Liquid	-	-	2.4E-01	2.4E-01	-	-	-	-	2.3E-01	2.3E-01	-	-
LAUNDRY COMPACT (AISE C2, PC35)	LAUNDRY COMPACT												
	Powder	-	-	1.7E-01	1.7E-01	-	-	-	-	1.4E-01	1.4E-01	-	-
	Liquid/gel [a]	-	-	2.4E-01	2.4E-01	-	-	-	-	2.3E-01	2.3E-01	-	-
	Tablet	-	-	2.2E-02	2.2E-02	-	-	-	-	1.3E-02	1.3E-02	-	-
FABRIC CONDITIONERS (AISE C3, PC35)	FABRIC CONDITIONERS												
	Liquid Regular [d]	-	-	2.2E-02	2.2E-02	-	-	-	-	1.3E-02	1.3E-02	-	-
	Liquid Concentrate	-	-	2.2E-02	2.2E-02	-	-	-	-	1.3E-02	1.3E-02	-	-
LAUNDRY ADDITIVES (AISE C4, PC35)	LAUNDRY ADDITIVES												
	Powder Bleach	-	-	1.3E-02	1.3E-02	-	-	-	-	1.1E-02	1.1E-02	-	-
	Liquid Bleach (ml) [d]	-	-	2.3E-01	2.3E-01	-	-	-	-	2.2E-01	2.2E-01	-	-
	Tablet	-	-	1.3E-02	1.3E-02	-	-	-	-	1.1E-02	1.1E-02	-	-
HAND DISHWASHING (AISE C5, PC35)	HAND DISHWASHING												
	Liquid Regular (a) [d]	-	-	3.1E-03	3.1E-03	1.5E-05	6.0E-06	-	-	2.1E-03	2.1E-03	1.5E-05	6.0E-06
	Liquid Concentrate (a)	-	-	3.1E-03	3.1E-03	1.5E-05	6.0E-06	-	-	2.1E-03	2.1E-03	1.5E-05	6.0E-06
MACHINE DISHWASHING (AISE C6, PC35)	MACHINE DISHWASHING												
	Powder [d]	-	-	-	-	1.5E-05	6.0E-06	-	-	-	-	1.5E-05	6.0E-06
	Liquid	-	-	-	-	1.5E-05	6.0E-06	-	-	-	-	1.5E-05	6.0E-06
	Tablet	-	-	-	-	1.5E-05	6.0E-06	-	-	-	-	1.5E-05	6.0E-06

AISE Product category	AISE Product subcategory	Acute exposure, mg/kg_day/day						Chronic exposure mg/kg_day/day					
		Inhalation		Dermal		Oral		Inhalation		Dermal		Oral	
		external	internal	external	internal	external	internal	external	internal	external	internal	external	internal
SURFACE CLEANERS (AISE C7, PC35)	SURFACE CLEANERS												
	Liquid (a)	-	-	9.4E-03	9.4E-03	-	-	-	-	2.7E-03	2.7E-03	-	-
	Powder (a)	-	-	3.4E-03	3.4E-03	-	-	-	-	9.8E-04	9.8E-04	-	-
	Gel (neat)	-	-	4.3E-01	4.3E-01	-	-	-	-	1.2E-01	1.2E-01	-	-
	Spray (neat) [d]	3.6E-03	3.6E-03	4.3E-01	4.3E-01	-	-	1.0E-03	1.0E-03	1.2E-01	1.2E-01	-	-
LAUNDRY AIDS (AISE C12, PC35)	LAUNDRY AIDS												
	Ironing Aids - Spray	3.6E-03	3.6E-03	1.0E-02	1.0E-02	-		5.1E-04	5.1E-04	1.0E-02	1.0E-02	-	
FURNITURE, FLOOR & LEATHER CARE	MAINTENANCE PRODUCTS												
(AISE C20, PC31)	Spray	1.1E-02	1.1E-02	1.8E-01	1.8E-01	-		2.7E-04	2.7E-04	6.1E-02	6.1E-02	-	
WIPES (AISE C15, PC35)	WIPES												
	Bathroom	-	-	4.3E-01	4.3E-01	-	-	-	-	4.3E-01	4.3E-01	-	-
	Kitchen	-	-	2.1E-01	2.1E-01	-	-	-	-	2.1E-01	2.1E-01	-	-
	Floor	-	-	1.3E-01	1.3E-01	-	-	-	-	1.2E-01	1.2E-01	-	-
Aggregate Exposure:		**1.8E-02**	**1.8E-02**	**1.9E+00**	**1.9E+00**	**3.0E-05**	**1.2E-05**	**1.8E-03**	**1.8E-03**	**1.4E+00**	**1.4E+00**	**3.0E-05**	**1.2E-05**

(a) per 5 L of wash water volume

[d] – amongst all product types in a category this particular one was taken for the calculation of aggregate exposure

A4-4 Input data for the tier 2 assessment for D5 and TCS

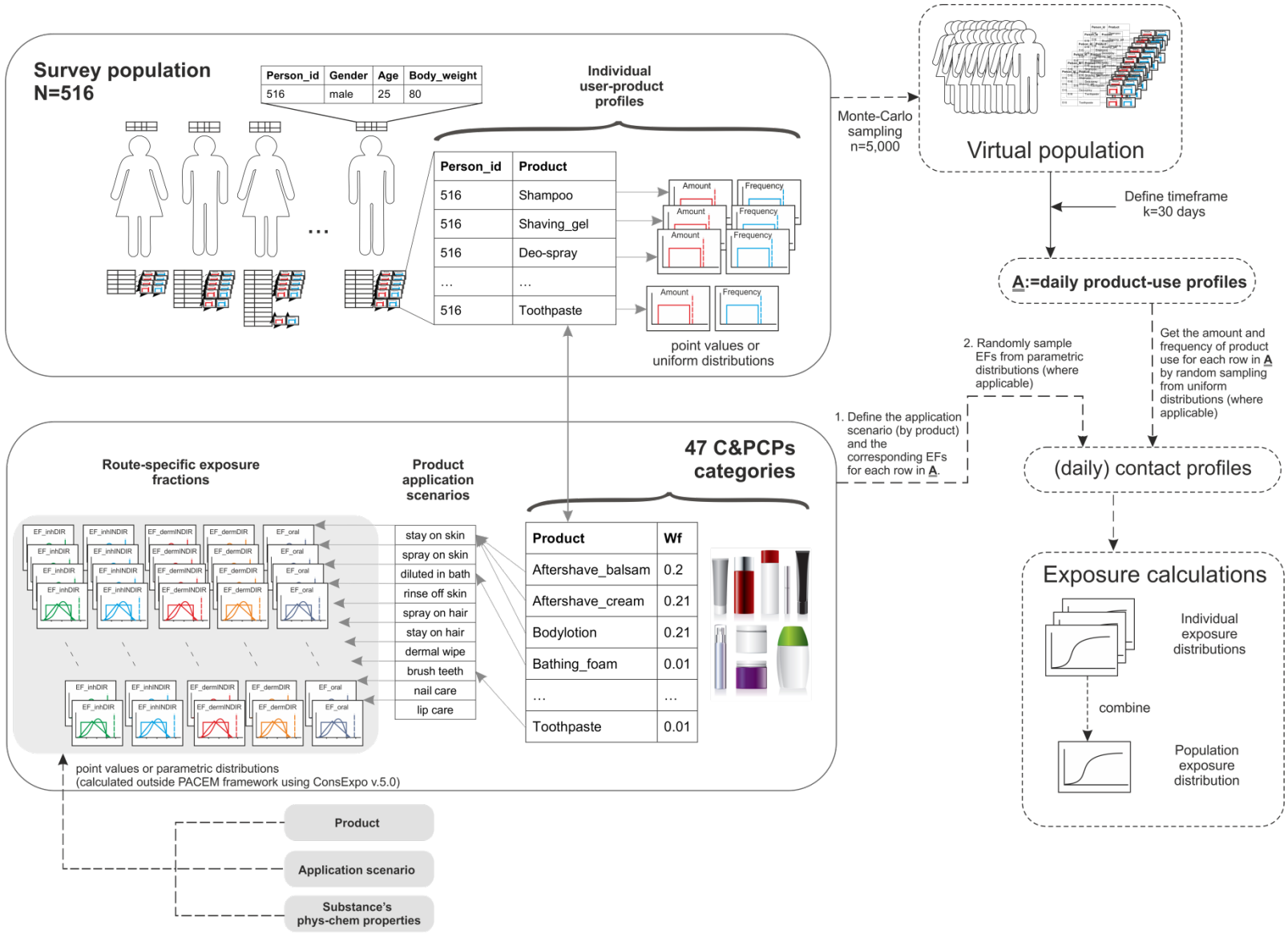

Figure A4 - 4.1. Dataflow for PACEM in the tier 2 assessment for D5

Table A4 - 4.1. Product weight fractions for D5 used in the tiered cons assessment

Product category	Product subcategory	D5 weight frac
		Tier 1
Shaving	Aftershave_balsam	0.2
Shaving	Aftershave_spray	-
Sun care	Aftersun_cream [a]	-
Bath and Shower	Bathing_foam	0.05
Bath and Shower	Bathing_oil	0.05
Bath and Shower	Bathing_both	-
Skin care	Bodylotion_milk [a]	0.9
Sun care	Bronzing_cream [a]	0.2
Skin care	Cleansing_lotion	0.01
Hair care	Conditioner_rinse [a]	0.2
Hair care	Conditioner_leave [a]	0.99
Hair care	Conditioner_both	-
Deodorants	Deo_cream [a]	0.5
Deodorants	Deo_roller_stick [a]	0.5
Deodorants	Deo_spray [a]	0.2
Deodorants	Deo_tissue	-
Bath and Shower	Douchegel_foam_scrub	0.01
Make-up	Eyepencil	0.5
Make-up	Eyebrowpencil	-
Make-up	Eyeshadow	0.7
Skin care	Face_daycream [a]	0.9
Skin care	Face_nightcream [a]	0.9
Hair care	Hairfoam [a]	0.99
Hair care	Hairgel [a]	0.99
Hair care	Hairlotion [a]	0.99
Hair care	Hairwax [a]	0.99
Hair care	Hairspray [a]	0.5
Skin care	Handcream [a]	0.9
Lip care	Lip balm [a]	0.65
Make-up	Lippencil	-
Make-up	Lipstick	0.65
Make-up	Liquid_foundation [a]	0.4
Make-up	Makeup_remover	0.5
Make-up	Mascara	0.8
Nail care	Nailpolish_feet	0.01
Nail care	Nailpolish_hands	0.01
Nail care	Nailpolish_both	-
Nail care	Nailpolish_remover	0.01
Fragrances	Perfume_eaudetoilette_spray	0.01
Make-up	Rouge_powder	0.45
Hair care	Shampoo	0.15
Shaving	Shavingfoam	0.1
Shaving	Shavinggel	0.1
Shaving	Shavingoil	0.1
Shaving	Shavingsoap	0.1
Sun care	Sunscreen_cream [a]	0.4
Oral care	Toothpaste	0.01

[a] – the maximum concentration of D5 determined in the products in a particular product category (Dudzina et al., 2014).

Table A4 - 4.2. Product subcategories linked to the application scenarios in the tier 2 model for D5

Product subcategory	Application scenario name
Aftershave_balsam	stay on skin
Aftershave_spray	spray on skin
Aftersun_cream	stay on skin
Bathing_foam	diluted in bath
Bathing_oil	diluted in bath
Bathing_both	diluted in bath
Bodylotion_milk	stay on skin
Bronzing_cream	stay on skin
Cleansing_lotion	rinse off skin
Conditioner_rinse	rinse off skin
Conditioner_leave	stay on hair
Conditioner_both	stay on hair
Deo_cream	stay on skin
Deo_roller_stick	stay on skin
Deo_spray	spray on skin
Deo_tissue	dermal wipe
Douchegel_foam_scrub	rinse off skin
Eyebrowpencil	stay on skin
Eyepencil	stay on skin
Eyeshadow	stay on skin
Face_daycream	stay on skin
Face_nightcream	stay on skin
Hairfoam	stay on hair
Hairgel	stay on hair
Hairlotion	stay on hair
Hairwax	stay on hair
Hairspray	spray on hair
Handcream	stay on skin
Lip balm	lip care
Lippencil	lip care
Lipstick	lip care
Liquid_foundation	stay on skin
Makeup_remover	stay on skin
Mascara	stay on skin
Nailpolish_feet	nail polish/remover
Nailpolish_hands	nail polish/remover
Nailpolish_both	nail polish/remover
Nailpolish_remover	nail polish/remover
Perfume_eaudetoilette_spray	spray on skin
Rouge_powder	stay on skin
Shampoo	rinse off skin
Shavingfoam	rinse off skin
Shavinggel	rinse off skin
Shavingoil	rinse off skin
Shavingsoap	rinse off skin
Sunscreen_cream	stay on skin
Toothpaste	brush teeth

Table A4 - 4.3. Product application scenarios linked to exposure fractions in the tier 2 model for D5

Application scenario	eF_inhDIR	eF_inhINDIR	eF_dermDIR	eF_dermINDIR	eF_oral
stay on skin	-	eF1	eF2	eF2	-
spray on skin	eF4	eF1	eF2	eF5	-
diluted in bath	-	eF8	eF7	eF2	-
rinse off skin	-	eF1	eF3	eF2	-
spray on hair	eF4	eF1	eF10	eF5	-
stay on hair	-	eF1	eF10	eF5	-
brush teeth	-	-	-	-	eF6
dermal wipe	-	eF1	eF9	eF2	-
nail polish/remover	-	eF12	eF11	eF2	-
lip care	-	-	eF10	eF2	eF13

eF=exposure fraction, inh=inhalation, derm=dermal exposure, oral= oral exposure, DIR= direct exposure, INDIR= indirect exposure

Table A4 - 4.4. Parameterization of exposure fractions (eFs) used in the tier 2 model for D5

eF	Application scenario	Type	Parameter 1[a]	Parameter 2[b]	Assumptions/Model	Notes
eF1	inh: evap from skin	beta	3.1	193.6	ConsExpo 5.0 evaporation model	
eF2	derm: stay on skin	point	1	-	worst-case	
eF3	derm: rinse off skin	point	0.01	-	1% of the product stays on skin after rinsing	
eF4	inh: spray to person	beta	4.3	8990.5	ConsExpo 5.0 spray model	
eF5	derm: stay on hair	point	0.85	-	85%	
eF6	oral: brush teeth	uniform	0.1	0.3	reasonable worst-case	
eF7	derm: immerse in solution	uniform	0.001	0.01	accounting for dilution of the product	
eF8	inh: evap from solution	beta	3.2	149508.9	ConsExpo 5.0 evaporation model	
eF9	derm: transfer wipe	uniform	0.01	0.2	from 1% to 20%	Gosens et al., 2013
eF10	derm: spray products or lip care	point	0.1	-	10%	see p.49-51 of RIVM Cosmetics Fact Sheet for details
eF11	derm: nail polish/remover	point	0.2	-	20% of product comes to direct contact with skin	
eF12	inh: nail polish/remover	beta	5.5	419.6	ConsExpo 5.0 evaporation model	
eF13	oral: lip care	point	0.9	-	worst-case	

a – the parameter denotes either a point value, or the minimum in uniform distribution, or shape parameter α in beta distribution

b – the parameter denotes either a point value, or the maximum in uniform distribution, or shape parameter β in beta distribution

Table A4 - 4.5. Tier 2 model equations for the calculation of exposure via different routes

Route exposure	Equation
direct inhalation exposure from spraying	$eF\_inhDIR \cdot (1 - eF\_dermINDIR) \cdot A$
indirect inhalation exposure to the material volatilized from skin	$eF\_inhINDIR \cdot eF\_dermINDIR \cdot eF\_dermDIR \cdot A$
direct dermal exposure	$(1 - eF\_inhINDIR) \cdot eF\_dermINDIR \cdot eF\_dermDIR \cdot A$
indirect dermal exposure (e.g. from hair spray)	0 (i.e. not calculated; needed as an intermediate value)
oral exposure	$eF\_oral \cdot A$

A – amount of product used, g/event

Table A4 - 4.6. Body weight characteristics of Dutch population (data for 2009)

Users	Stat	Age categories						
		18-24	25-34	35-44	45-54	55-64	65-74	all
Male	mean	78.1	83.8	85.1	86.4	84.4	83.4	83.9
Male	sd	0.8	0.6	0.5	0.5	0.5	0.6	0.2
Female	mean	63.2	68.5	70.3	70.5	71.6	70.9	69.6
Female	sd	0.6	0.6	0.5	0.5	0.5	0.6	0.2

Table A4 - 4.7. Age probability vector for Dutch population (the data refer to the situation on 1 January 2013)

Age	Probability		Age	Probability		Age	Probability		Age	Probability	
	men	women		men	women		men	women		men	women
18	0.0086	0.0082	35	0.0082	0.0082	52	0.0102	0.0101	69	0.0064	0.0066
19	0.0086	0.0083	36	0.0083	0.0083	53	0.0101	0.0100	70	0.0058	0.0061
20	0.0088	0.0085	37	0.0083	0.0084	54	0.0098	0.0098	71	0.0054	0.0057
21	0.0089	0.0087	38	0.0087	0.0088	55	0.0096	0.0096	72	0.0054	0.0059
22	0.0090	0.0088	39	0.0090	0.0091	56	0.0095	0.0094	73	0.0050	0.0056
23	0.0087	0.0086	40	0.0098	0.0099	57	0.0091	0.0092	74	0.0048	0.0054
24	0.0087	0.0086	41	0.0103	0.0103	58	0.0091	0.0090			
25	0.0087	0.0086	42	0.0108	0.0107	59	0.0089	0.0089			
26	0.0087	0.0086	43	0.0111	0.0109	60	0.0089	0.0089			
27	0.0085	0.0084	44	0.0106	0.0105	61	0.0086	0.0085			
28	0.0084	0.0083	45	0.0106	0.0104	62	0.0086	0.0085			
29	0.0082	0.0081	46	0.0106	0.0104	63	0.0086	0.0086			
30	0.0083	0.0082	47	0.0108	0.0106	64	0.0089	0.0088			
31	0.0084	0.0084	48	0.0110	0.0108	65	0.0092	0.0093			
32	0.0086	0.0085	49	0.0108	0.0106	66	0.0094	0.0095			
33	0.0083	0.0083	50	0.0106	0.0105	67	0.0067	0.0068			
34	0.0083	0.0083	51	0.0105	0.0104	68	0.0069	0.0071			

Table A4 - 4.8. The input parameters for the tier 2 exposure model for TCS

Product Name	User Gender	Percent of Users	amount_par1	amount_par2	amount_par3	amount_dist	freq_par1	freq_par2	freq_par3	freq_dist	WFs
Hand diswash liquid regular	Female	1	3	10		uniform	0.43	3.00	2.00	triangular	0.003
Hand diswash liquid regular	Male	1	3	10		uniform	0.43	3.00	2.00	triangular	0.003
All-purpose cleaner (spray)	Female	0.85	5	30	.	uniform	0.14	1.00	0.29	triangular	0.003
All-purpose cleaner (spray)	Male	0.81	5	30	.	uniform	0.14	1.00	0.29	triangular	0.003
Body wash	Female	0.858	1.806958	7.165478	.	weibull	0.068	1.74	0.803	triangular	0.003
Body wash	Male	0.71	1.656328	6.492729	.	weibull	0.051	2.079	0.718	triangular	0.003
Hand soap	Female	1	0.6	1.8	0.92	triangular	3	5	.	uniform	0.003
Hand soap	Male	1	0.6	1.8	0.92	triangular	3	5	.	uniform	0.003
Facial cleanser	Female	0.444	1.592257	1.713327	.	weibull	0.021	2.675	1	triangular	0.003
Facial cleanser	Male	0.029	1.581712	1.352702	.	weibull	0	0.3	.	uniform	0.003
Toothpaste	Female	0.977	2.246801	1.202394	.	weibull	1	3	2	triangular	0.003
Toothpaste	Male	0.776	2.355537	1.25702	.	weibull	1	3	2	triangular	0.003
Deo Spray	Female	0.947	0.46763163	0.5727457	.	lnorm	0.146	2.855	1	triangular	0.003
Deo Spray	Male	0.867	0.31361802	0.6313613	.	lnorm	0.045	2.702	1	triangular	0.003
Shaving gel	Female	0.235	1.21830706	0.788004	.	lnorm	3.545719	.	.	exp	0.003
Shaving gel	Male	0.533	0.77731251	0.9334663	.	lnorm	1	.	.	point	0.003

_par1 and _par2 – the first and the second parameters of a factor distribution, respectively; _dist – type of a factor distribution

WFs – weight fraction of TCS in the product

Table A4 - 4.9. Exposure fractions for inhalation route of exposure use in the tier 2 model for TCS

Product Name	User Gender	Parameter1 for eF_inhDIR	Parameter2 for eF_inhDIR	Distribution for eF_inhDIR
Hand diswash liquid regular	Female	.	.	.
Hand diswash liquid regular	Male	.	.	.
All-purpose cleaner (spray)	Female	2.000121	80.89363	beta
All-purpose cleaner (spray)	Male	2.000121	80.89363	beta
Body wash	Female	.	.	.
Body wash	Male	.	.	.
Hand soap	Female	.	.	.
Hand soap	Male	.	.	.
Facial cleanser	Female	.	.	.
Facial cleanser	Male	.	.	.
Toothpaste	Female	.	.	.
Toothpaste	Male	.	.	.
Deo Spray	Female	4.013056	148.8133	beta
Deo Spray	Male	4.013056	148.8133	beta
Shaving gel	Female	.	.	.
Shaving gel	Male	.	.	.

Table A4 - 4.10. Exposure fractions for dermal route of exposure use in the tier 2 model for TCS

Product Name	User Gender	Parameter1 for eF_dermDIR	Parameter2 for eF_dermDIR	Distribution for eF_dermDIR	Parameter1 for eF_dermINDIR	Parameter2 for eF_dermINDIR	Distribution for eF_dermINDIR
Hand diswash liquid regular	Female	0.00009	0.00017	uniform	1	.	point
Hand diswash liquid regular	Male	0.00009	0.00017	uniform	1	.	point
All-purpose cleaner (spray)	Female	1	.	point	0.15	.	point
All-purpose cleaner (spray)	Male	1	.	point	0.15	.	point
Body wash	Female	0.01	.	point	1	.	point
Body wash	Male	0.01	.	point	1	.	point
Hand soap	Female	0.01	.	point	1	.	point
Hand soap	Male	0.01	.	point	1	.	point
Facial cleanser	Female	0.01	.	point	1	.	point
Facial cleanser	Male	0.01	.	point	1	.	point
Toothpaste	Female	.	.	.	.	.	.
Toothpaste	Male	.	.	.	.	.	.
Deo Spray	Female	1	.	point	0.85	.	point
Deo Spray	Male	1	.	point	0.85	.	point
Shaving gel	Female	0.01	.	point	1	.	point
Shaving gel	Male	0.01	.	point	1	.	point

Table A4 - 4.11. Exposure fractions for oral route of exposure use in the tier 2 model for TCS

Product Name	User Gender	Parameter1 for eF_oral	Parameter2 for eF_oral	Distribution for eF_oral
Hand diswash liquid regular	Female	.	.	.
Hand diswash liquid regular	Male	.	.	.
All-purpose cleaner (spray)	Female	.	.	.
All-purpose cleaner (spray)	Male	.	.	.
Body wash	Female	.	.	.
Body wash	Male	.	.	.
Hand soap	Female	.	.	.
Hand soap	Male	.	.	.
Facial cleanser	Female	.	.	.
Facial cleanser	Male	.	.	.
Toothpaste	Female	0.1	0.3.	uniform
Toothpaste	Male	0.1	.0.3	uniform
Deo Spray	Female	.	.	.
Deo Spray	Male	.	.	.
Shaving gel	Female	.	.	.
Shaving gel	Male	.	.	.

A4-5 Parameterization of exposure fractions

Parameterization of exposure fractions for D5
ConsExpo 5.0 report

Compound

Compound name :	D5	
CAS number :	541-02-6	
molecular weight	3.7E2	g/mol
vapour pressure	33	Pascal
KOW	8	10Log

Populations

test

body weight	1	kilogram

Products

D5

weight fraction compound	1	fraction

Aggregate Exposures

Aggregate exposure for test :

Total chronic potential dose (mg/kg/day):

Median:	28
Standard deviation:	0.33
90-Percentile:	45
99-Percentile:	59

Total chronic systemic dose (mg/kg/day):

Median:	25
Standard deviation:	0.48
90-Percentile:	49
99-Percentile:	74

Inhalation chronic potential dose (mg/kg/day):

Median:	28
Standard deviation:	0.33

90-Percentile:	45
99-Percentile:	59

Inhalation chronic systemic dose (mg/kg/day):

Median:	25
Standard deviation:	0.48
90-Percentile:	49
99-Percentile:	74

Dermal chronic potential dose (mg/kg/day):

--

Dermal chronic systemic dose (mg/kg/day):

--

Oral chronic potential dose (mg/kg/day):

Median:	0
Standard deviation:	0
90-Percentile:	0
99-Percentile:	0

Oral chronic systemic dose (mg/kg/day):

Median:	0
Standard deviation:	0
90-Percentile:	0
99-Percentile:	0

Details for scenario: test, D5 : eF1 – indirect inhalation of D5 evaporating from skin

Inhalation model: Exposure to vapour : evaporation

weight fraction compound	1 fraction		
exposure duration :Uniform	From: 1 To: 30	minute	Distr.
room volume	From: 2 To: 10	m3	Distr. :Uniform
ventilation rate	From: 1 To: 5	1/hr	Distr. :Uniform
applied amount	1 gram		
release area :Uniform	From: 1E2 To: 1.7E4	cm2	Distr.
application duration :Uniform	From: 1 To: 10	minute	Distr.
mass transfer rate	0.18 m/min		

Uptake model: Fraction

uptake fraction	1 fraction

inhalation rate :Uniform	From: 11 To: 14	m3/day	Distr.

Details for scenario: test, D5 : eF4 –direct inhalation to spray deodorant

Inhalation model: Exposure to spray : spraying

weight fraction compound	0.03 fraction		
exposure duration :Uniform	From: 1 To: 30	minute	Distr.
room volume	From: 2 To: 10	m3	Distr. :Uniform
ventilation rate	From: 1 To: 5	1/hr	Distr. :Uniform
mass generation rate	From: 0.3 To: 0.79	g/sec	Distr. :Uniform
spray duration :Uniform	From: 1 To: 5	second	Distr.
airborn fraction	1 fraction		
weight fraction non-volatile	0.03 fraction		
density non-volatile :Uniform	From: 1.5 To: 1.8	g/cm3	Distr.
room height :Uniform	From: 2 To: 4	meter	Distr.
inhalation cut-off diameter	15 micrometer		
cloud volume	From: 0.063 To: 0.1	m3	Distr. :Uniform
non-respirable uptake fraction	0 fraction		

Uptake model: Fraction

uptake fraction	1 fraction		
inhalation rate :Uniform	From: 11 To: 14	m3/day	Distr.

Details for scenario: test, D5 : eF8 – indirect inhalation of D5 evaporating from a solution

Inhalation model: Exposure to vapour : evaporation

weight fraction compound :Uniform	From: 0.008 To: 0.021	fraction	Distr.
exposure duration :Uniform	From: 1 To: 30	minute	Distr.
room volume	From: 2 To: 10	m3	Distr. :Uniform
ventilation rate	From: 1 To: 5	1/hr	Distr. :Uniform
applied amount	1 gram		
release area :Uniform	From: 1.5E3 To: 2E3	cm2	Distr.
application duration	From: 1 To: 30	minute	Distr.

:Uniform			
mol weight matrix :Uniform	From: 21 To: 25	g/mol	Distr.
mass transfer rate	0.18 m/min		

Uptake model: Fraction

uptake fraction	1 fraction		
inhalation rate :Uniform	From: 11 To: 14	m3/day	Distr.

Details for scenario: test, D5 : eF12 – indirect inhalation from nailpolish application

Inhalation model: Exposure to vapour : evaporation

weight fraction compound	1 fraction		
exposure duration :Uniform	From: 10 To: 60	minute	Distr.
room volume	From: 0.5 To: 1	m3	Distr. :Uniform
ventilation rate	From: 1 To: 5	1/hr	Distr. :Uniform
applied amount	1 gram		
release area :Uniform	From: 15 To: 50	cm2	Distr.
application duration :Uniform	From: 10 To: 60	minute	Distr.
mass transfer rate	0.18 m/min		

Uptake model: Fraction

uptake fraction	1 fraction		
inhalation rate :Uniform	From: 11 To: 14	m3/day	Distr.

Parametric distributions of inhalation exposure fractions for D5 obtained from the ConsExpo 5.0 modelling data by maximum-likelihood estimation (MLE) method

eF_id	method	type	parameter 1	parameter 2
eF1	MLE	beta	3.1	193.6
eF4	MLE	beta	4.3	8990.5
eF8	MLE	beta	3.2	149508.9
eF12	MLE	beta	5.5	419.6

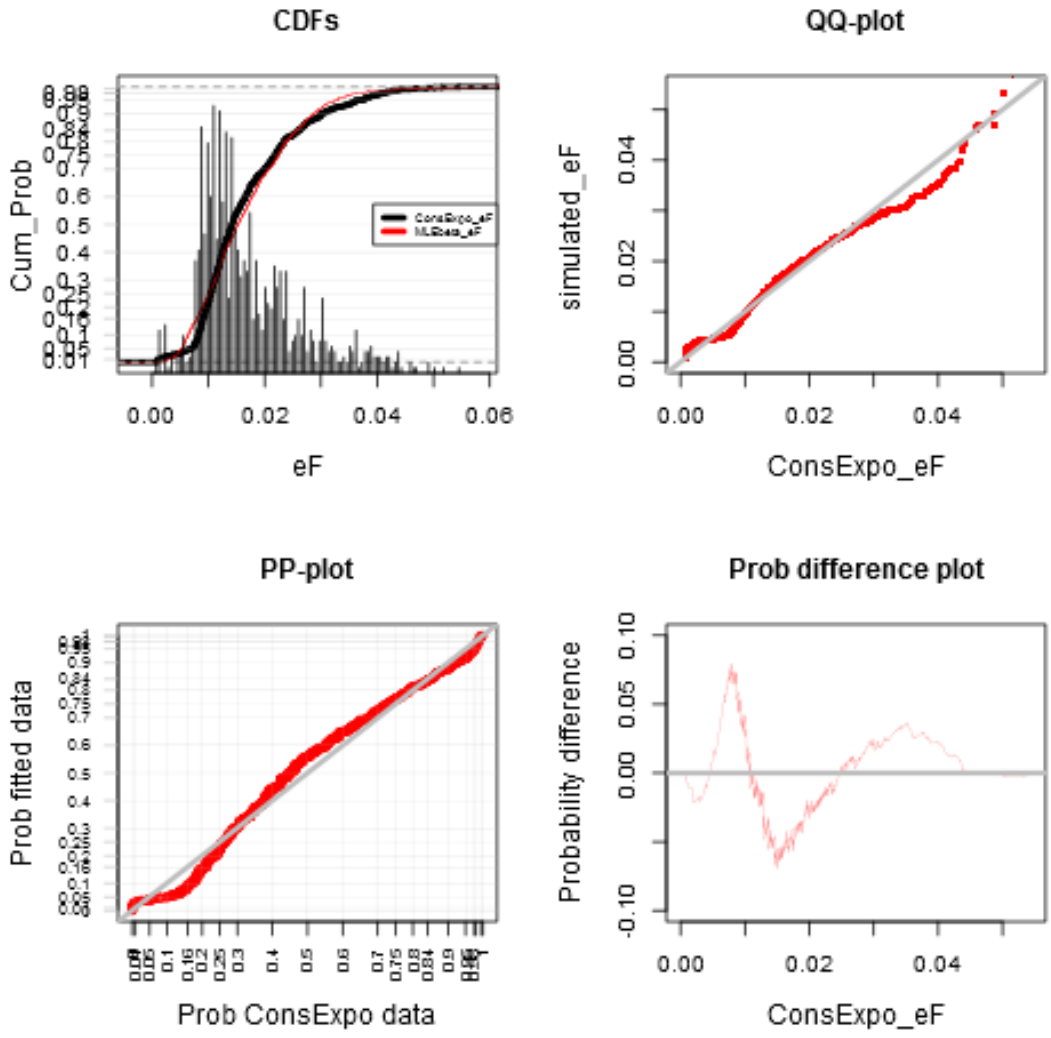

Figure A4 - 5.1. eF1 (tier2 for D5)

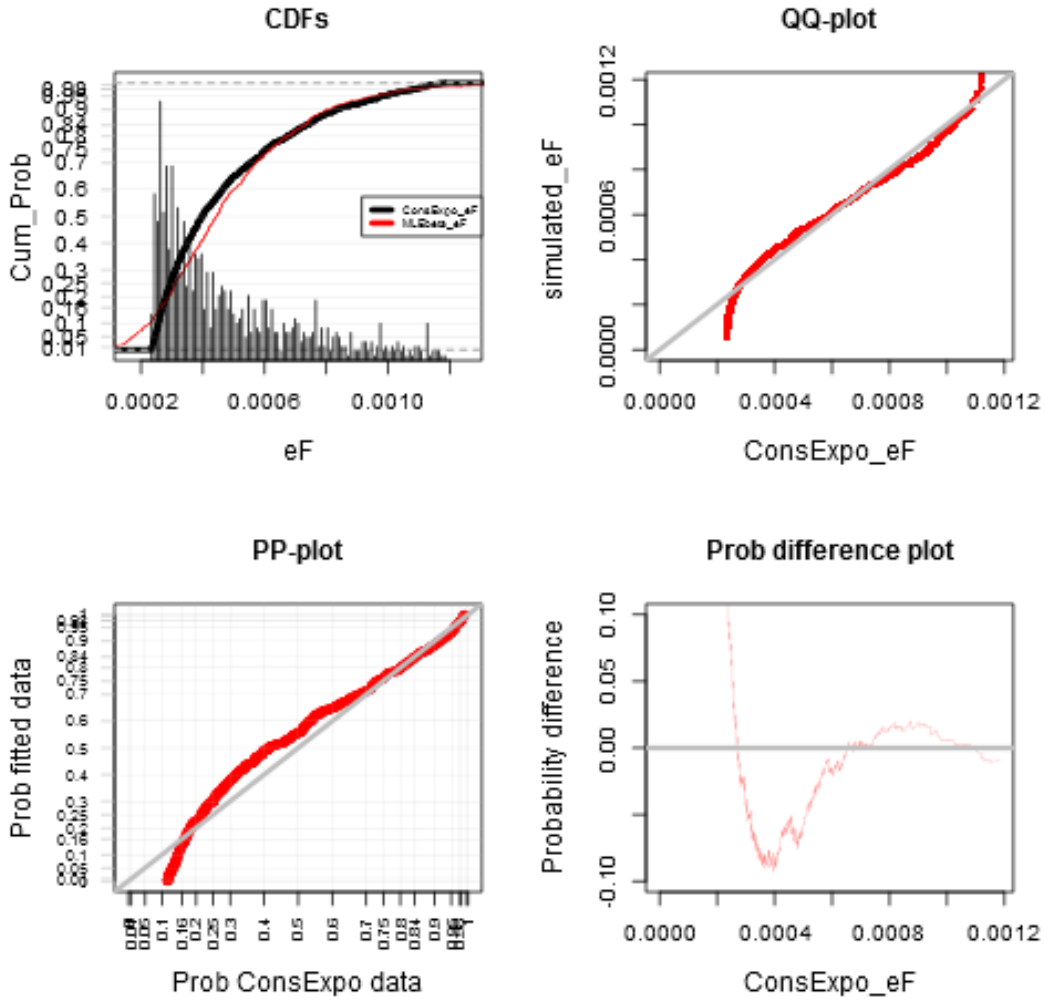

Figure A4 - 5. 2. eF4 (tier2 for D5)

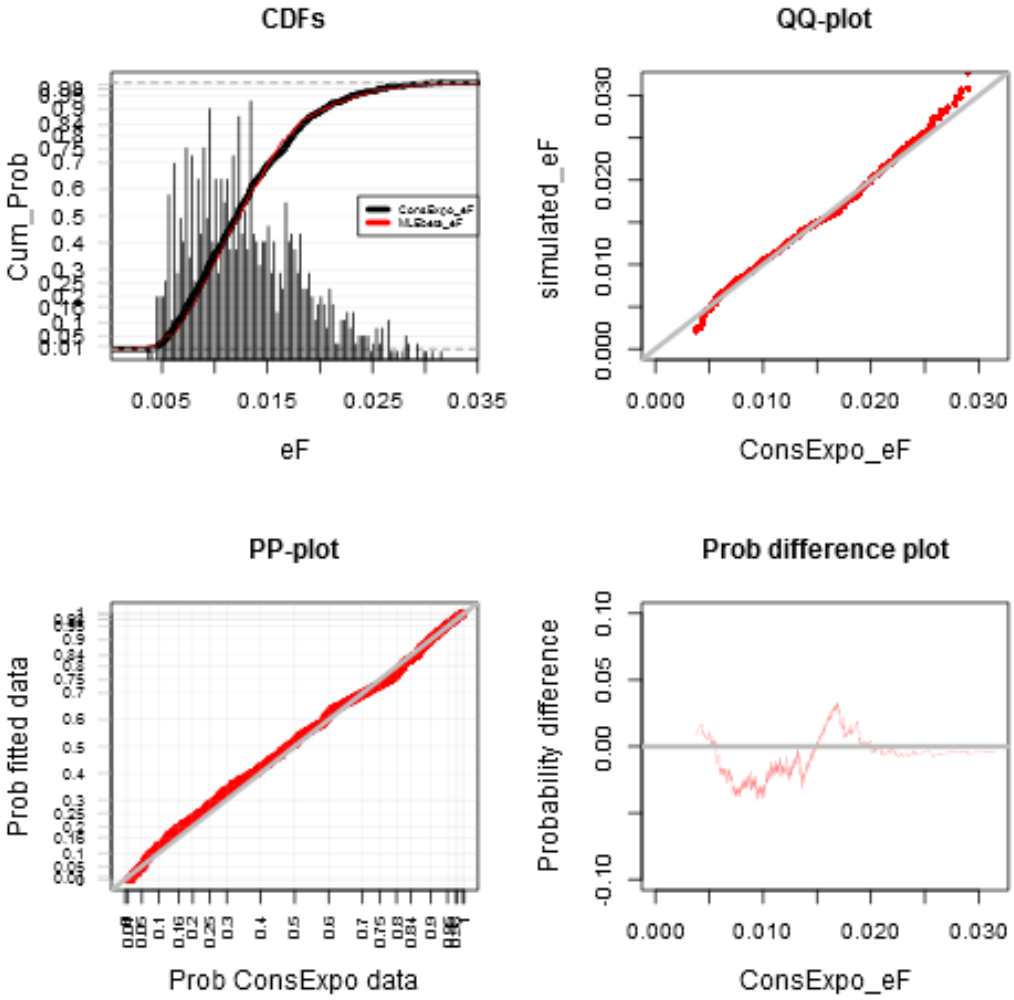

Figure A4 - 5.3. eF8 (tier2 for D5)

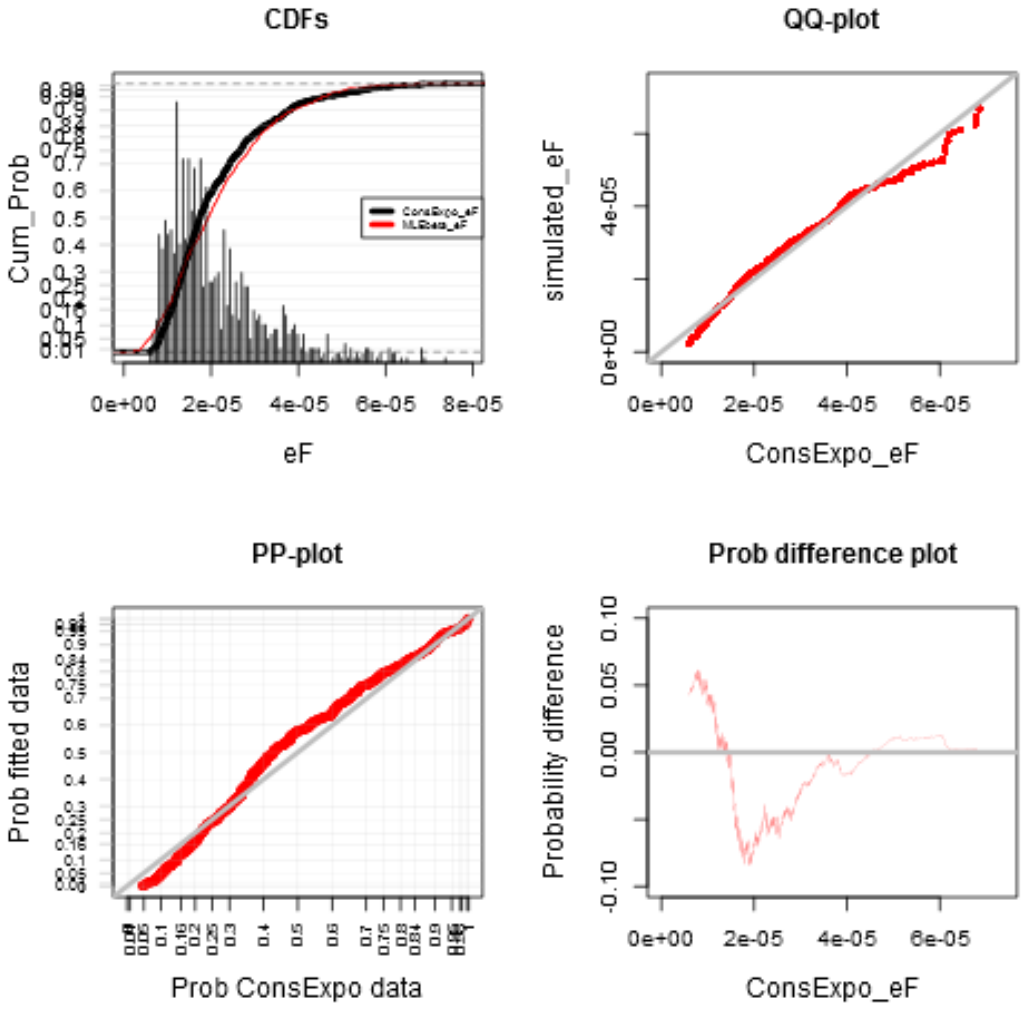

Figure A4 - 5.4. eF12 (tier2 for D5)

Parameterization of exposure fractions for TCS

ConsExpo 5.0 report

Compound

Compound name :	TCS	
CAS number :	3380-34-5	
molecular weight	2.9E2	g/mol
vapour pressure	0.00053	Pascal
KOW	4.8	10Log

Populations

test

body weight	1	kilogram

Products

TCS

weight fraction compound	1	fraction

Aggregate Exposures

Aggregate exposure for test :

Total chronic potential dose (mg/kg/day):

Median:	41
Standard deviation:	0.21
90-Percentile:	55
99-Percentile:	65

Total chronic systemic dose (mg/kg/day):

Median:	47
Standard deviation:	0.49
90-Percentile:	78
99-Percentile:	1.2E2

Inhalation chronic potential dose (mg/kg/day):

Median:	39
Standard deviation:	0.21
90-Percentile:	53
99-Percentile:	63

Inhalation chronic systemic dose (mg/kg/day):

Median:	47
Standard deviation:	0.49
90-Percentile:	78
99-Percentile:	1.2E2

Dermal chronic potential dose (mg/kg/day):

Median:	0.13
Standard deviation:	0.00056
90-Percentile:	0.16
99-Percentile:	0.17

Dermal chronic systemic dose (mg/kg/day):

Median:	0.13
Standard deviation:	0.00056
90-Percentile:	0.16
99-Percentile:	0.17

Oral chronic potential dose (mg/kg/day):

Median:	0
Standard deviation:	0
90-Percentile:	0
99-Percentile:	0

Oral chronic systemic dose (mg/kg/day):

Median:	0
Standard deviation:	0
90-Percentile:	0
99-Percentile:	0

Details for scenario: test, TCS : eF1 – direct inhalation to spray-deodorant

Inhalation model: Exposure to spray : spraying

weight fraction compound	1 fraction		
exposure duration :Uniform	From: 1 To: 30	minute	Distr.
room volume	From: 2 To: 5	m3	Distr. :Uniform
ventilation rate	From: 1 To: 5	1/hr	Distr. :Uniform
mass generation rate	From: 0.6 To: 0.9	g/sec	Distr. :Uniform
spray duration :Uniform	From: 1 To: 5	second	Distr.
airborn fraction	0.9 fraction		

weight fraction non-volatile	1 fraction		
density non-volatile :Uniform	From: 1.5 To: 1.8	g/cm3	Distr.
room height :Uniform	From: 2 To: 4	meter	Distr.
inhalation cut-off diameter	15 micrometer		
cloud volume	From: 0.063 To: 1	m3	Distr. :Uniform
non-respirable uptake fraction	0 fraction		

Uptake model: Fraction

uptake fraction	1 fraction		
inhalation rate :Uniform	From: 11 To: 14	m3/day	Distr.

Details for scenario: test, TCS : eF2 – direct inhalation to spray cleaner

Inhalation model: Exposure to spray : spraying

weight fraction compound	1 fraction		
exposure duration :Uniform	From: 2 To: 10	minute	Distr.
room volume	From: 2 To: 10	m3	Distr. :Uniform
ventilation rate	From: 1 To: 5	1/hr	Distr. :Uniform
mass generation rate	From: 1 To: 1.7	g/sec	Distr. :Uniform
spray duration :Uniform	From: 2 To: 10	minute	Distr.
airborn fraction	0.006	fraction	
weight fraction non-volatile	1 fraction		
density non-volatile :Uniform	From: 1 To: 1.2	g/cm3	Distr.
room height :Uniform	From: 2 To: 4	meter	Distr.
inhalation cut-off diameter	15 micrometer		
non-respirable uptake fraction	0 fraction		

Uptake model: Fraction

uptake fraction	1 fraction		
inhalation rate :Uniform	From: 11 To: 14	m3/day	Distr.

Details for scenario: test, TCS : eF3 – direct dermal exposure to hand dishwashing liquid

Dermal model: Direct dermal contact with product : diffusion

weight fraction compound	1 fraction		
exposed area	8.6E2	cm2	
diffusion coefficient :Uniform	From: 1E-7 To: 5E-7	cm2/sec	Distr.
layer thickness	0.01 millimetre		
release duration :Triangular	low: 10 high: 45 mode: 30	minute	Distr.

Uptake model: fraction

uptake fraction	1 fraction	

Parametric distributions of exposure fractions for TCS obtained from the ConsExpo 5.0 modelling data by maximum-likelihood estimation (MLE) method

eF_id	method	type	parameter 1	parameter 2
eF1	MLE	beta	4.013056	148.8133
eF2	MLE	beta	2.000121	80.89363
eF3	-	uniform	0.00009	0.00017

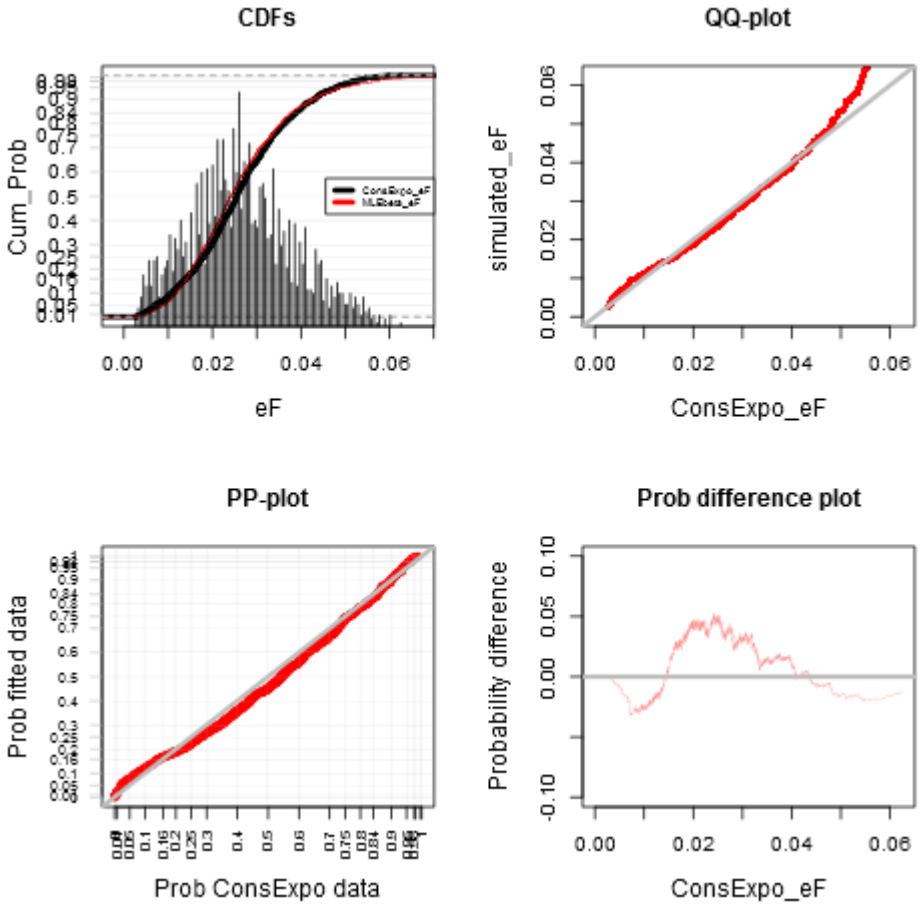

Figure A4 - 5. 5. eF1 (tier2 for TCS)

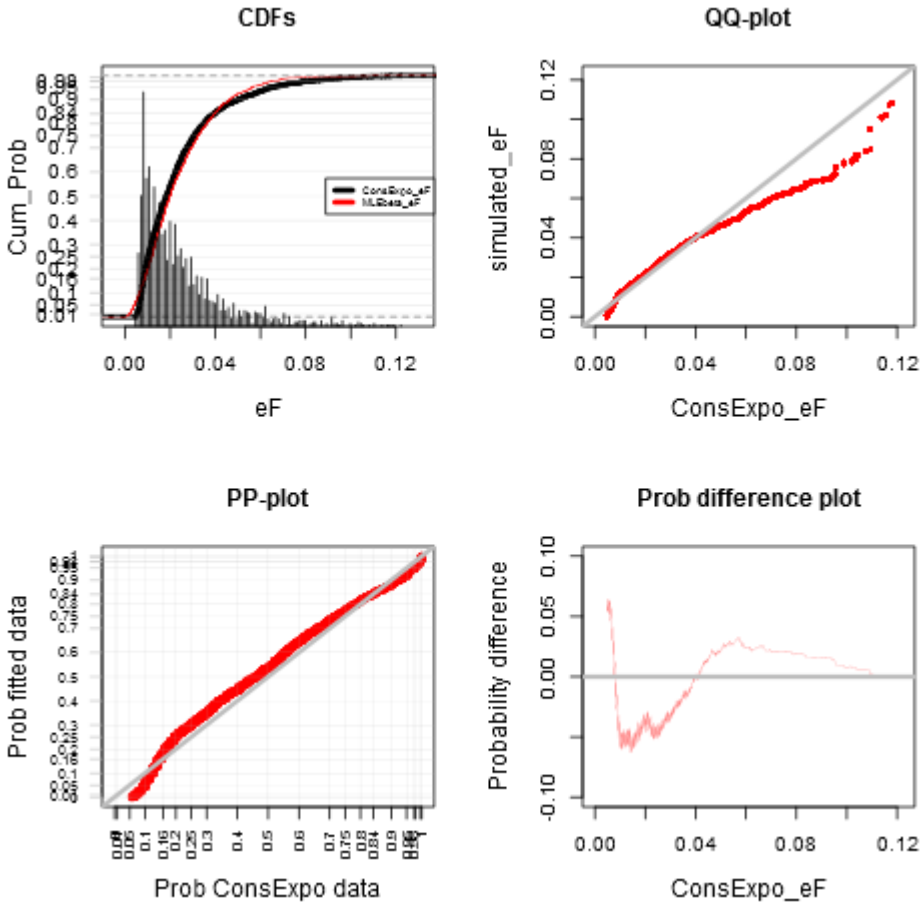

Figure A4 - 5. 6. eF2 (tier2 for TCS)

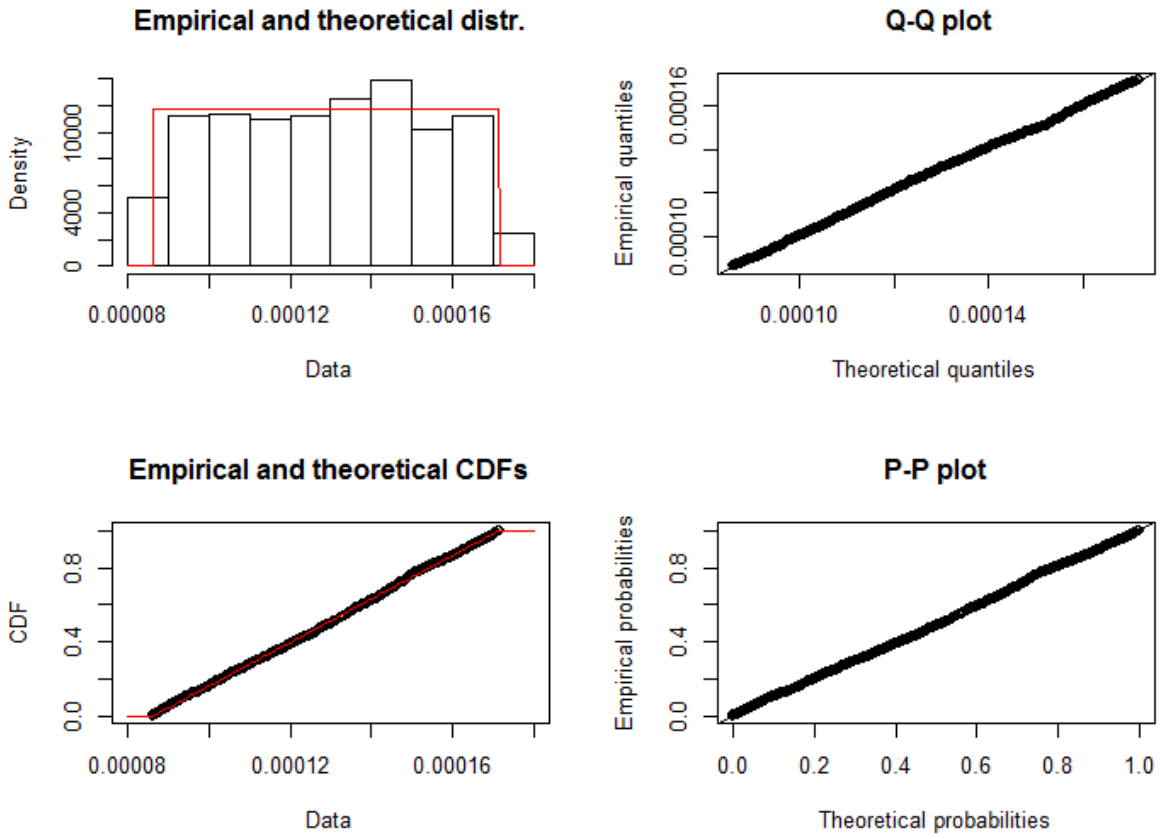

Figure A4 - 5. 7. (tier2 for TCS)

Appendix 5

Appendix A5-2 – A5-9

Graphical representations of D4 and D5 concentrations in end-exhaled air and ambient air (ng/L) are plotted against time. Separate figures are presented for male (M) and female (F) volunteers. On the left y-axis the D4 or D5 concentration (ng/L) is shown. The black line in the graph represents the D4 or D5 concentration in end-exhaled air. The orange line in the graph represents the D4 or D5 concentration in ambient air during the period of dermal administration (60 min) and the blue line represents the D5 concentration in ambient air during the post-exposure period.

Appendix A5-10

Graphical representations of D5 concentrations in end-exhaled air and ambient air (ng/L) are plotted against time. Separate figures are presented for male (M) and female (F) volunteers. On the left y-axis the D5 concentration (ng/L) is shown. The black line in the graph represents the D5 concentration in end-exhaled air. The orange line in the graph represents the D5 concentration in ambient air during dermal administration in the toilet area (5 min), the blue line represents the D5 concentration in ambient air during the post-exposure period inside the toilet area and the green line represents the D5 concentration in ambient air during the post-exposure period outside the toilet area.

A5-1 Information obtained from 24-hour diaries

Table A5-1 shows information on regular use of C&PCPs of our volunteers. The information was collected using 24-hour diaries, which had to be filled out 24 hours before the baseline measurement. In the table information about the product used, the time of day, the amount and the exposed body parts is given. The amount of use was calculated by the method described in Biesterbos et al. (2013).

Table A5-1. Overview of the information on regular use of C&PCPs by participants in the volunteer study. Note: the table continues until page xx.

Volunteer	Product applied	Time of day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
1	Cien handcreme anti age	17:55	0,7		Hands
	Ombia Bath Creme Seife Samt & Seide	19:00	2,7		Hands
	Mildeen Body Care Creme zeep Fruit	3:10	2,7		Hands
	Tandpasta Prodent Menthol Power	3:25	1,5		Mouth/Teeth
	Mildeen Body Care Creme zeep Fruit	9:00	2,7		Hands
	Seba Med 'Unreine Haut' Creme Mattierend	11:28	0,9		Face
	Manhattan Ciear Face Compact Powder 75 beige	11:35	8,0 mg		Face
	Alverde Naturkosmetik Puderrouge Pretty Terra (03)	11:35	3,0 mg		Face
	Alverde Naturkosmetik 'Schwung + Verlängerung'	11:40	2 layers		Face
	Women Rexona shower fresh motion sense	11:45	1 time per axilla	4	Axilla
	Tandpasta Prodent Menthol Power	11:47	1,1		Teeth
	Mildeen Body Care Creme zeep Fruit	13:20	2,7		Hands
	Mildeen Body Care Creme zeep Fruit	14:30	2,7		Hands
	Mildeen Body Care Creme zeep Fruit	15:49	2,7		Hands
	Hirschtalg creme Fusswohl	15:49	2,7		Hands

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
2	Labello classic	17:00	NS*		Mouth
	Bodyshop handcreme 'hemp'	17:00	0,2		Hands
	Handzeep in restaurant	15:00	1,0		Hands
	Handzeep thuis, Kruidvat cremezeep sensitive	18:00	2,7		Hands
	Bodylotion Vaseline essential moisture	22:00	8,9		Arms/Legs/Stomach/Bottom/Shoulders
	Paradontax fluoride	22:00	0,9		Teeth
	Nachtcreme aloe sooting bodyshop	22:00	0,4		Face and neck
	Lenzenvloeistof bewaren & schoonmaken	22:00	NS		NS
	Handzeep thuis, Kruidvat cremezeep sensitive	22:00	2,7		Hands
	Labello repair&beauty	22:00	11,3 mg		Mouth
	Tandpasta paradontax	9:00	0,9		Teeth
	Lenzenvloeistof	9:00	NS		Eyes
	Handzeep thuis, Kruidvat cremezeep sensitive	9:00	2,7		Hands
	Deodorant Sanex sensitive skin	9:00	NS	2	Axilla
	Labello olijf&citroen	9:00	11,3 mg		Mouth
	Dagcreme body shop aloe sooting	9:00	0,2		Face

* NS = not specified by the volunteer.

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
3	Shampoo Wezza	11:15	2,7		Hair
	Douchegel Neutral	11:20	5,2		Whole body, except Face
	Deodorant Neutral Anti-Transpirant	11:30	1x spray per axilla	1	Axilla
	Bodymilk neutral	11:35	5,6		Whole body, except Legs and Face
	Beenbalsum Gehwol	11:40	5,6		Legs
	Dagcreme Ariane Iden (huismerk schoonheidsspecialiste)	11:50	0,2		Face and neck
	Tandverzorging huismerk tandarts cleaner	11:55	0,4		Teeth
	Handzeep Uni-Cura	13:10	1,0		Hands
	Facesverzorging reinigingsdoekjes Etos	23:15	2 sheets		Face and neck
	Tandverzorging huismerk tandarts cleaner	23:20	NS		Teeth
	Douchegel Neutral	8:30	NS		Whole body, except Face
	Deodorant Neutral Anti-Transpirant	8:40	1x spray per axilla	1	Axilla
	Bodymilk neutral	8:45	5,6		Whole body, except Legs and Face
	Beenbalsum Gehwol	8:48	5,6		Legs
	Tandverzorging huismerk tandarts cleaner	8:55	0,4		Teeth
	Dagcreme Ariane Iden (huismerk schoonheidsspecialiste)	9:30	0,2		Face and neck

* NS = not specified by the volunteer.

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
4	Zeep Ombia-med	13:30	2,7		Hands
	Zeep Ombia-med	17:00	2,7		Hands
	Zeep Ombia-med	0:15	2,7		Hands, Head
	Tandpasta Lido-dent	0:20	1,1		Teeth
	Shower & shampoo man	7:30	7,7		Whole body
	Deodorant mildeen	7:45	NS*	4	Both axilla
	Eau de Toilette Davidoff	7:46	NS	4	Neck
	Eyeliner HEMA	7:47	0,2 mg		NS
	Gel Shegron	7:49	1,8		NS
	Tandpasta Lido-dent	8:15	1,1		Teeth
5	Tandpasta Elmex	19:30	1,9		Teeth
	Shampoo Andrelon glans	19:30	7,7		NS
	Zeep Hands Palmolive naturals	19:30	1,0		Head/neck/body
	Ciel body look	19:30	3,8		Hair
	Aftershave Paco Rabanne + Maroc	19:30	2,5		Face/body
	Body lotion/melk Biocura	19:30	8,9		Whole body
	Sexy man 212 Hugo Boss sport	19:30	2,5		NS
	Stick deodorant Hugo Boss	19:30	7x		Axilla
	Tandpasta Elmex	7:00	1,9		Teeth
	Zeep Hands Palmolive naturals	7:00	Bar of soap		Head/body
	Ciel body look	7:00	3,8		Head
	Aftershave Paco Rabanne	7:00	3x		Face/body
	Stick deodorant Hugo Boss	7:00	7x per axilla		Axilla
	Tandpasta Elmex	10:30	1,9		Teeth

* NS = not specified by the volunteer.

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
6	Head and shoulders anti roos shampoo	15:45	5,2		Hair
	Axe dark temptation douchegel	15:45	10,1		Whole body
	Elmex (groen)	22:45	1,1		Teeth
	Adidas ice dive	7:30	NS*	2 per axilla	Axilla
	Elmex (groen)	7:30	1,1		Teeth
7	Himalaya Shampoo anti-dandruff	7:15	7,7		Hair/Head
	Sanex Protector	7:20	7,7		Whole body
	Axe Dry Excite	7:30	1 time	1	Axilla
	Tandpasta Sensodyne Gentle Whitening	7:45	0,9		Teeth
	Himalaya Shampoo anti-dandruff	6:30	7,7		Hair/Head
	Sanex Protector	6:35	7,7		Whole body
	Axe Dry Excite	6:45	1 time	1	Axilla
	Tandpasta Sensodyne Gentle Whitening	7:15	0,9		Teeth
	Tandpasta Sensodyne	11:15	0,9		Teeth

* NS = not specified by the volunteer.

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
8	Handzeep vinolia	22:30	7,7		Face and neck
	Niveau oogmake-up reinigingslotion	22:30	2,5		Eyes
	Tonic Nivea	22:30	2,5		Face
	Nachtcreme Biocura	22:30	0,9		Face
	Handcreme clycerona	22:30	0,9		Hands and nails
	Tandpasta McCleans	22:30	1,1		Teeth
	Vinolia handzeep	7:00	2,7		Face and Hands
	Vinolia handzeep	8:00	2,7		Face and Hands
	Dagcreme Biocura	8:00	0,7		Face and neck
	Gekl. Creme?	8:00	0,7		Face
	L'oreal creme puf poeder	8:00	1,0 mg		Face
	Oogschaduw (groen)	8:00	ND*		Above the eyes
	Oogschaduw (bruin)	8:00	ND		Eyebrow
	Miss Helen mascara	8:00	>17,9 mg		Eyelashes
	Bodyshop kleurkorrels	8:00	24 mg		On the cheek
	Tandpasta McCleans	8:00	1,1		Teeth
	Lenzenvloeistof	8:00	2,5		Eyes
	Lipfinity	8:00	6,5 mg		On the lips
	Lippotlood	8:00	1,1 mg		On the lips
	Wenkbrauwpotlood	8:00	0.7 mg		Face

* ND = not determined.

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
9	Sensodyne fresh gel	13:45	0,9		Teeth
	Maybelline lippenstift	14:00	>6,5 mg		Upper and lower lip
	Kappus nature cream soap	17:15	1,0		Hands, Face
	AH babyolie (make-up remover)	17:20	1,2		Eyes
	Colgate tandpasta	17:30	0,9		Teeth
	Vaseline pure petroleum jelly	17:45	0,3		Fingers
	Sensodyne fresh gel	1:00	0,9		Teeth
	Labello lipcare Med protection	1:10	>1,5 mg		Upper and lower lip
	Kappus nature cream soap	8:15	1,0		Hands
	Natusan baby softwash	8:45	1,0		Whole body
	Sensodyne gel	9:00	0,9		Teeth
	Maybelline lippenstift	9:05	>6,5 mg		Lips
	Natusan baby softwash	9:10	1,0		Face
	Kneipp Intensive cream	9:12	0,3		Face
	L'oreal eyeliner	9:30	0,4 mg		Underneath the eye, on the eye lid
	L'oreal contour khôl	9:35	0,4 mg		On the eye lid
	Rimmel mascara (exaggerate)	9:40	>17,9 mg		Eyelashes
	Max Factor eye brow pencil	9:42	>0,5 mg		Eyebrow

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
10	Handzeep vanille Yves Rocher (blok)	6:30	Bar of soap		Hands
	Handzeep vanille Yves Rocher (blok)	11:00	Bar of soap		Hands
	Handzeep vanille Yves Rocher (blok)	13:30	Bar of soap		Hands
	Handzeep vanille Yves Rocher (blok)	16:15	Bar of soap		Hands
	Handzeep vanille Yves Rocher (blok)	19:30	Bar of soap		Hands
	Handzeep vanille Yves Rocher (blok)	0:00	Bar of soap		Hands
	Handzeep vanille Yves Rocher (blok)	7:15	Bar of soap		Hands
	Zeep (onbekend merk)	10:00	1,0		Hands
	Zeep (onbekend merk)	0:00	1,0		Hands
	Oral B Tandpasta multi-bescherming	11:15	1,5		Teeth
	Oral B Tandpasta multi-bescherming	23:50	1,5		Teeth
	Oral B Tandpasta multi-bescherming	7:15	1,5		Teeth
	Blistex Medplus	13:00	1,0		Lips
	Blistex Medplus	19:00	1,0		Lips
	Rexona cotton ultra dry (roller)	19:00	3,0		Axilla
	Rexona cotton ultra dry (roller)	7:45	3,0		Axilla
	Yves Rocher bio-glansshampoo	7:20	2,7		Hair
	Yves Rocher nutritioning conditioner	7:25	1,0		Hair
	Bodyshop strawberry shower gel	7:26	1,0		Everywhere
	Yves Rocher anti-fatigue Facescreme	7:40	0,2		Face
	Herbacin wuta kamille	8:25	0,4		Hands

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
11	Baleno handzeep	8:15	1,0		Hands
	HEMA douchegel	9:15	2,7		Whole body
	Tandpasta Colgate	9:20	0,4		Teeth
	Handzeep	13:30	1,0		Hands
	Handzeep	17:00	1,0		Hands
	Handzeep	17:15	1,0		Hands
	Handcreme alverde	19:00	0,3		Hands
	Handzeep	20:00	0,3		Hands
	Tandpasta Colgate	21:00	0,4		Teeth
	Handcreme alverde	21:00	0,3		Hands
	Lavendel olie waleda	21:10	0,2		Feet
	Handzeep	7:00	1,0		Hands
	Douchegel HEMA	7:30	2,7		Whole body
	Tandpasta Colgate	7:40	0,4		Teeth
12	Oral-B tandpasta	0:07	0,7		Teeth
	Lippenbalsem Blistex	0:09	11,3 mg		Lips
	Andrelon shampoo	9:30	2,7		Hair
	Niveau douchegel	9:30	2,7		Everywhere
	Odorex deodorant	9:42	1 time	1	Axilla
	Andrelon haarschuim	9:45	3,0		Hair
	Oral-B tandpasta 3D white munt	10:15	0,7		Teeth
	Parfum Celine Dion signature	11:00	2 times	1	Neck and wrists

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
13	Shampoo	23:10	2,7		Hair
	Conditioner	23:12	2,7		Hair
	Douchegel	23:13	2,7		Axilla
	Nachtcreme	23:20	0,3		Face
	Deo	7:14	1,2		Axilla
	Nachtcreme	7:15	0,3		Face
	Tandpasta	23:25	0,7		Teeth
	Tandpasta	7:45	0,7		Teeth
	Purol	7:58	11,3 mg		Lips
	Purol	10:15	11,3 mg		Lips
	Himalaya herbald tandpasta	10:33	0,7		Teeth
	Purol	11:05	11,3 mg		Lips
	Purol	15:43	11,3 mg		Lips
	Handcreme kneip	15:47	0,4		Hands
	Deo… going bio?	15:48	1,2		Axilla
	Himalaya herbald tandpasta	18:30	0,7		Teeth
	Purol	20:00	11,3 mg		NS*
	Purol	20:45	11,3 mg		NS

* NS = not specified by the volunteer.

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
14	Prodent natural & fresh	23:45	0,7		Teeth
	Chanel lotion comfort	23:50	1,8		Face and neck
	La Mer Handcreme	0:00	0,9		Hands and wrists
	Andrelon glans shampoo	6:56	5,2		Hair
	Andrelon conditioner care&repair	6:50	7,7		Hair
	Body shop Scent-me shower gel	6:50	2,7		Whole body
	Garnier Pure 3in1	6:50	2,7		Face and neck
	Prodent natural & fresh	7:05	0,7		Teeth
	Chanel lotion comfort	7:16	1,8		Face and neck
	Nivea deodorant dry comfort 48 uur	7:15	1x	2	Axilla
	L'oreal Triple active dagcreme	7:17	0,4		Face and neck, not on the eyes
	Chanel ultra correction lift eye creme	7:17	0,1		Eyes
	Body shop Perfume Oil tea rose	7:18	1,8		Behind the ears and on clevage
	La Mer Handcreme	7:20	0,9		Hands and wrists
	Gosh amazing length 'n build waterproof mascara	7:46	12,0 mg		Eyelashes

Volunteer	Product applied	Time point of the day (h)	Amount (g)	Duration of spraying (sec)	Exposed body parts
15	Kruidvat natural lippenbalsem	11:15	11,3 mg		Lips
	MacCleans tandpasta	12:00	1,1		Teeth
	Pure nourishing dagcreme kruidvat	12:00	0,4		Face
	Deodorant 8x4 rock cherry	12:00	1x	2	Axilla
	Zinksulfaat apothekers (zalf tegen lipblaasjes)	12:00	NS*		Lip
	Zinksulfaat apothekers (zalf tegen lipblaasjes)	14:00	NS		Lip
	Zinksulfaat apothekers (zalf tegen lipblaasjes)	16:00	NS		Lip
	Zinksulfaat apothekers (zalf tegen lipblaasjes)	20:00	NS		Lip
	Calendulan zalf (homeopathisch geneesmiddel)	20:00	NS		Hands
	Lippenbalsem kruidvat natural	20:00	11,3 mg		Lips
	Calendulan zalf	0:00	NS		Hands
	Pure nourishing dagcreme kruidvat	0:00	0,4		Face
	MacCleans tandpasta	0:00	1,1		Teeth
	Skin therapy oil (Palmers)	0:00	NS		Hands and upper leg
	Zinksulfaat apothekers	0:00	NS		Lip
	Natural kruidvat lippenbalsem	0:00	11,3 mg		Lips
	Natural kruidvat lippenbalsem	7:45	11,3 mg		Lips
	Shower gel wellnes Hegron	8:00	5,2		Whole body

* NS = not specified by the volunteer.

A5-2 Control experiments (D4)

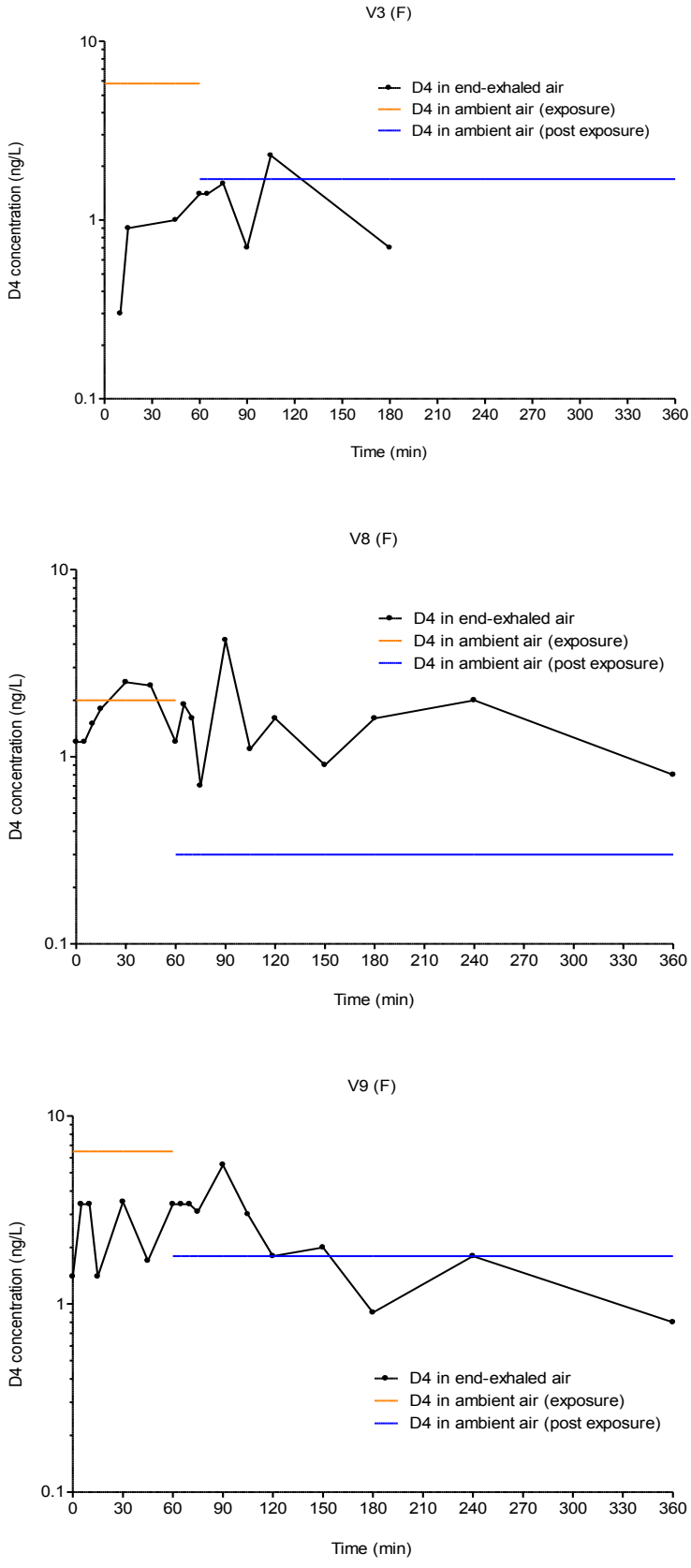

Figure A5-2.1. The mean D4 concentrations in end-exhaled air (ng/L) and the mea
average D4 concentration in ambient air (ng/L) during the control experiments of volu

A5-3 Control experiments (D5)

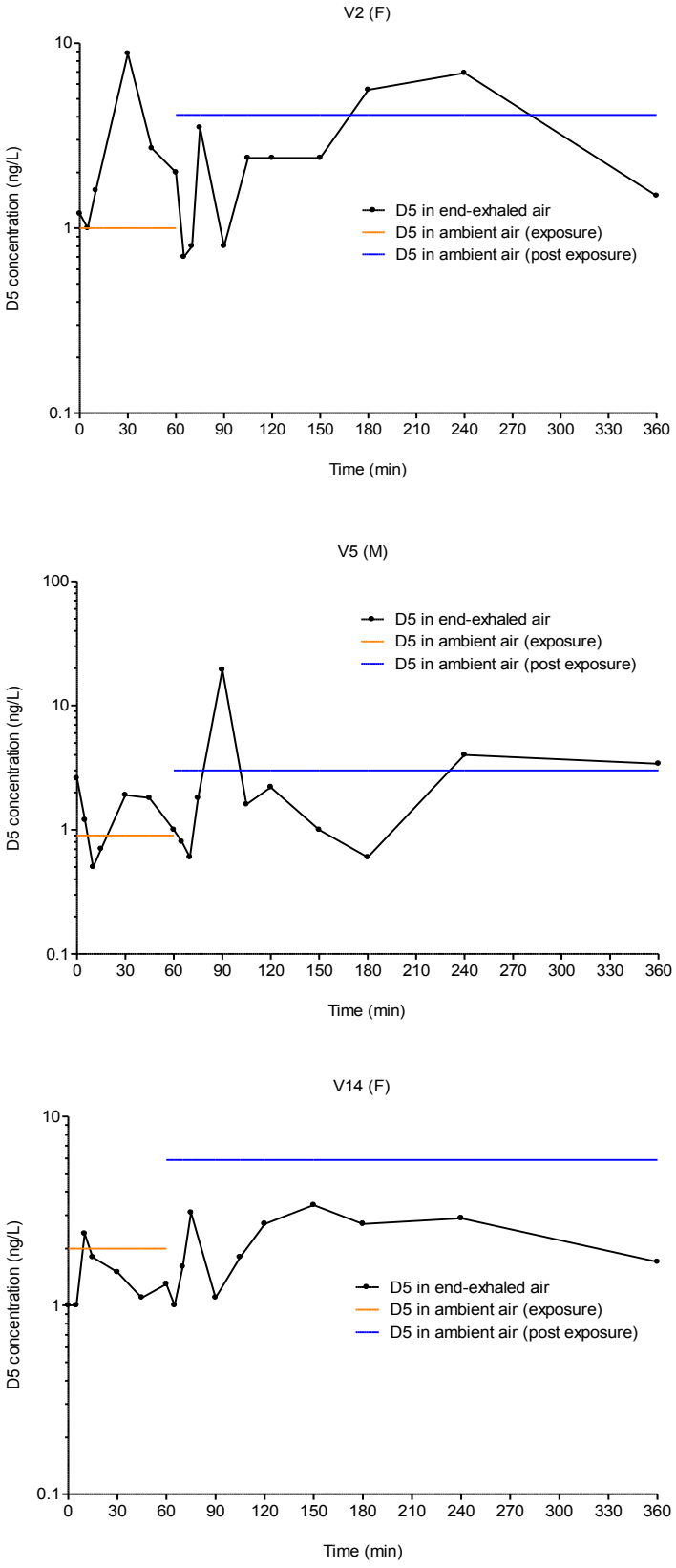

Figure A5-3.1. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) during the control experiments of volunteer 2, 5 and 14.

A5-4 Exposure to D5 as a pure substance

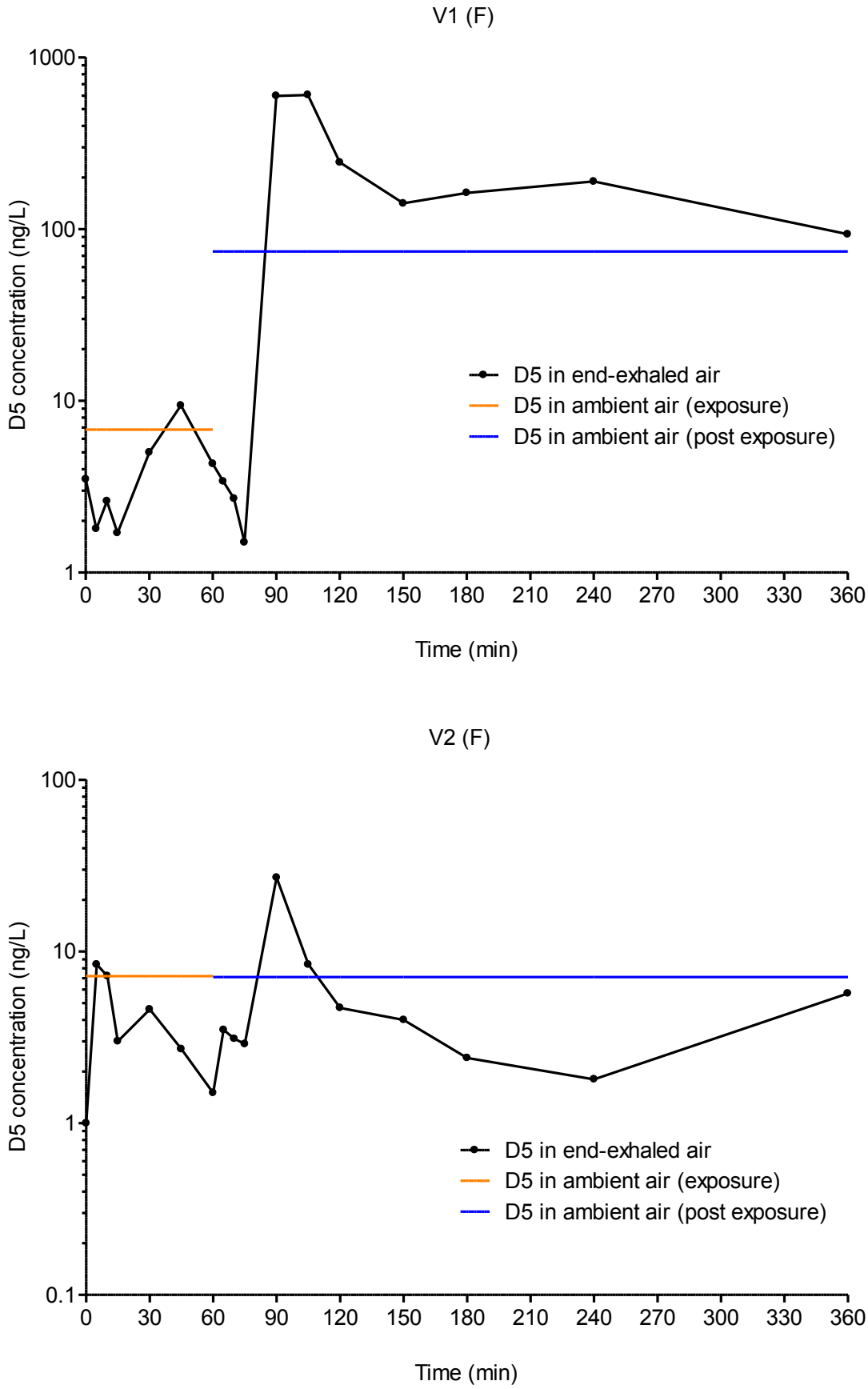

Figure A5-4.1. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 pure substance of volunteer 1 and 2.

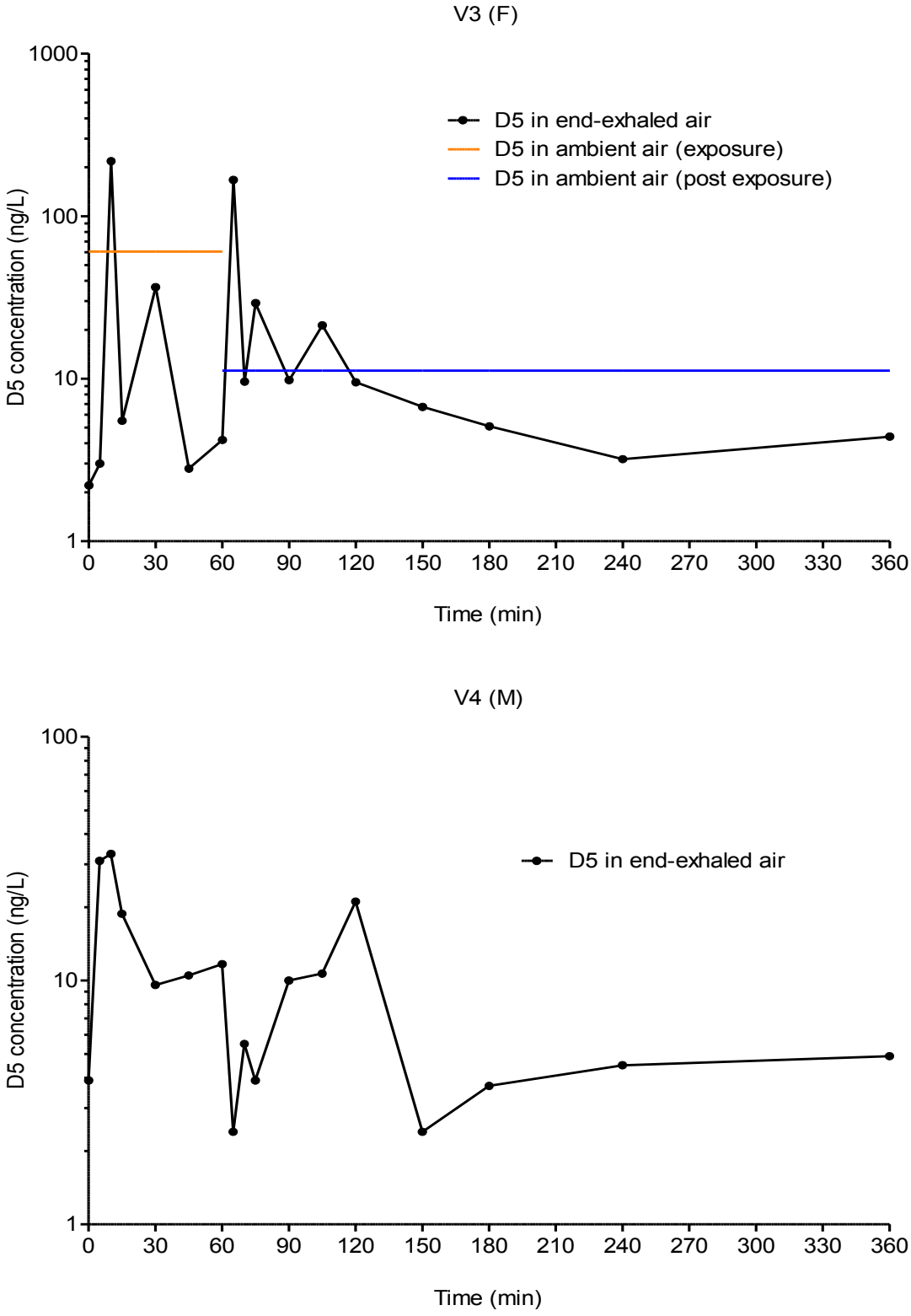

Figure A5-4.2. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 pure substance of volunteer 3 and 4**. Note:** Due to a technical error no data for the time-weighted average D5 concentration in ambient air are presented for volunteer 4.

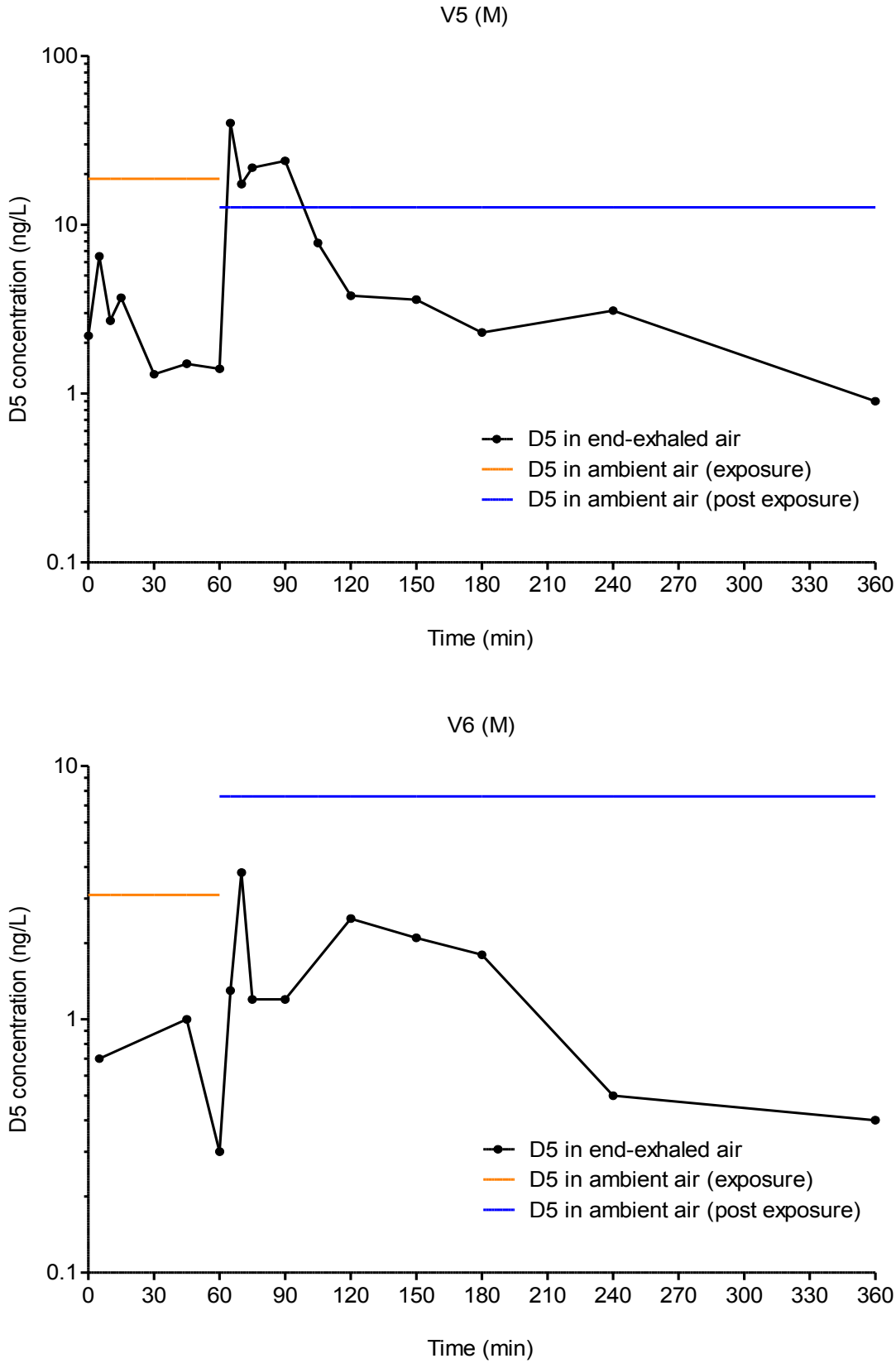

Figure A5-4.3. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 pure substance of volunteer 5 and 6.

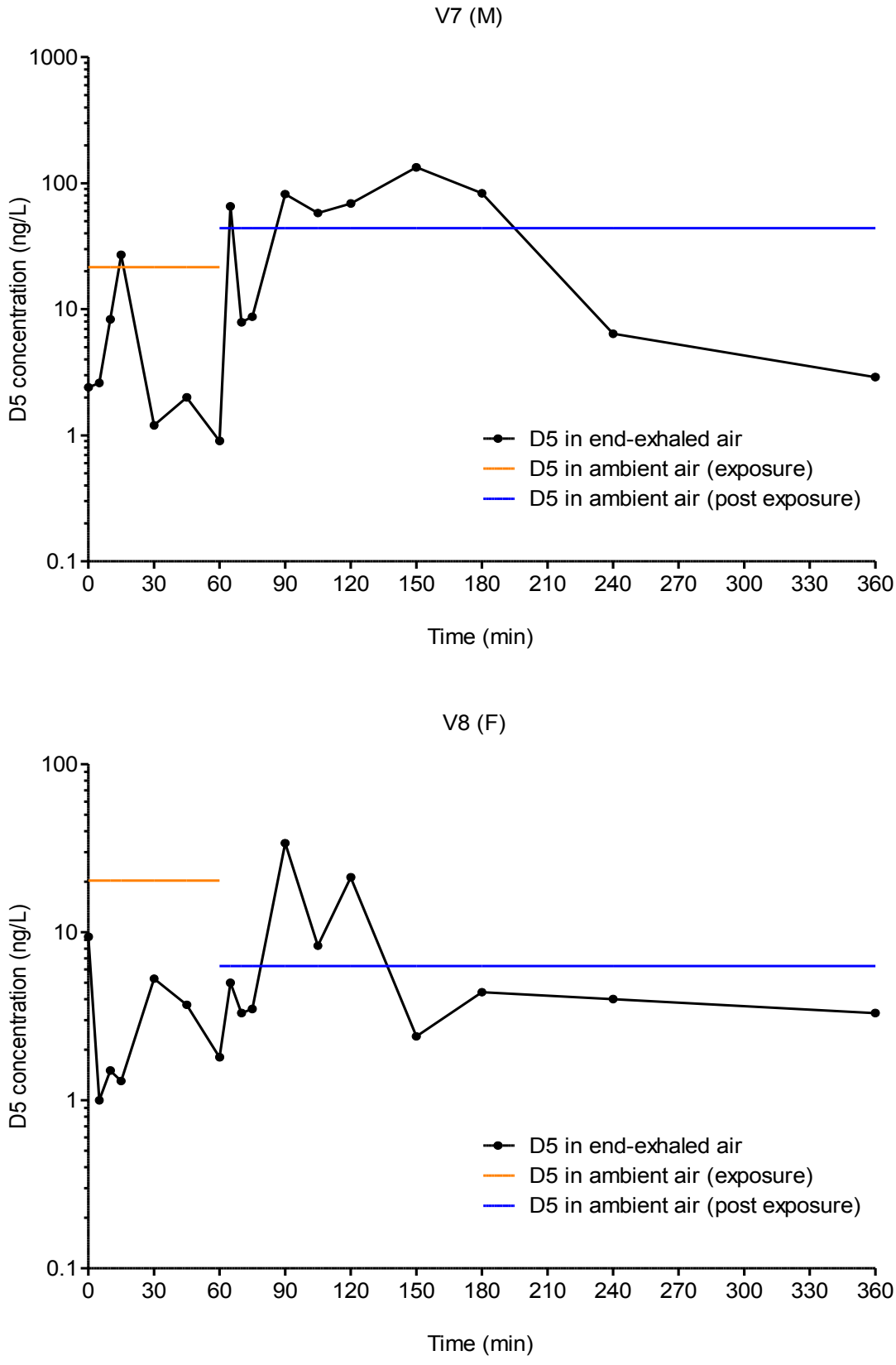

Figure A5-4.4. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 pure substance of volunteer 7 and 8.

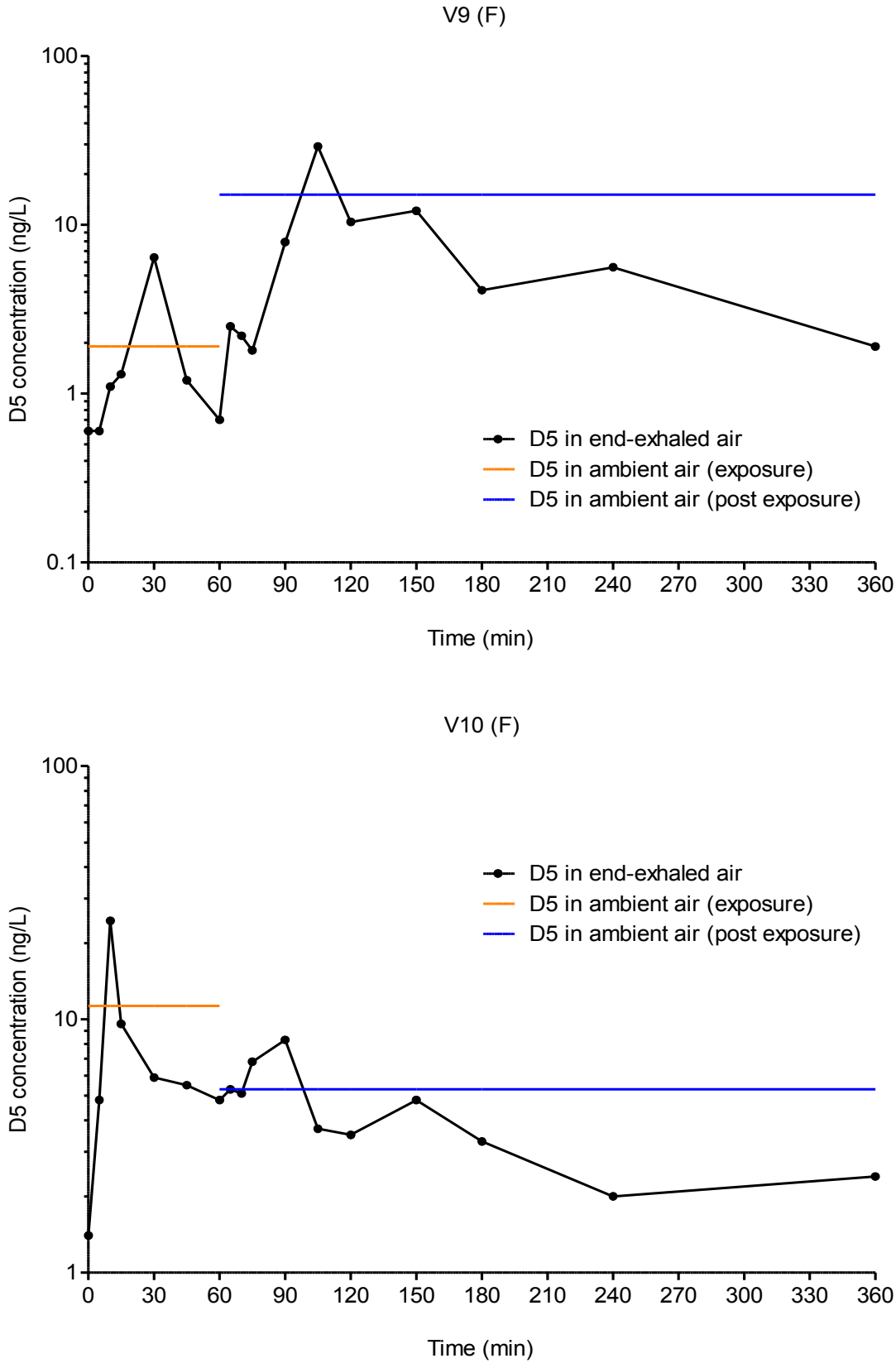

Figure A5-4.5. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 pure substance of volunteer 9 and 10.

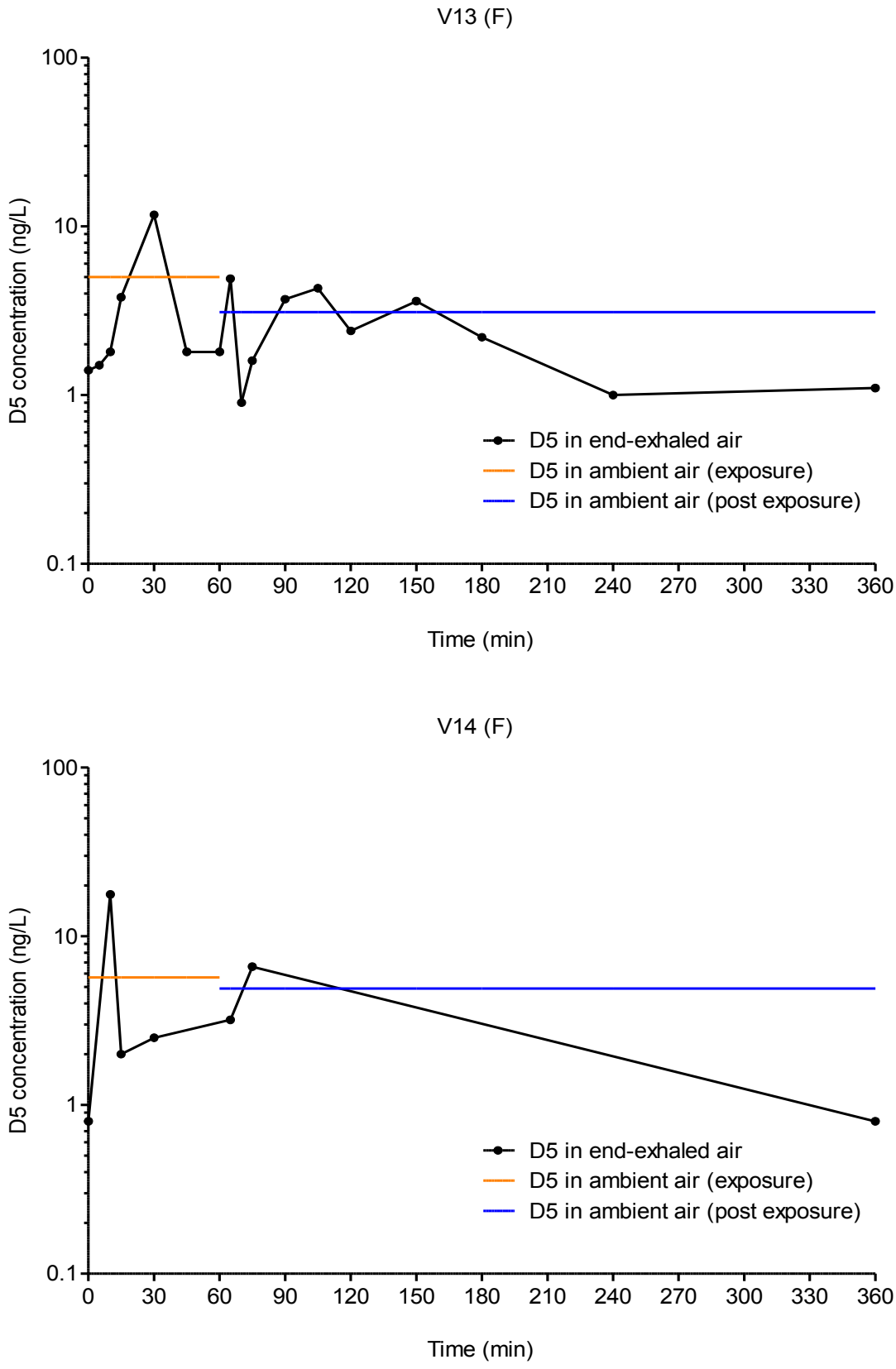

Figure A5-4.6. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 pure substance of volunteer 13 and 14.

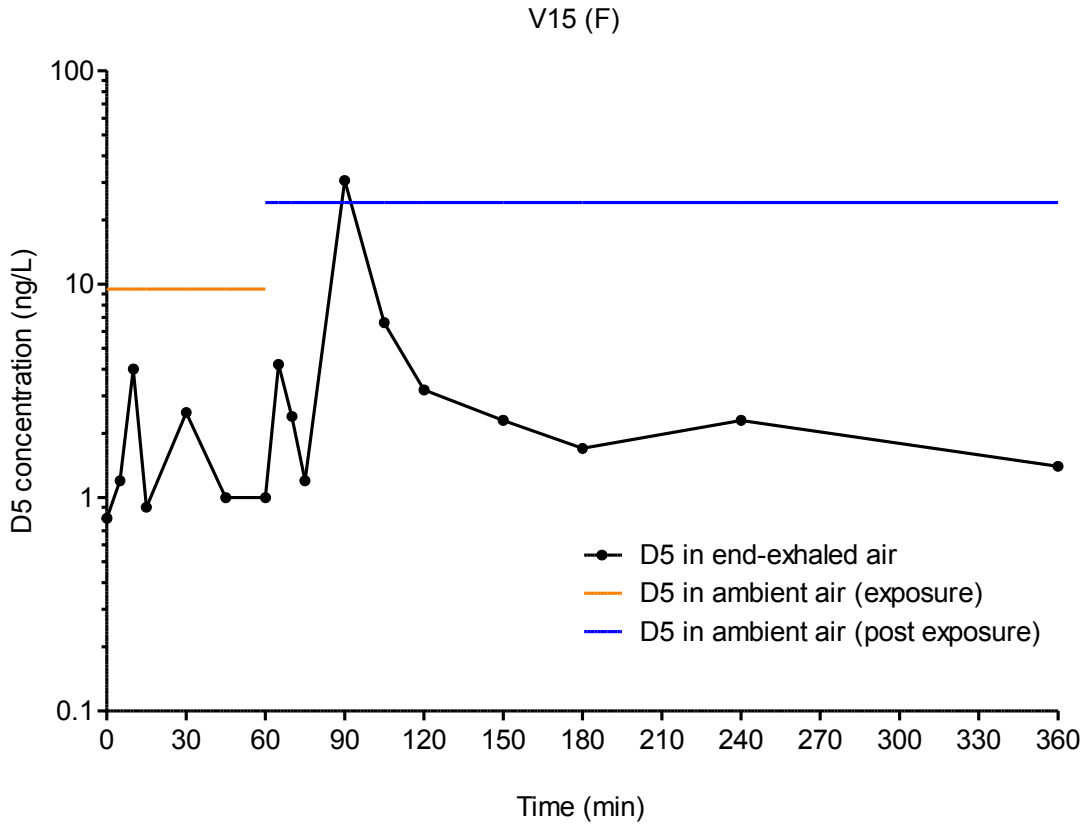

Figure A5-4.7. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 pure substance of volunteer 15.

A5-5 Exposure to D5 as a pure substance – no toilet visit at t=90 min

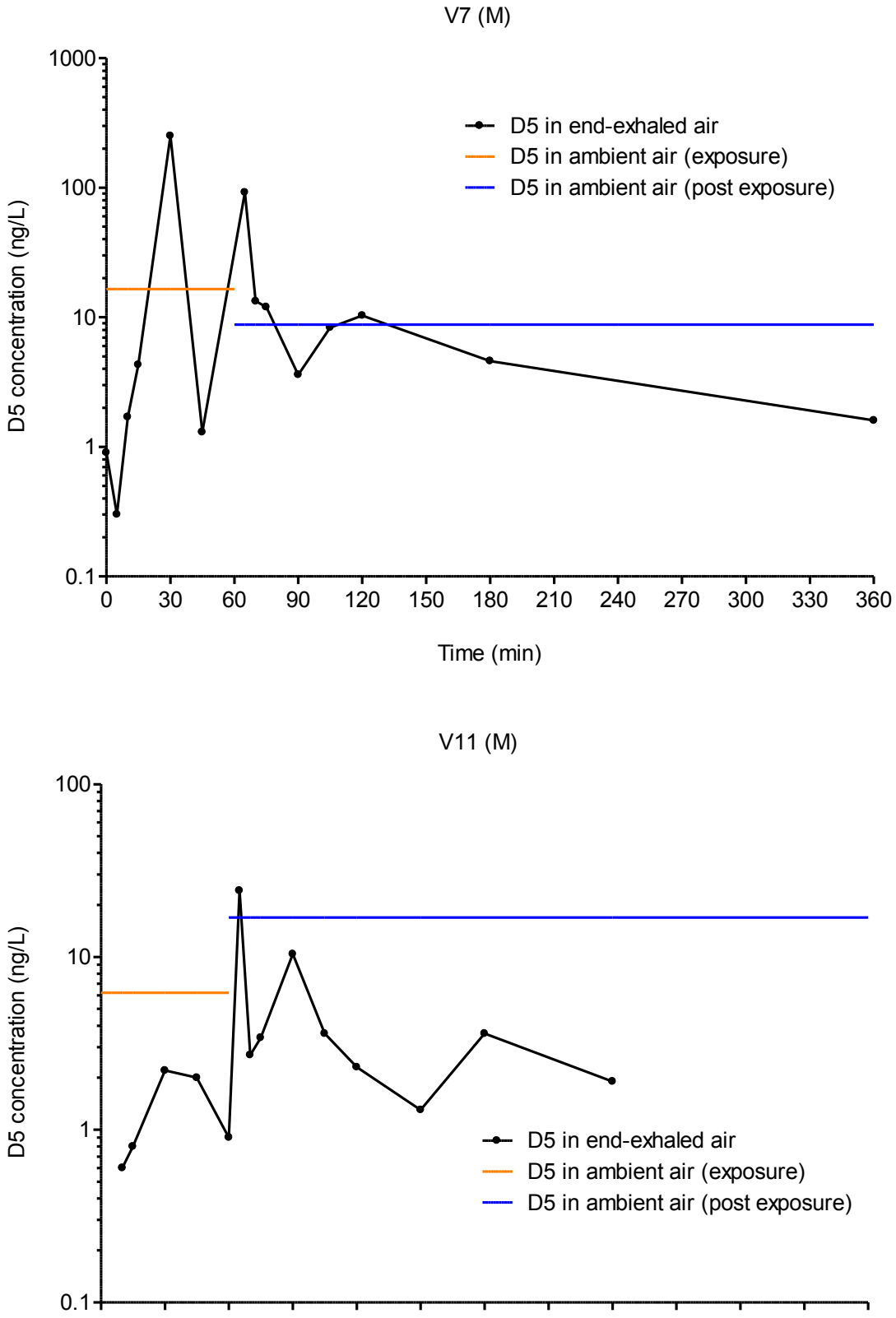

Figure A5-5.1. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 pure substance of volunteer 7 and 11.

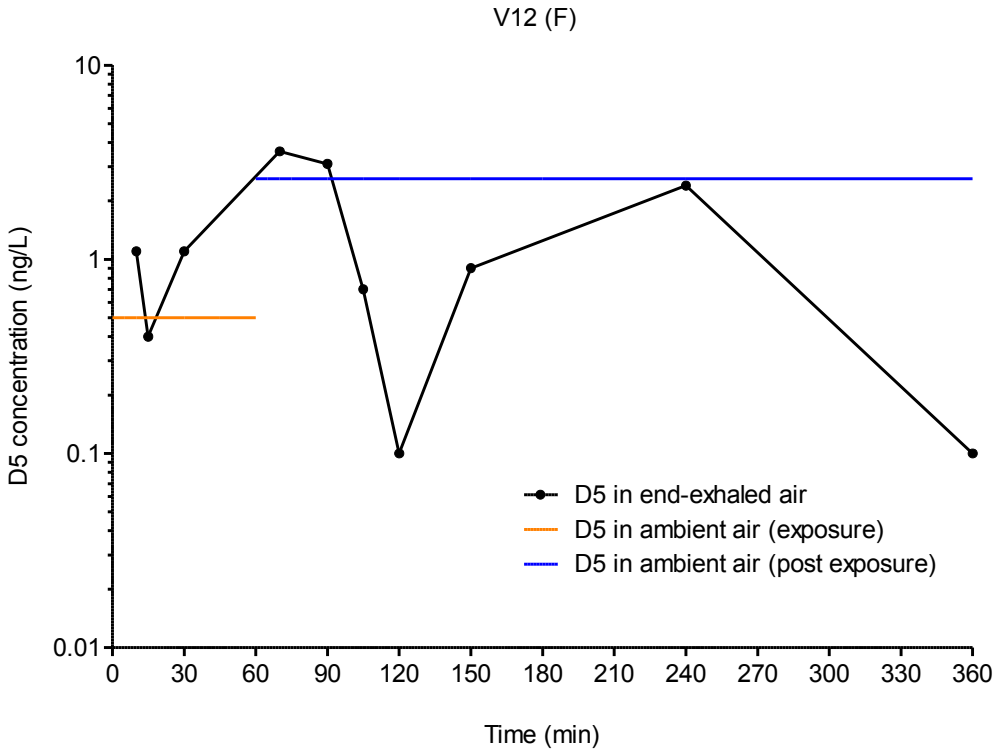

Figure A5-5.2. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to D5 pure substance of volunteer 12.

A5-6 Exposure to cream

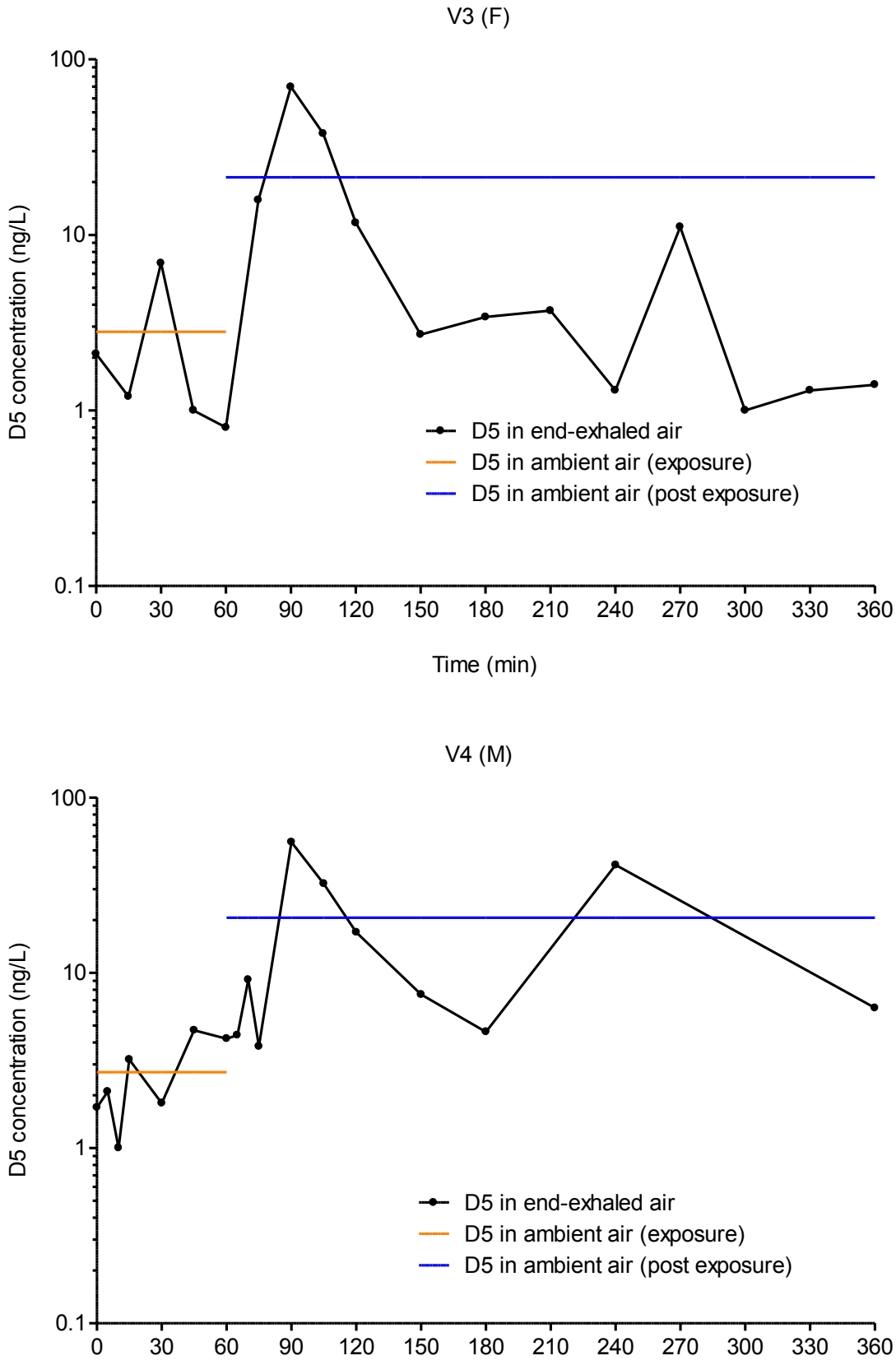

Figure A5-6.1. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to cream of volunteer 3 and 4.

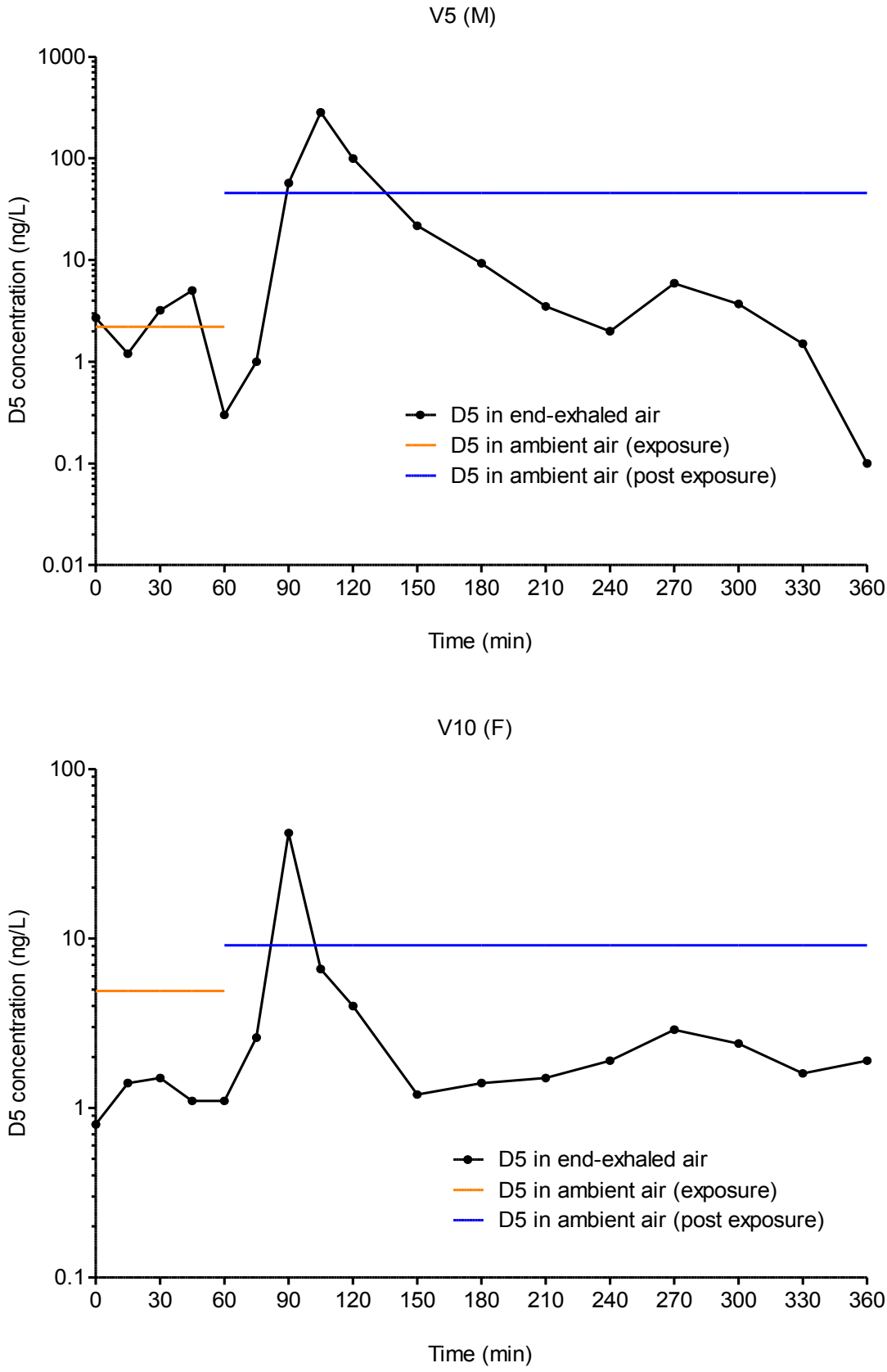

Figure A5-6.2. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to cream of volunteer 5 and 10.

A5-7 Exposure to deodorant

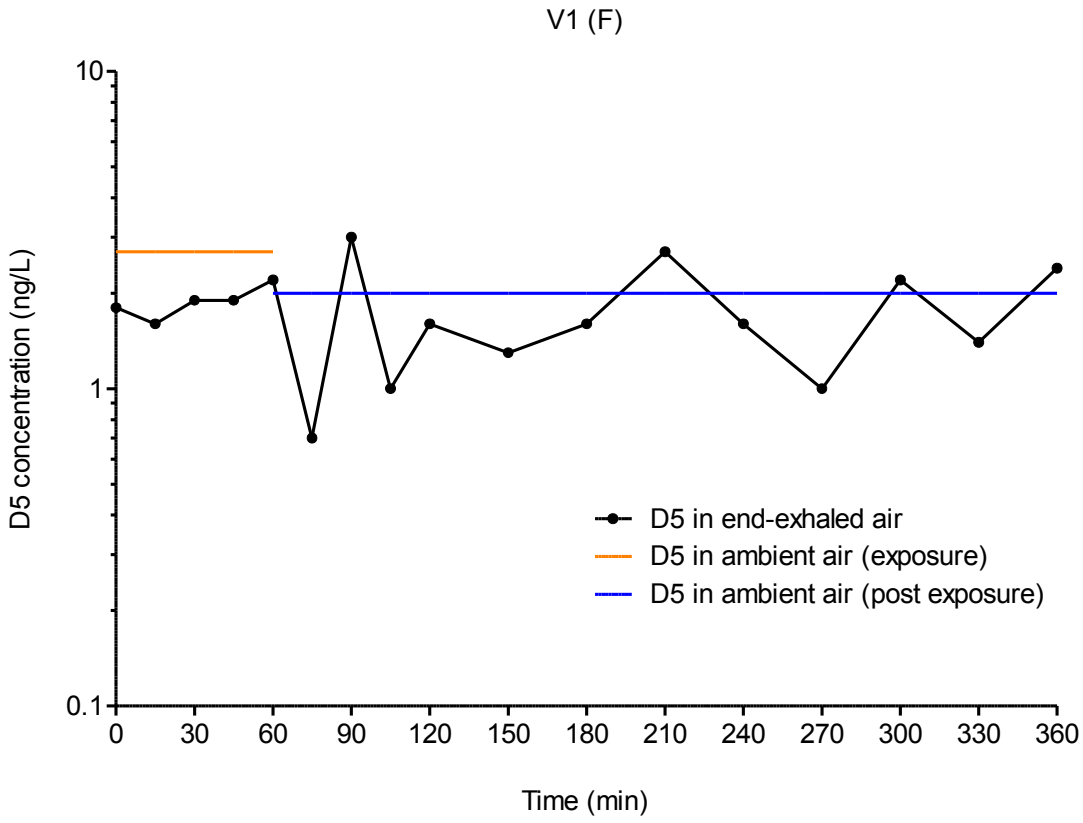

Figure A5-7.1. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to deodorant of volunteer 1.

A5-8 Exposure to cream and deodorant

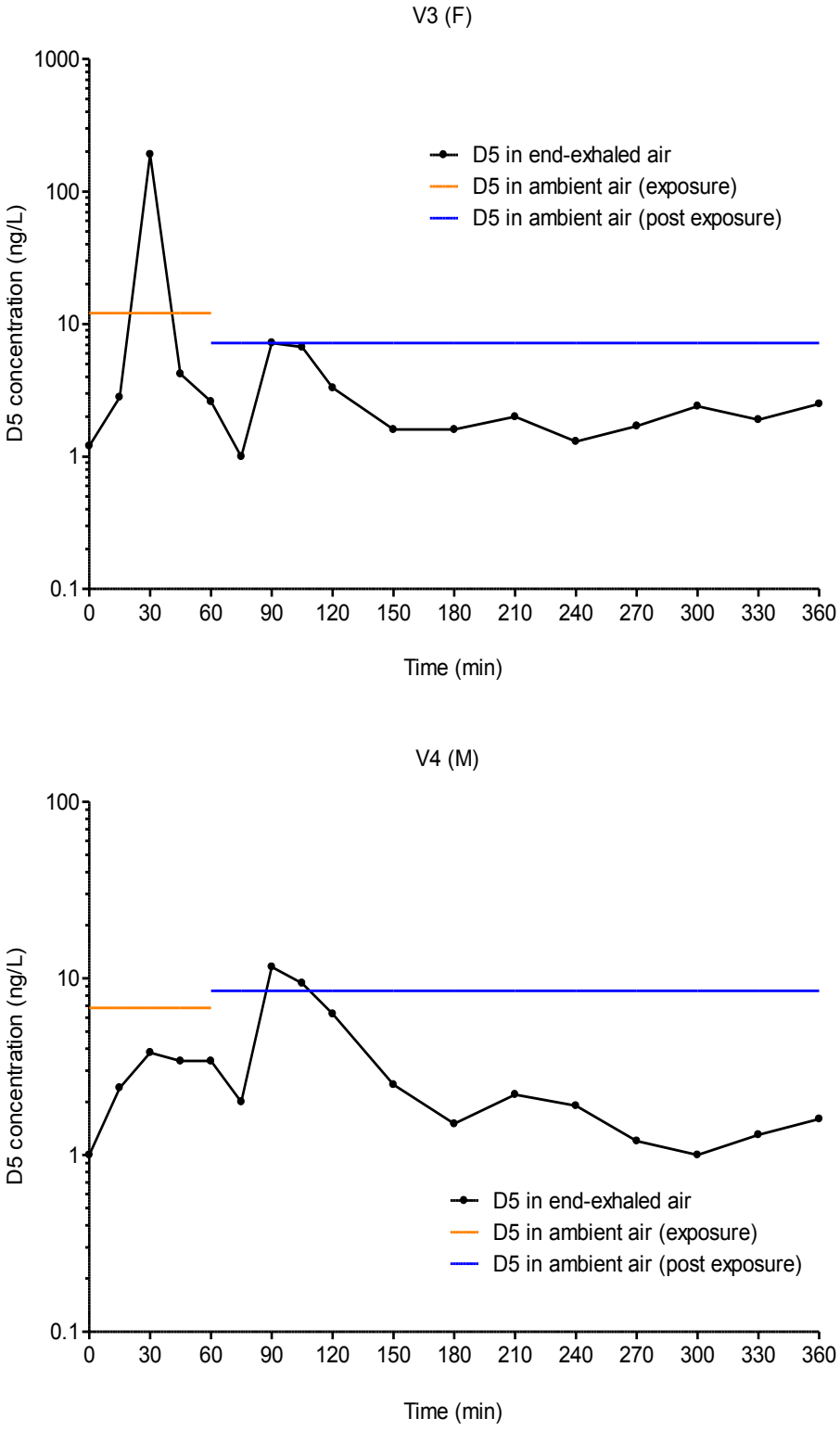

Figure A5-8.1. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) after dermal exposure to cream and deodorant of volunteer 3 and 4**.**

A5-9 Exposure to D4 as a pure substance

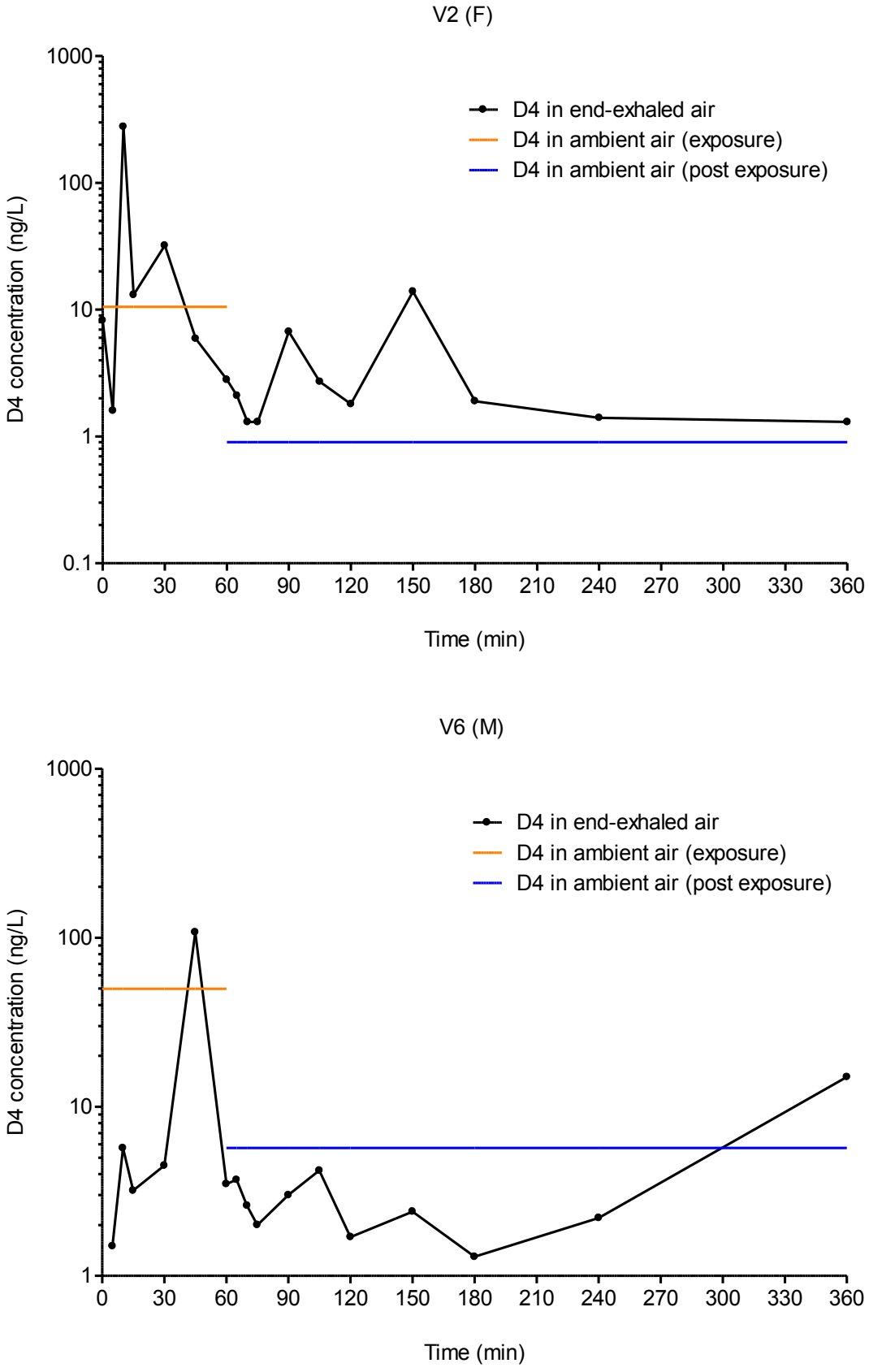

Figure A5-9.1. The mean D4 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D4 concentration in ambient air (ng/L) after dermal exposure to D4 as a pure substance of volunteer 2 and 6.

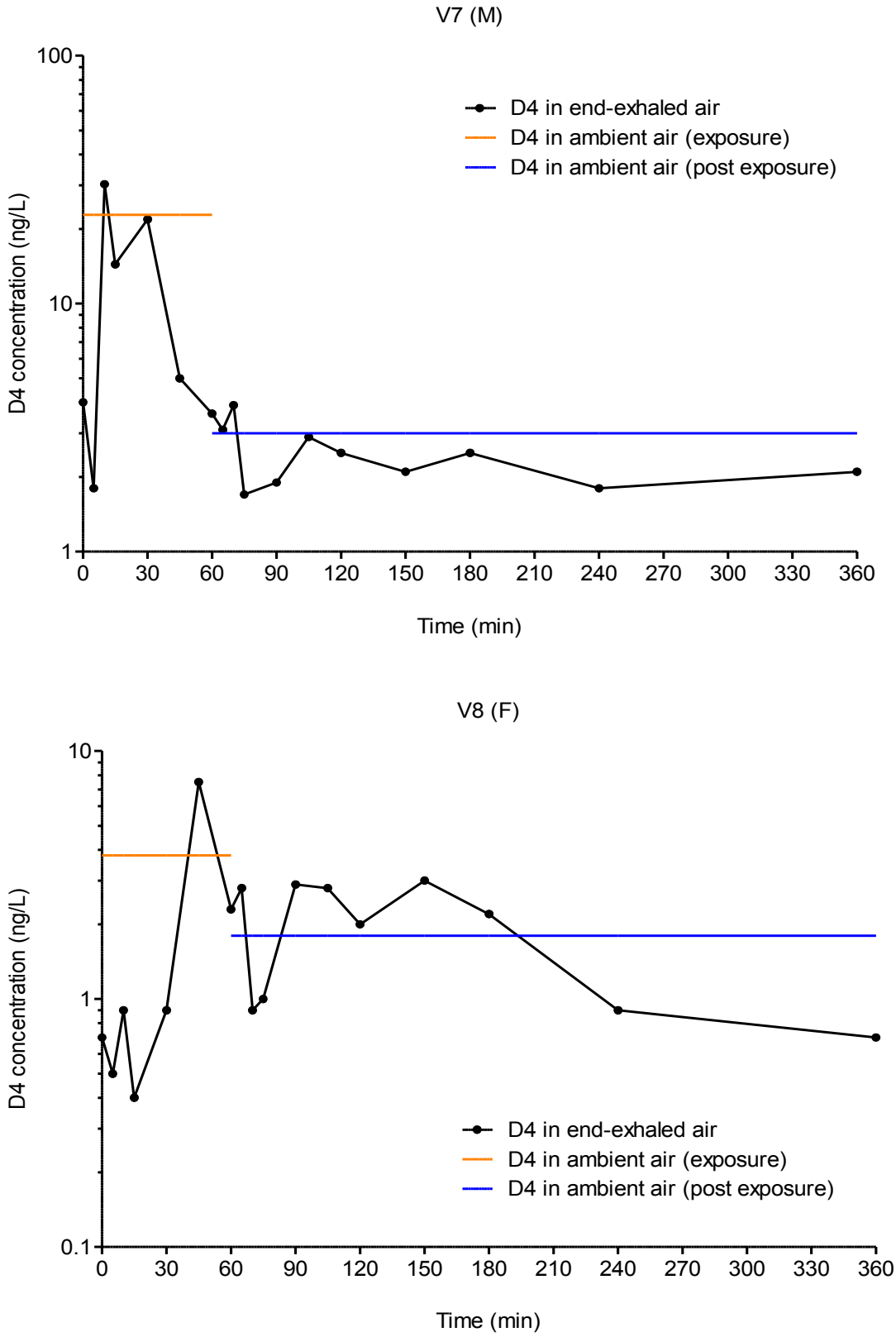

Figure A5-9.2. The mean D4 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D4 concentration in ambient air (ng/L) after dermal exposure to D4 as a pure substance of volunteer 7 and 8.

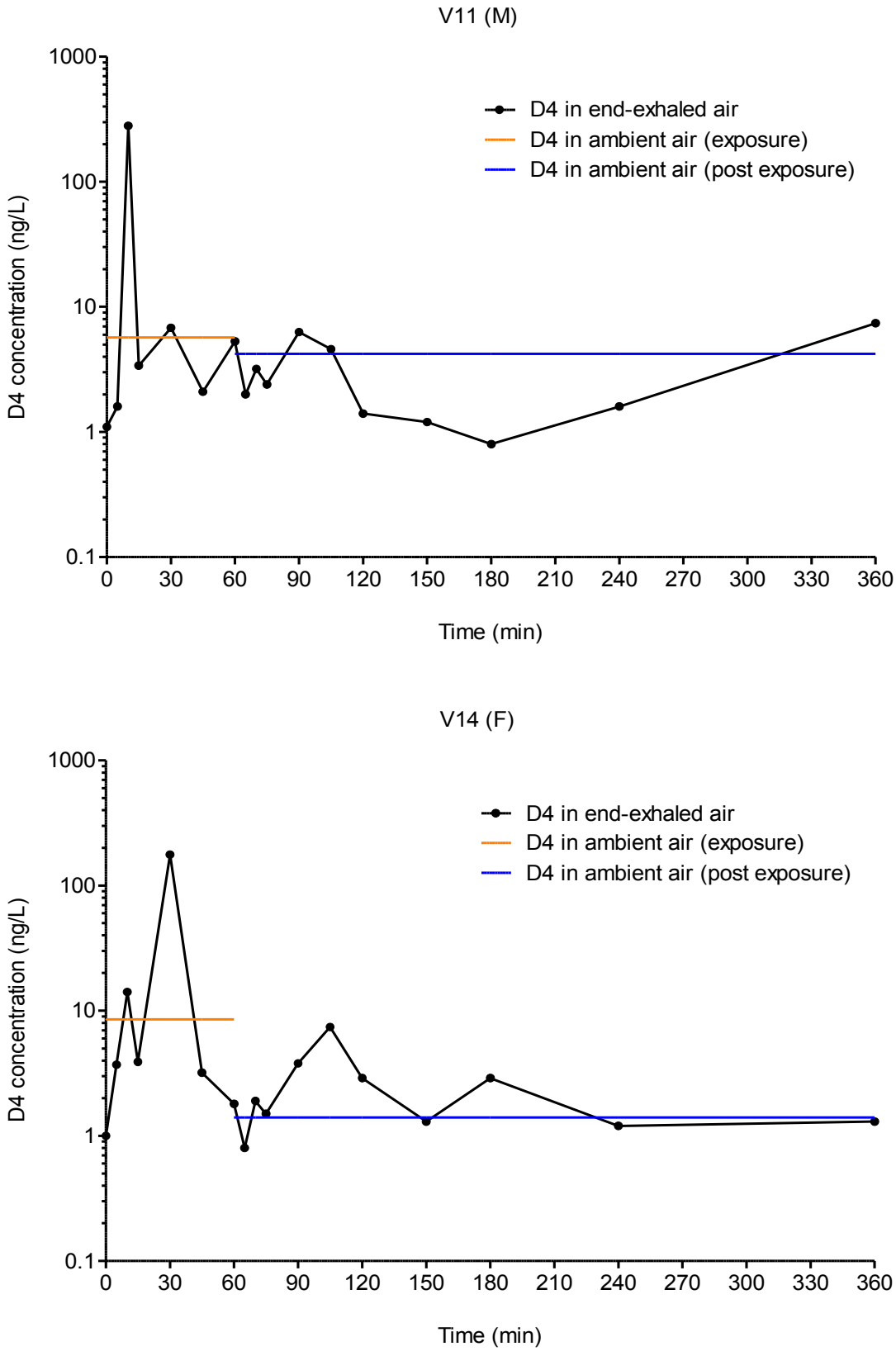

Figure A5-9.3. The mean D4 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D4 concentration in ambient air (ng/L) after dermal exposure to D4 as a pure substance of volunteer 11 and 14.

A5-10 Exposure experiments without the prevention of inhalation

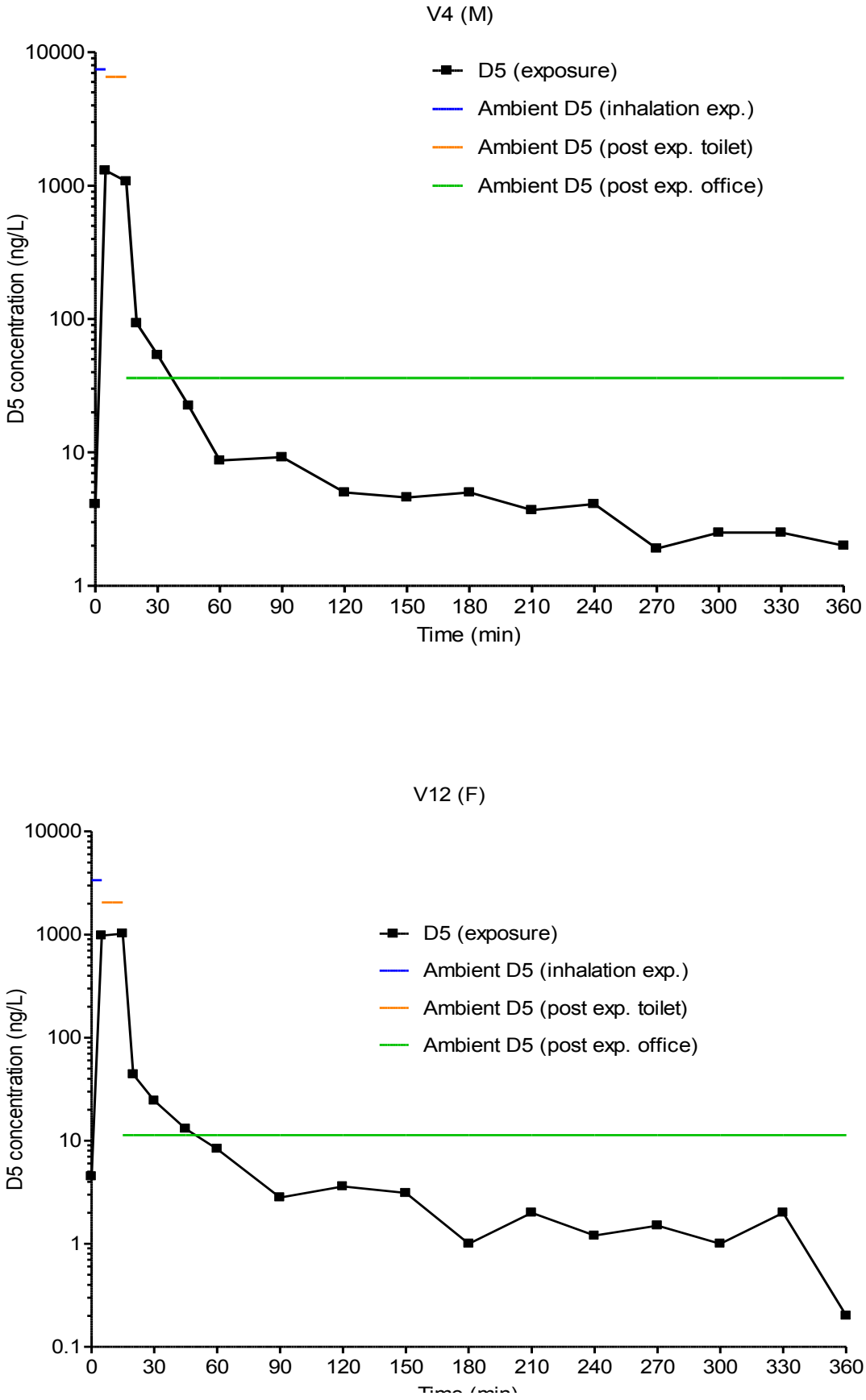

Figure A5-10.1. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) during inhalation experiments of volunteer 4 and 12.

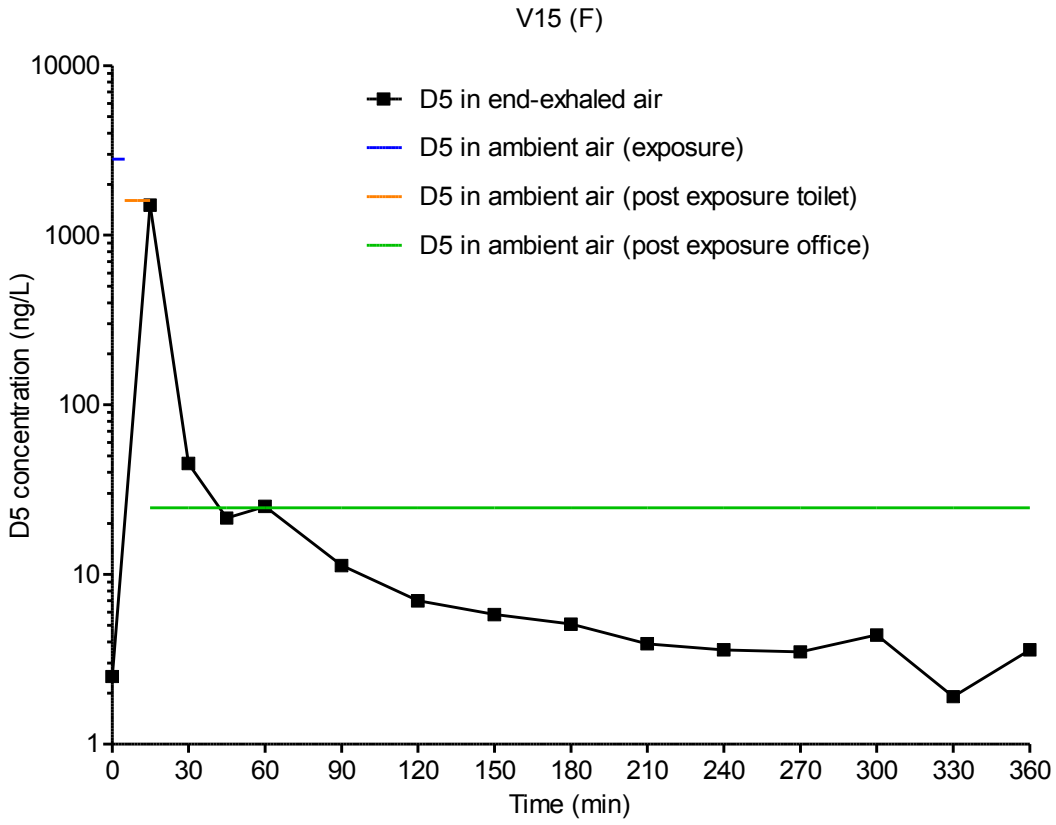

Figure A5-10.2. The mean D5 concentrations in end-exhaled air (ng/L) and the mean time-weighted average D5 concentration in ambient air (ng/L) during inhalation experiment of volunteer 15.