Simplified human exposure assessment of chemicals with the help of *intake fraction*?

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Abstract

The concept of intake fraction (iF) relates the emitted amount of a particular chemical to the subsequent human intake of that substance. Intake fractions have been calculated for more than 300 substances, spanning a range of up to seven orders of magnitude. It has furthermore been suggested that intake fractions can be estimated based on a few properties of the chemical. In this study, the following two questions are discussed: *Can this type of relationships be used for simplified human exposure assessment? Does high total production volume of a chemical imply high human exposure?* In this report the available research on the concept of intake fraction is scrutinized, including the suggested methods to calculate intake fractions. It is concluded that variability and uncertainty in the intake fractions estimated so far is considerable, implying that the concept needs further development before it can be used for simplified exposure analysis in the regulatory context. It is furthermore concluded that there seem to be a positive correlation between the amount of a chemical emitted into the environment and the magnitude of human exposure to that particular substances. This does however not imply that a high total production volume of a chemical necessarily will result in high human exposure.

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Summary

Between 30 000 and 70 000 chemical substances are available on the commercial market in the European Union. The substances are used for a variety of applications and people are exposed to a multitude of different chemicals every day. To prevent unnecessary risk to humans from these chemicals require regulations. In the European Union chemicals are currently being regulated according to if they are “existing” substances (existed on the market before 1981), “new” chemicals (chemicals introduced on the market after 1981) and how they are classified and labelled. The “existing” and “new” substances are to be risk assessed by authorities in the EU. The “existing” substances, more than 100 000 substances, are to be risk assessed according to priority lists. This has proven to be a slow and resource demanding process.

Currently a new regulation of chemicals within the EU is being developed called REACH (Registration, Evaluation, Authorization and restriction of Chemicals). In the new system all chemicals are regulated in the same system and the regulatory requirements are based on, among other things, the annual production volume of the chemical. Similar to the old system high volume chemicals are prioritised in the way that more data are required than for low volume chemicals. This prioritisation of high volume chemicals is based on the assumption that the higher production volume the higher exposure and thus higher risk. This is a major simplification since exposure is dependent on several factors including the release of the chemical into the environment, its transportation, transformation and fate in various media and that contact with individuals actually occur. The risk is dependent, besides on the total exposure of a chemical, on for example the chemical and physical properties of the chemical, how the chemical is metabolised, and the susceptibility of exposed individuals.

With the introduction of REACH the responsibility of performing exposure assessments and risk assessments is shifted from the authorities to manufacturers and importers of chemicals. Currently there are no guidelines for them to perform a preliminary assessment and in many cases they lack the proper expertise to use complex tools used by the authorities. This is expected to be a problem and therefore there exists a need to develop simplified assessment tools.

A group of researchers have developed the concept of intake fraction and used it to derive empirical relationships that could potentially simplify exposure assessments of chemicals. Intake fraction (iF) is defined as *the fraction of chemical mass emitted into the environment that eventually passes into a member of the population through inhalation, ingestion or dermal exposure* and can be calculated according to the equation given below:

$$iF = \frac{\sum_{people,time} \text{mass intake of pollutant by an individual}}{\text{mass released into the environment}}$$

Intake fraction has only been in use since the beginning of the 21:th century but similar concepts, linking source-to-intake, have existed for more than twenty years and one reason for developing the concept of intake fraction was to unify this multitude of concepts.

Current research has showed that intake fraction can be estimated based on a few properties of the chemical studied. Intake fractions for more than 300 substances have been calculated and

together they span a range of up to seven orders of magnitude. If theses values are accurate it implies that if the same amount of different chemicals is emitted there could be a big difference in human intake between them.

Can this type of empirical relationships be used to simplify human exposure assessments?
Does high total production volume of a chemical imply high human exposure?

This study aims to answer these two questions, through an extensive literature search scrutinising available research and possible methods to calculate intake fraction.

Eleven scientific articles were found and intake fractions for a variety of chemicals have been calculated. The most extensive study calculated intake fractions for more than over 300 substances, and the intake fractions ranged from 10^{-10} to 10^{-3}.

Most estimates of intake fractions have been derived using different kind of models, where the dominating one has been the dispersion model CALPUFF. Other models used are CalTOX, IMPACT 2002, (S-R) matrix and a Mackay type level III multimedia fate model with a food-chain exposure model in succession. The only measurement based intake fractions were calculated for dioxins, furans and PCBs. Measured ambient levels of chemicals have also been used to calculate intake fractions but it was still necessary to use a model to calculate the amount of emission and to calculate how much the intake actually was from the ambient concentrations.

In the study on over 300 substances a uniform population density was assumed. Several of the other available studies showed that for dioxins this assumption can be a sufficiently approximation but for other chemicals spatial variance could be important. The results from one study showed that the use of continentally averaged parameters for population density and food production provided an accurate estimate of the median intake fraction calculated for emissions in individual regions, however the intake fraction could range from this median by up to 3 orders of magnitude, especially for chemicals transferred through foods. When comparing spatial and a-spatial model prediction with measurements the spatial model was seen to predict higher concentration that was closer to monitored values. This indicates that a spatial model should be used so as to not underestimate calculated intake fractions.

The conclusions of this study is that relationships that have been used so far for estimating intake fractions for a multitude of chemicals can not be used for simplifying exposure assessments for new chemicals as it exists today. Further research is recommended to initially focus on determining the relevance of population density, the relevance of where food is produced relative to emission source and lack and uncertainty of available data. The relationships are based on K_{ow} (octanol-water partitioning coefficient), K_{aw} (air-water partitioning coefficient) and half-life. Half-life is one of the most uncertain parameters used in multimedia modelling and it is questionable if relationships based on this parameter are useful since they must be highly uncertain.

A high volume of a chemical does not ultimately result in a high human exposure since the exposure is dependent on several factors including production processes, pathways, and use patterns. However the higher emitted volume of a chemical into the environment the higher the exposure of humans will be, this is based on that chemical exposure can be considered to be

linear with concentration when considering chemicals that is released to the environment. This assumption has been seen to be a good approximation when validating multimedia models.

However differences in exposure between chemicals could vary significantly since emission of 1 000 tonnes of one chemical with an intake fraction of $1 \cdot 10^{-9}$ could potentially result in the same intake as emission of 1 kg of a chemical with an intake fraction of $1 \cdot 10^{-3}$, although how big this span between chemicals actually could be requires further research.

Intake fraction could then potentially be used to identify chemicals that can result in a high human exposure although they are not produced or imported in high volumes. This requires that calculated generalisable intake fractions are available for a multitude of chemicals.

It is important to remember that exposure can occur not only through the environment but also through more direct ways in the form of consumer products and the working environment. It is possible to calculate intake fractions for these scenarios also, but the generalisability and usefulness of these calculations would need to be further investigated.

The applicability of the concept for risk assessments will furthermore be limited in the way that it is most appropriate for chemicals, whose effects on human health show no dependencies on intake dosage rate, no thresholds between dose and effect and proportionality to cumulative exposure.

Sammanfattning

Mellan 30 000 och 70 000 kemiska substanser finns tillgängliga på den kommersiella marknaden i Europeiska Unionen. Substanserna används inom en mängd olika områden och människor är exponerade dagligen för en mängd olika substanser. För att förhindra att människor utsätts för onödiga risker från dessa krävs någon form av reglering. I EU regleras kemikalier för närvarande enligt om de är ”existerande” substanser (fanns tillgängliga på marknaden innan 1981), ”nya” substanser (på marknaden efter 1981) och hur de klassificeras och märks. Riskbedömningen av nya och existerande substanser utförs av myndigheter i EU. De existerande substanserna, som är mer än 100 000, riskbedömds enligt prioriteringslistor. Detta har visat sig vara både en långsam och resurskrävande process.

En ny lagstiftning håller på att arbetas fram inom EU kallat REACH. I REACH är alla substanser reglerade enligt samma system. Regleringen baseras bland annat på den årliga produktionsvolymen av kemikalien. På ett liknande sätt som i det gamla systemet prioriteras högvolym kemikalier på det sättet att mer data krävs för dessa än för lågvolym kemikalier. Denna prioritering bygger på antagandet att högre produktionsvolymer leder till högre exponering och högre risk. Detta är en stor förenkling eftersom exponering är beroende av flera faktorer, bland annat att kemikalien släpps ut i miljön, dess transport, omvandling, och fördelning mellan olika medier och att kontakt mellan dessa medier och individer sker. Risken beror, förutom på den totala exponering, även på till exempel de kemiska och fysikaliska egenskaperna hos kemikalien, hur den metaboliseras och känsligheten hos exponerade individer.

I och med implementeringen av REACH överförs ansvaret för att utföra riskbedömningar från myndigheter till tillverkare och importörer. För tillfället finns det inga riktlinjer för dessa att utföra preliminära riskbedömningar och de saknar kunskap att använda komplexa verktyg som för närvarande används av myndigheterna. Detta förväntas bli ett problem och därför existerar det ett behov av att utveckla förenklade bedömningsverktyg.

En grupp forskare har utvecklat begreppet intake fraction (”intagsfraktion”) och använt det till att ta fram empiriska samband som potentiellt skulle kunna förenkla exponeringsbedömningar av kemikalier rörande exponering av människan. Intake fraction definieras som *fraktionen av den mängd kemikalie som emitteras ut i miljön och som slutligen tas upp av populationen genom inandning, förtäring och upptag genom huden* och kan beräknas enligt nedan:

$$iF = \frac{\sum_{\text{exp. ind., tid}} \text{Mängd upptagen av en individ}}{\text{Mängd utsläppt i miljön}}$$

Intake fraction har endast använts sedan början av 2000-talet men liknade begrepp, som relaterar källa till upptag, har funnits i mer än 20 år och en av anledningarna till att begreppet utvecklades var för att förena dessa olika varianter i ett enda för att underlätta jämförelser mellan olika studier.

Tillgänglig forskning har visat att intake fraction kan beräknas baserat på några få egenskaper hos den studerade kemikalien. Intake fraction har beräknats för mer än 300 substanser, exponeringen

för dessa substanser kan skilja åt med mer än sju tiopotenser. Om dessa värden är korrekta innebär det att det finns en stor skillnad mellan exponering för olika kemikalier, förutsatt att samma mängd släpps ut.

Kan dessa typer av empiriska samband användas för förenklad bedömning av människors exponering för kemikalier?
Innebär en hög produktionsvolym av en kemikalie en hög exponering?

Det är dessa två frågor som försökt besvarats i detta arbete, genom en omfattande litteratursökning där tillgänglig forskning och möjlig metoder att beräkna intake fraction har analyserats.

Elva vetenskapliga artiklar hittades och intake fraction för en rad kemikalier finns tillgängliga. Den mest omfattande studien omfattar över 300 kemikalier och beräknade intake fraction varierar från 10^{-10} till 10^{-3}.

De flesta beräkningarna av intake fraction har gjorts med hjälp av olika modeller, där den dominerande har varit dispersionsmodellen CALPUFF. Andra använda modeller är CalTOX, IMPACT 2002, (S-R) matrix och en Mackay type level III multimedia modell sammankopplad med en näringskedjeexponeringsmodell. Intake fractions baserade på uppmätta värden har beräknats för dioxiner, furaner och PCB:er. Uppmätta miljöhalter av andra föroreningar har även använts men då var det nödvändigt att använda en modell för att uppsatta utsläppet och för att beräkna människan upptag av substansen.

I studien som omfattade över 300 substanser antogs en uniform populationsdensitet. Flertalet av de andra studerade studierna visade att detta kan vara ett korrekt antagande för dioxiner men för andra substanser kan spatial varians ha betydelse. Resultatet från en studie visade på att användandet av medelvärden omfattande en hel kontinent för populationsdensitet och matproduktion gav korrekta beräkningar av median intake fraction, men att intake fraction kunde skilja från denna median med så mycket som tre tiopotenser, speciellt för kemikalier som tas upp genom mat. I jämförelse med en spatial och en icke-spatial modell sågs den spatiala modellen prediktera högre värden än den icke-spatiala och även närmare uppmätta värden. Detta indikerar att en spatial modell skulle behöva användas för att inte underestimera beräknad intake fraction.

Slutsatserna i denna studie är att de samband som hittills använts för att estimera intake fractions inte kan användas för förenklad exponeringsbedömning av flera olika kemikalier som de existerar idag. Eventuell fortsatt forskning är rekommenderad att till en början fokusera på att bestämma relevansen av populationsdensitet, av var mat produceras relaterat till utsläpps källa och brist och osäkerhet i tillgängliga data. Sambanden baseras på K_{ow}, K_{aw} och halveringstid. Halveringstid är en av de mest osäkra parametrarna som används i multimediamodeller och det kan ifrågasättas om samband baserade på denna parameter är användbara då de troligtvis är högst osäkra.

En hög produktionsvolym av en kemikalie resulterar inte automatiskt i en hög exponering av människan eftersom exponering beror av flera olika faktorer inklusive produktionsprocesser, transport, metabolism och användningsmönster. Om kemikalien däremot släpps ut i miljön kommer exponeringen att öka proportionellt mot ökad utsläpps volym, detta baserat på att

exponeringen av kemikalier som släppts ut i miljön kan antas vara linjär med koncentrationen, detta har setts vara en godtagbar approximering vid utvärdering av multimedia modeller.

Skillnaden mellan olika kemikalier skulle däremot kunna variera kraftigt då utsläpp av 1 000 ton av en kemikalie med en intake fraction $1 \cdot 10^{-9}$ skulle potentiellt resultera i samma upptag som utsläpp av 1 kg av en annan kemikalie med intake fraction $1 \cdot 10^{-3}$. För att avgöra om skillnaden mellan olika kemikaliers intake fraction faktiskt kan vara i denna storleksordning krävs ytterliggare forskning.

Intake fraction skulle potentiellt kunna användas för att identifiera låg volym kemikalier som skulle kunna resultera i en hög mänsklig exponering. Detta förutsatt att generaliserbara intake fractions finns tillgängliga för många olika kemikalier.

Det är också viktigt att inte glömma att kemikaliexponering av människan inte endast kan ske genom miljön utan också genom konsumentprodukter och i arbetsmiljön. Det är möjligt att beräkna intake fractions även för dessa scenarier men generaliserbarheten och användbarheten kräver ytterliggare efterforskning.

Användbarheten av begreppet för riskbedömningar kommer även att vara begränsad då intake fraction är främst lämplig för kemikalier vars hälsoeffekt uppvisar inga beroenden av frekvens och varaktighet av intagen dos, inga tröskelvärden mellan dos och effekt, och proportionalitet mot kumulativ exponering.

Preface

This master thesis is performed in collaboration between the department of Fire Safety Engineering at Lund Institute of Technology (www.brand.lth.se), the Philosophy unit at the Royal Institute of Technology (www.infra.kth.se/phil) through Christina Rudén and the department of Environmental Chemistry at Stockholm University (www.mk.su.se) through Ulrika Örn. It is a part of the research program NewS *(A New Strategy for Risk Assessment and Management of Chemicals* www.infra.kth.se/phil/news). NewS focuses on developing better test methods and test strategies for toxicological and ecotoxicological testing of chemicals and to improve and simplify the risk assessment and risk management processes.

To prepare for the thesis a course in scientific methodology and seeking of information was attended the 18-19 of March 2004. The course is a mandatory part of the thesis and is given by the department of Structural Mechanics at LTH (Lund Institute of Technology).

The thesis leads to a degree in Master of Science in risk management and safety engineering and consists of 20 Swedish credits. The work with the thesis started in the summer of 2004 and was completed in November 2004.

Several people have helped me during the work with this thesis and I would especially like to thank my supervisors Christina Rudén and Ulrika Örn for taking their time and giving me valuable advice during the whole process.

I would also like to thank Gunnar Bengtsson, Stellan Fischer, Thomas E. McKone, Manuele Margni, and Ian Cousins, who have helped me with information and ideas.

Christina Björkdahl
10th November 2004

Content

1 Introduction

Between 30 000 and 70 000 chemical substances are available on the commercial market in the European Union.[1] The substances are used for a variety of different applications, for example the glue holding together a child's toy, the print of this paper, washing detergents and various chemicals used in industrial processes. Thus people get exposed on a daily basis to a multitude of chemicals, in the air we breathe, the food we eat, the water we drink and surfaces that we are in contact with. The chemicals are not necessarily good for human health and therefore it is important to asses the risks of chemicals before people get exposed. To do this requires regulations, to prevent potential health hazards from getting onto the market, or to make sure that chemicals on the market are used in a way that they cannot have an unacceptable adverse effect on people.

The chemicals in EU are currently being regulated according to if they are "existing" substances, "new" substances and how they are classified and labelled.[1]

The "existing" substances are the substances that existed on the market prior to the establishment of the EINECS (the European Inventory of Existing Commercial Chemical Substances) database in 1981. EINECS contains 100 106 substances.[2] These chemicals are to be risk assessed according to priority lists, which are established by the EU commission. Factors that are considered when drawing up priority list are, among other things, the effects, and lack of data on effects, of the substance and the exposure of man and the environment to the substance. The basis for the priority lists lies on national priority lists and reported data, which is mandatory to submit if the yearly amount of manufactured or imported substance, per manufacturer or importer, exceeds 10 tonnes per year. If the amount produced or imported lies between 10 tonnes per year and 1000 tonnes per year the following information is required: the name, the quantity, the classification and reasonably foreseeable uses of the substance. Does the amount exceed 1000 tonnes per year, information about physico-chemical properties, pathways and environmental fate, ecotoxicity, acute and sub acute toxicity, carcinogenicity, mutagenicity and/or mutagenicity for reproduction and any other indication relevant to the risk evaluation must also be submitted if available. If the manufacturers or importers have made reasonable efforts to obtain this data but it is still lacking they are not obliged to carry out further tests on animals in order to submit it.[3]

The current risk assessment process for existing chemicals is slow and resource intensive and the system is neither efficient nor effective.[2]

Chemical substances that are not registered in EINECS are named "new" substances. These substances must be tested and notified before they are allowed on the European market. The data necessary for notification include information on the notifier/manufacturer, identity of the chemical, physical and chemical properties, toxicity, ecotoxicity, proposals for classification and labelling, and information on the substance as such e. g. production process and proposed uses. A draft to a risk assessment should also be submitted. The amount of data necessary to submit increases

[1] Hansson & Rudén (2004)
[2] Commission of the European communities (2001)
[3] Council Regulation (EEC) No 793/93 (1993)

according to substance quantity with the following thresholds: 10 kg, 100 kg and 1000 kg per year per manufacturer. If the amount exceeds 100 tonnes and 1000 tonnes more toxicological and ecotoxicological testing is required,[4] focusing more on long term and chronic effects.[2] The notification data are submitted to the national Competent authority (a national authority or authorities designated by each Member State to implement legislation[5]), which then evaluates the information.

Risk assessments for new substances are performed by the competent authority, which assigns one from four available conclusions:[4]

1. *The substance is of no immediate concern …*
2. *The substance is of concern …further information for revision of the assessment is required, but deferred until next tonnage threshold attainment.*
3. *The substance is of concern …further information is required immediately.*
4. *The substance is of concern …recommendations for risk reduction to be instigated immediately.*

The notifications are then sent to the European Chemicals Bureau. Since April 1992 more than 1 000 notifications have been submitted with a risk assessment report, 25 % of them had the conclusion that further information will be needed when the next tonnage trigger is reached.[4]

All general industrial chemical substances also have to be classified based on their available toxicological and ecotoxicological properties and labelled accordingly, regardless of the production volume[6]

Currently a new regulation of chemicals within the EU is being developed called REACH (Registration, Evaluation, Authorization and restriction of CHemicals). In REACH the concept of "existing" and "new" chemicals is abandoned and all chemicals are regulated in the same system. The regulatory requirements are based on, among other things, the annual production volume of the chemical. Similar to the old system high volume chemicals are prioritised, in the way that more data are required than for low volume chemicals. A difference in the new system is that the current 10 kg threshold, for "new" chemicals, is raised to 1 tonne and there are also differences in the amount of testing deemed necessary for different quantities.[7]

The prioritisation of high volume chemicals is based on the assumption that the higher production volume, the higher exposure and thus higher risk. This is a major simplification since exposure is dependent on several factors including the release of the chemical into the environment, its transportation, transformation and fate in various media and that contact with individuals actually occurs.[8] The risk is dependent, besides on the total exposure of a chemical, on for example the chemical and physical properties of the chemical, how the chemical is metabolised, and the susceptibility of exposed individuals.[9]

[4] European chemicals bureau (2004-08-04)
[5] Commission of the European communities (2001)
[6] Hansson & Rudén (2004)
[7] European chemicals bureau (2004-08-04)
[8] WHO (2000)
[9] Klaasens, C. D. (1996)

In the new system the responsibilities for risk assessment of substances is shifted from the Competent Authority to the producer or manufacturer of chemicals. The producer or manufacturer should also provide adequate information to downstream users, which in their turn are obliged to assess the safety of their products for the part of the life cycle that they contribute to, including disposal and waste management. The risk assessment shall include the whole life cycle of the substance, including disposal, with respect to particular uses.[10]

The principles of risk assessment for new substances in the EU are defined in a directive. The directive states that a risk assessment, for environment and health, shall include:

- Hazard identification, *the identification of the adverse effects that a substance has an inherent capacity to cause*,

and if appropriate:

- Dose (concentration) – response (effect) assessment, *the estimation of the relationship between dose, or level of exposure to a substance and severity of an effect*.

- Exposure assessment, *the determination of the emissions, pathways, and rates of movement of a substance and its transformation or degradation in order to estimate the concentrations/doses to which human populations or environmental compartments are or may be exposed*.

- Risk characterization, *the estimation of the incidence and severity of the adverse effects likely to occur in a human population or environmental compartment due to actual or predicted exposure to a substance, and may include 'risk estimation', i. e., the quantification of that likelihood*.[11]

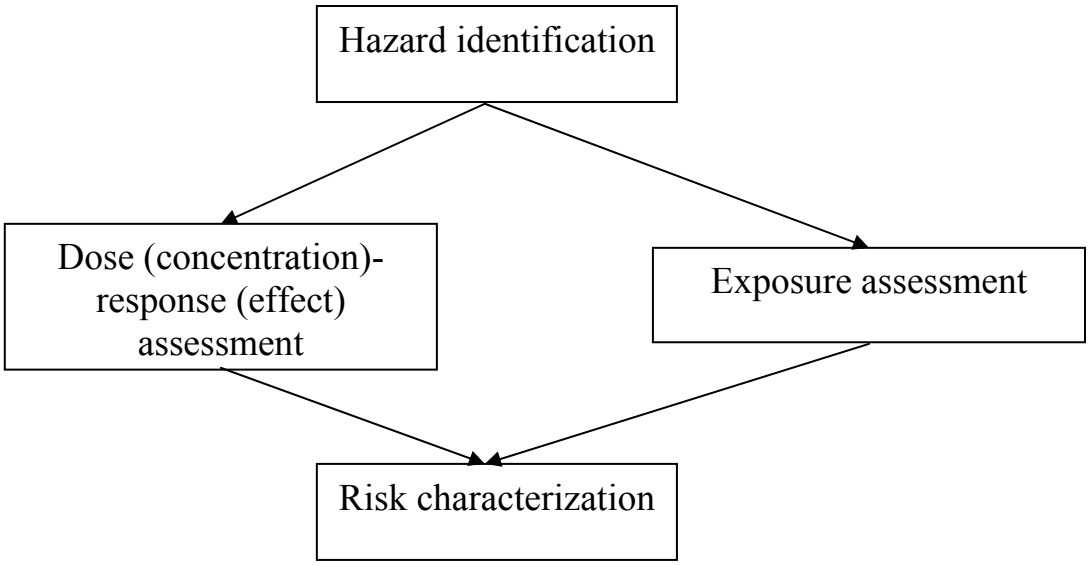

Figure 1: The four components of a risk assessment for environment and health.

[10] European chemicals bureau (2004-08-04)
[11] Commission Directive 93/67/EEC (1993)

Currently exposure assessments are performed by the Competent Authority. They use the European Union System for the Evaluation of Substances, EUSES, which is a modelling system for risk assessments when dealing with local and regional exposure. In the regional assessment several emission sources are weighed together. Only generate generic exposure scenarios are used and EUSES is mostly used to simplify comparisons. For local exposure scenarios the exposure calculation is often adapted to specific site conditions.[12]

Performing a risk assessment with EUSES requires that the following input data are available: the chemical and physical data of the substance, the use pattern during it's total life cycle, manufactured, exported and imported amounts of the substance on the EU-level, toxicity data on mammals and on organisms relevant from an ecotoxicological point of view, quantitative data on all major uses of the chemical, and its degradability. If more data is known for the substance this can also be added into the analysis, otherwise the model can, in many cases, estimate them by using e. g. QSAR[13] (Quantitative Structure Activity Relationship) which are models used to predict properties of chemicals based on their molecular structure.[14] EUSES is a highly complex model and the user needs a sufficient degree of expertise to be able to use it properly.[15]

With the introduction of REACH the responsibility of performing exposure assessments and risk assessments is shifted from the authorities to manufacturers and importers. Currently there are no guidelines for manufacturers and importers to perform a preliminary risk assessment and in many small and medium sized companies the proper expertise to use a complex tool like EUSES is lacking. This is expected to be a problem and therefore there exists a need to develop simplified assessments tools.[13]
A group of researchers have developed the concept of intake fraction and used it to derive empirical relationships that could potentially simplify exposure assessments of chemicals. Intake fraction is defined as *the fraction of chemical mass emitted into the environment that eventually passes into a member of the population through inhalation, ingestion or dermal exposure.*[16] Current research has showed that intake fraction can be estimated based on a few properties of the chemical studied.[17,18] Intake fractions for more than 300 substances have been calculated and together they span a range of seven orders of magnitude. [19] If these values are accurate it indicates that there is a big difference in human intake between different chemicals, when the same amount of chemicals is emitted.

This study aims to answer two questions:

Can the type of empirical relationships described above be used to simplify human exposure assessments?
Does high total production volume of a chemical imply high human exposure?

[12] Fischer, S. (2004-09-09) pers. comm.
[13] Fischer, S. (2004-09-09) pers. comm.
[14] Commission of the European communities (2001)
[15] Vermiere, et al. (1997)
[16] Bennett, et al. (2002a) p. 905
[17] Levy, et al. (2000)
[18] Hao, et al. (2003)
[19] Bennett, et al. (2002a)

The paper is divided into eight sections. The first two sections explain why intake fraction was studied and how it was done. In the third section the concept of intake fraction is presented, and in the fourth section the history and the background of the concept are outlined followed by current available research, methods to determine intake fraction, and a short summary of factors that have the potential to influence human exposure, followed by a final discussion and conclusions.

2 Method

To see if the concept of intake fraction can be useful for simplified exposure assessments the underlying assumptions and models to determine intake fraction were studied. A thorough literature search of the available studies made in this area was performed by using the databases Cambridge Scientific Abstracts, SciFinder Scholar, Google, an Internet based search engine, and Elin@Lund, Electronic Library Information Navigator available at the Lund University Libraries. The articles that were found in this manner were also used to find further material by using the stated references. The search for relevant literature and potential angles for approaching the problem also included personal communications with exposure assessment experts, Stellan Fischer at the Swedish National Chemicals Inspectorate, and Gunnar Bengtsson former director general of the Swedish National Chemicals Inspectorate.

Eleven scientific articles directly associated with intake fraction were found. The gathered material was analysed, the articles with focus on chemicals studied, method to derive intake fraction (through modelled or measured exposure and emission), the study scenario, the aim of the study, relevant results, and range of calculated intake fractions. This, combined with information on methods to determine amount emission and human exposure, provided the base upon which the concept of intake fraction, and the method to determine it was scrutinised and evaluated from a regulatory point of view, with the focus on the two questions posed in the beginning. These results also provided the base for which suggestions to improve future uses of the concept were derived.

The intention was also to perform an empirical study in the area, which included identification and gathering of an appropriate dataset and analysis of the data. Since empirical relationships already have been determined for intake fraction based on modelled estimates the intention was to find a data set based on measurements to investigate if it was possible to find similar relationships without using models that already contain certain simplifications and assumptions that can influence the result. As the work progressed however this step was omitted. This was mostly due to difficulties in finding an appropriate data set that did not contain a high degree of uncertainty. After the available articles on intake fraction were scrutinised it also raised a lot of questions and it was considered that more information would be gained if trying to find answers to these questions by studying the models used and parameters that have the potential to affect human exposure instead of performing the empirical study.

The empirical study could have showed if it is feasible to calculate intake fractions based on a few properties, but if the dataset contained a high degree of uncertainty it would be quite probable that the wrong conclusion could have been drawn from the study.

3 The concept of Intake fraction

Bennett and co-workers defined the concept of intake fraction (*iF*), which relates the amount of pollutant emitted by a source to the human intake. Intake fraction can be described through the equation given below and it is *the integrated incremental intake of a pollutant released from a source or source category (such as mobile sources, power plants, or refineries) summed over all exposed individuals during a given exposure time, per unit of emitted pollutant*.[20]

$$iF = \frac{\sum_{people,time} \text{mass intake of pollutant by an individual}}{\text{mass released into the environment}}$$

The equation assumes a linear relationship between emissions and population intake and leads to a dimensionless estimate of the intake fraction.

If the relationship between emission and population intake is not linear an incremental intake fraction could be defined as the first derivative of the relationship between emission and population intake.[21]

Intake fraction ranges from zero, indicating that nothing of the pollutant is taken up, to one, indicating that all of the pollutant is taken up. An intake fraction of 10^{-6} can be interpreted as for every kg of pollutant released into the environment 1 mg of the pollution will be taken up by the exposed population.[22]

Three different intake routes are included in the concept: intake through ingestion or inhalation, and dermal uptake. Intake by the routes is defined as the amount of pollutant that enters an individual after crossing a specific contact boundary; the nose or mouth (for oral breathing) for the inhalation route, mouth for the ingestion route and skin for the dermal route.[21] The different routes are related to the total intake fraction according to the following relationship for all exposure pathways.[23] (A pathway can for example be eating contaminated food, breathing contaminated workplace air or touching residential surfaces.[24])

$$iF(total) = iF(inhalation) + iF(ingestion) + iF(dermal)$$

This summation is relevant for health effects under the assumption that the intake response functions are the same for each route.[23] This means that the health effect must be independent of how it is taken in. This is not always the case. For example a chemical that is detoxified in the liver would be expected to be less toxic if received through ingestion than inhalation.[25] This makes it necessary to sometimes disaggregate intake fraction. Bennett and co-workers suggests the following notation: iF(route, media, subpopulation), where route refers to ingestion, inhalation, dermal uptake or

[20] Bennett, et al. (2002b) p. 208A
[21] Bennett, et al. (2002b)
[22] Marshall, et al. (2003)
[23] Bennett, et al. (2002a)
[24] WHO (2000)
[25] Klaasens, C. D. (1996)

total, media refers to release to air, water and soil, and subpopulation refers to exposed group e. g. workers, residents or all exposed.

It is also possible to derive intake fractions for individual exposure of humans. The total intake fraction can then be calculated as the sum of all of the individual intake fractions (iF_i) for an exposed population.[26]

Intake fractions for chemicals can be calculated through either models or by measured data. The obtained values are not chemical specific but will vary as a function dependent on several factors for example population patterns, meteorological conditions, background pollutant concentration and source characteristics.[27]

[26] Bennett, et al. (2002b)
[27] Levy, et al. (2002)

4 History of Intake fraction

The concept of intake fraction has only been in use since the beginning of the 21:th century, but similar concepts, linking the source of emission to human intake, have existed for more than twenty years.

The first application to use a similar emission-to-intake relationship was the introduction of *committed dose,* which describes the fraction of released radioactive elements entering a defined population.[28] This concept was later developed and applied for other fields.[29]

Since then a lot of different terms have been used, e. g. exposure efficiency, exposure factor, exposure effectiveness, inhalation transfer factor, exposure constant, potential intake, population-based potential dose and fate factor.[28] The concepts vary in meaning but all have in common the emission-to-intake relationship. For example exposure efficiency, as described by Evans and others, deals only with the pathways of inhalation and ingestion and is mainly used for air pollution. The same authors have compiled previously published estimates of exposure efficiency. Most of the published estimates have been derived using Gaussian air pollution models, when focusing on local exposure (within 20-100 km of the source), or compartmental models, when focusing on exposure very close to the source (e.g. indoor) and very far from the source (e.g. regional and global).[29]

To unify the multitude of concepts and to simplify the comparison of results from different research groups the concept of intake fraction was developed by the IFWG (Intake Fraction Working Group). The group consists of D. H. Bennett, T. E. McKone, J. S. Evans, W. W. Nazaroff, M. D. Margni, O. Jolliet, K. R. Smith, J. I. Levy, D. Hattis, E. G. Hertwich, D. W. Pennington and W. J. Riley.[28] Most of the published articles, dealing with the concept of intake fraction, available when this papers was finalised are written by, or in collaboration with, one or more of the members of the Intake Fraction Working Group.

[28] Bennett, et al. (2002b)
[29] Evans, et al. (2002)

5 Previously published estimates of Intake fraction

Bennett et al. (2002a)
Bennett and co-workers used CalTOX, a level III multimedia model, to calculate intake fractions for 308 organic chemicals released to air, water and soil. They chose the United States as a scenario and defined it as an open environmental system with landscape and climate parameters reflecting averages in the US, except for the atmospheric mixing height, which was assumed to be fixed at 700 m. They also used population-based lifetime average exposure parameters to determine for example breathing rates, diets and activity patterns. For consumption they assumed that it was equal to the agricultural production and that the food concentration was uniform. For fish rates they used the U.S. inland fish production.

A continuous release was simulated for 100 years, with exposure occurring during the last 70 years of the release. The initial 30 years brought the model to steady-state conditions for all of the chemicals. The same release amount was used for all of the chemicals, to enable comparison between different chemicals.[30] The authors did not take into consideration the eventual fate of pollutants that travel out of the system, the relationship between releases and food production regions or movement of food between regions, neither do they account for variation in pollutant concentration or population density.

The studied chemicals were classified according to dominant exposure route for the compound (more than 90 % of the total intake is through one specific route) or as multi-pathway. Then with the help of K_{aw} (air-water partitioning coefficient) and K_{ow} (octanol-water partitioning coefficient) relationships could be given to classify a pollutant as inhalation dominant, ingestion dominant or as multi-pathway. Relationships were given for release to water and to air. No pollutant had the dermal route as the dominant route.

The calculated intake fractions ranged from $8.6 \cdot 10^{-9}$ to $9.1 \cdot 10^{-4}$ for air and $1.9 \cdot 10^{-10}$ to $1.1 \cdot 10^{-3}$ for water.

A relationship for emissions to air was found for the inhalation dominant pollutants ($K_{aw} > 1 \cdot 10^{-4}$, $K_{ow}/K_{aw} < 1 \cdot 10^{6}$) relating individual intake fraction (iF_i) to the reaction half-life for the chemical in the release medium according to the following equations:

Chemicals with a reaction half-life under 35 days
$\log [iF_i(total,air)] = 0.87 \cdot \log(\text{reaction half-life in air [days]}) - 14.4,$

Chemicals with a reaction half-life over 35 days
$\log [iF_i(total,air)] = -13$

The derived relationships showed a good correlation to the inhalation dominant compounds (standard error of 0.09). For the multi-pathway compounds ($1 \cdot 10^{6} < K_{ow}/K_{aw} < 2 \cdot 10^{8}$ and $K_{ow} > 1 \cdot 10^{2}$; or $1 \cdot 10^{-4} < K_{aw} < 2 \cdot 10^{-6}$ and $K_{ow} < 1 \cdot 10^{2}$) the correlation was worse (standard error of 0.40). When the multi-pathway compounds were plotted into

[30] McKone, T. E. (2004-09-04) pers. comm.

the same diagram as the inhalation dominant they tended to lie slightly above the inhalation dominant ones. No relationship could be determined for the ingestion dominant ones ($K_{aw}<2\cdot10^{-6}$, $K_{ow}/K_{aw}>2\cdot10^{8}$)

Relationships for emission to water were found for ingestion dominant compounds, which were separated into two different groups, ingestion dominant through fish consumption and ingestion dominant through tap water ingestion, depending on K_{ow} and K_{aw} values. The following correlation functions were proposed:

For tap water ingestion
log [iF_i(total,water)] = 0.98·log(reaction half-life in water [days]) -15,
standard error 0.05

For fish consumption
log [iF_i(total,water)] = 0.56·log((reaction half-life in water [days]) ·K_{ow}) -17.5,
standard error 0.63

There were no inhalation dominant chemicals for the water release scenario and no correlation with chemical properties was found for the multi-pathway pollutants.

The authors calculated similar estimates of intake fraction for release to soil but they did not include them in the article since many of the trends were similar to those for the release to air because of the used models rapid exchange between thin soil layers and the air.

To see if the calculated estimates of intake fraction were reasonable a case study was carried out for dioxin-like compounds. Measured concentrations of dioxin toxic equivalents (TEQ) in air, vegetable fat, meat, dairy, milk, eggs, poultry, pork, fish and soil were used to estimate the human intake (63 picogram TEQ per day.) This combined with the amount of emissions released (~3.3 kg) were then used to estimate an intake fraction, which was compared to the intake fraction derived from the model. The estimated value (iF $2\cdot10^{-3}$) was approximately higher by a factor of three than the value calculated with CalTOX (iF $6\cdot10^{-4}$). [31] It should be noted however that the measured TEQ value was compared to the value calculated by CalTOX for the dioxin 2,3,7,8 TCDD, which is only one out of the 17 different PCDD/F compounds that contributes to the TEQ (Toxic EQuivalents) value.[32]

A model evaluation was also performed where a theoretical maximum of intake fraction was compared with the model estimations. It was found that the calculated upper bound of 0,001 for chemicals that were released to air and that partition into soil where in fact exceeded for some of the chemicals. This resulted in a re-examination of the model and revealed that it was probably due to a lack of fit between high K_{ow} values and biotransfer factors to meat and milk. This was corrected for and the intake fractions were recalculated. The model uncertainties were also scrutinised, and the modelling of transfer into the food pathway was found to contain a high uncertainty that needed further research. Another uncertainty was due to the lack of reliable chemical property values for a many of the chemicals and the calculated values were expected to be accurate only within one order of magnitude.[31]

[31] Bennett, et al. (2002a)
[32] Margni, et al. (2004)

Levy et al. (2002)

Levy and co-workers have developed log-linear regression relationships to predict intake fractions for primary fine particles ($PM_{2.5}$), secondary sulphate and nitrate particles from power plants and mobile sources in the United States. The regression relationships are based on calculations presented in a doctoral thesis by Wolff where he uses CALPUFF to model dispersion of $PM_{2.5}$, secondary sulphate particles and secondary nitrate particles from 40 coal-fired power plants and 40 interstate highway stretches across the United States. The derived intake fractions from this study was, for primary $PM_{2.5}$, $2.2 \cdot 10^{-6}$ for coal-fired power plants, $9.1 \cdot 10^{-6}$ for mobile sources. For secondary sulphate the intake fraction was $2.2 \cdot 10^{-7}$ for power plants and $1.8 \cdot 10^{-7}$ for mobile sources. For secondary nitrate the intake fraction was $3.5 \cdot 10^{-8}$ for power plants and $3.1 \cdot 10^{-8}$ for mobile sources.

This study suggests that it is possible to predict intake fractions with a limited knowledge about local conditions and source characteristics. Six different regression relationships were given (three pollutants and emission by power plants or mobile sources). The parameters for which correlations were found are summarised in Table 1

Table 1: Regression equation parameters for determining intake fractions as derived by Levy et al. (2000)

$PM_{2.5}$				Goodness of fit R^2	Residual error
Power plants	pop. within 500 km.	mixing height	Inverse stack height	0.86	0.30
Mobile sources	pop. within 500 km	temp.	relative humidity	0.75	0.36
Secondary sulphate					
Power plants	pop. within 1000 km	relative humidity		0.53	0.22
Mobile sources	pop. within 1000 km	wind speed		0.61	0.32
Secondary nitrate					
Power plants	relative humidity	ln(sulphate *iF*)	wind speed	0.67	0.26
Mobile sources	temp	ln(sulphate *iF*)	relative humidity	0.60	0.32

Background concentrations of ozone and ammonia were not included in the study since the background material by Wolff used constant background pollutant values. The authors concluded that more nuanced measures of intake fraction are needed to be able to construct generalisable equations. Limitations lay in the relative coarse grid spacing that Wolf used, lack of background data, the fact that nitrate output was divided by four in all settings to reflect the predominant particle formation in winter seasons, and possible inherent uncertainties in the model CALPUFF. They also conclude that it is possible that some of the derived parameters to predict intake fraction can be proxies for other characteristics and therefore cannot be generalised to other settings where other relationships exist. They identify that future analysis is needed with focus on similar approaches to derive relationships for intake fraction but with other data sets and in other settings to see if the relationships still persist. If so intake fraction have the

potential to greatly enhance the ability to incorporate risk into life cycle impact assessment or conduct screening level analyses for large-scale risk assessments.[33]

Nishioka et al. (2002)
The derived equations from the study by Levy, et al. (2000) were used in a study by Nishioka and co-workers. In the study an approach for integrating risk assessment and life cycle impact assessment is demonstrated. They show how a policy shift to a more strict control concerning insulation in American homes could save energy and thus decrease pollutant emission, which would save lives.[34]

Brauer et al. (2002)
Brauer and co-workers have looked at the policy uses of particulate exposure estimates and have proposed a set of normative factors to guide the selection and application of various approaches for exposure assessment. They express the view that exposure analysts must work diligently to produce knowledge about the determinants of exposure that can be generalised instead of approaching the problem one source or one receptor at a time. They identify exposure efficiency (will here be referred to as intake fraction) as a deceptively simple exposure measure that can be used in the effort to advance exposure-based regulation. The determinants for intake fraction concerning air pollution are identified, by the authors, to include:

- Meteorological factors which influence the dispersive capacity of the atmosphere (e.g. wind speed, mixing height, direction, atmospheric turbulence)
- The attributes of the pollutant which influence the atmospheric residence time of the pollutant (and, for reactive compounds, the levels of other pollutants in the atmosphere)
- Characteristics of the exposed populations such as population density, proximity to the source and time activity patterns

They also identify that to what extent, and in what way, the following five factors that influence intake fraction need to be further determined before a wider application can be possible:

1. The approaches used to model intake fraction
2. The scale of the analysis
3. The properties of the source
4. The population density in the region
5. The characteristics of the pollutants, such as size and chemistry , which influence residence time

In addition they also emphasise that more attention is needed to both uncertainty and variability. They also feel a need for more sophisticated variants to be developed which can handle non-linearities in dose-response, deal with shorter averaging times, and handle a variety of approaches for aggregating social utility.[35]

[33] Levy, et al. (2002)
[34] Nishioka, et al. (2002)
[35] Brauer, et al. (2002)

Zhou et al. (2003)
Zhou and co-workers calculated intake fractions for particulate matter ($1.5 \cdot 10^{-5}$ $PM_{2.5,}$) sulphur dioxide ($8.4 \cdot 10^{-5}$), sulphate ($6.0 \cdot 10^{-6}$), and nitrate ($6.5 \cdot 10^{-6}$) for a power plant in Beijing using the long range dispersion model CALPUFF. They tested the sensitivity of the results to key assumptions within the model and came to the conclusion that the size distribution of primary particles was important, that the background ammonia concentration was an important factor influencing the intake fraction for nitrate and that the background ozone concentration had a moderate impact on the intake fraction of sulphate and nitrate.[36]

Marshall et al. (2003)
Marshall and co-workers used California's South Coast Air Basin in the U.S. as a case study for estimating intake fractions for carbon monoxide and benzene emitted from motor vehicles during 1996-1999. They used measured ambient concentrations to calculate concentrations in different microenvironments. The time spent in the different microenvironments was then estimated from an activity pattern survey and combined with the concentration data to give an estimation of the exposure. To determine emissions released from motor vehicles the model EMFAC was used, which combines emission factors and a motor vehicle emission inventory to calculate evaporative and exhaust emissions from on road mobile sources. The results for carbon monoxide and benzene were similar and consistent with previous studies, and a conclusion of the study was that intake fraction summarizes the emission-to-intake relationship in a concise and easy to understand manner.[37]

Levy et al. (2003)
Levy and co-workers used intake fraction to provide insight about population exposures and model performances. They used the regional scale dispersion model CALPUFF to model the emission of fine particulate matter ($PM_{2.5}$), secondary formed ammonium sulphate and ammonium nitrate particles from seven power plants in Georgia. The results of the model were compared to the results of a frequently applied source receptor (S-R) matrix. The matrix contains county-to-county transfer factors across the United States based upon an adjusted version of the Climatological Regional Dispersion Model, which uses simple climatological summaries based on 1990 meteorological data. The study showed that the two models gave similar intake fractions when calculating emission-weighted averages, with greater difference for ammonium nitrate (CALPUFF: $6.4 \cdot 10^{-8}$, (S-R) matrix $2.5 \cdot 10^{-8}$) than for ammonium sulphate (CALPUFF: $1.6 \cdot 10^{-7}$, (S-R) matrix $1.7 \cdot 10^{-7}$) or primary $PM_{2.5}$ (CALPUFF: $6.2 \cdot 10^{-7}$, (S-R) matrix $5.3 \cdot 10^{-7}$). The CALPUFF version that was used assumed a constant ammonium background concentration, however in the (S-R) matrix model the concentration could be assumed to be unlimited which resulted in an intake fraction of $4.1 \cdot 10^{-8}$ instead of $2.5 \cdot 10^{-8}$ for ammonium nitrate.[38]

Hao et al. (2003)
Hao and co-workers used a, previously not tried, approach to estimate the total exposure and resulting health damage from sulphur dioxide emissions applied to the Hunan province in China. The approach included using the concept of intake fraction, CALPUFF and multiple regression technique. 180 sample sources were used combined

[36] Zhou, et al. (2003)
[37] Marshall, et al. (2003)
[38] Levy, et al. (2003)

with CALPUFF and the calculated intake fractions, ranging from $1.17 \cdot 10^{-6}$ to $3.16 \cdot 10^{-6}$, were used for a multiple non-linear regression analysis. The analysis showed that population density was a key parameter for determining intake fraction and that the characteristics of emission source, i.e. stack height, exit gas velocity and exit gas temperature, had insignificant impact. Predicted values from the derived regression equation ($\ln(iF) = -14.46+4.46 \cdot 10^{-8}P_1 + 4.88 \cdot 10^{-9}P_2$, were P_1 and P_2 is population in local and remote subregions respectively) were compared with values calculated from the CALPUFF model and showed a good correlation, ($r = 0.85$). The equation was used together with population distributions to calculate intake fractions on county level for the Hunan province. The results were then used to calculate total health damage costs by using two different approaches, willingness to pay (WTP) and loss of human capital.

To be able to estimate health impact from intake fraction requires that there are no strong dependencies of the health effect on intake dosage rate and that the health effects are proportional to cumulative exposure.[39]

Margni, et al. (2004)
Margni and co-workers used intake fractions for dioxin in Western Europe to evaluate a chemical fate and multi-pathway model IMPACT 2002. The model was evaluated with and without spatial resolution. For the spatial resolution a distinction is made between the release location of the pollutant and where the pollutant passes into food, drinking water, or directly into populations through inhalation. Measurement values for PCDD/F (polychlorodibenzo-p-dioxins/-furans) emissions were obtained from the European Commission DG Environment survey and intake fractions were calculated based on the annual estimated emission with 1994 as base year. They used three differently derived intake fractions, iF(estimated) which was extrapolated from risk assessment studies in several European countries, iF(monitored) which was based on median values of monitored concentrations combined with food production statistics and iF(predicted) predicted values from the model. The results were iF(estimated) $3.5 \cdot 10^{-3}$, iF(monitored) $\sim 1.4 \cdot 10^{-2}$, iF(predicted) spatial $1.1 \cdot 10^{-2}$ and a-spatial $3.9 \cdot 10^{-3}$. The spatial model was better than the a-spatial one in accounting for where a product is grown compared to the source of emission, but the extent of this influence on the results for intake fraction were limited.[40]

Hirai, et al. (2004)
Hirai and co-workers calculated intake fractions for 17 PCDD:s/DF:s and 12 CoPCB:s by using a Mackay type level III multimedia fate model and a food-chain exposure model in succession. The model had three geographical subdivisions: local, national (Japan), and global (Northern Hemisphere, excluding Japan). The two integrated models were evaluated by comparing the calculated values to intake fractions derived from measured values. The estimation of exposure was 7.5 kg TEQ/year to air in Japan in 1997 and the congener profile of air deposition, based on measurements in 1998, was used to derive the amount of each congener (chemicals are referred to as congeners when they are chemically related compounds that are formed during the same process[41]). A human intake of 116 picogram TEQ per day and per person was estimated from total diet studies and the measured concentrations in air and soil. The measured based intake fraction ranged from $2.8 \cdot 10^{-5}$ to $2.6 \cdot 10^{-2}$ and the model derived intake

[39] Hao, et al. (2003)
[40] Margni, et al. (2004)
[41] Hemond, et al. (2000)

fraction ranged from $3.7 \cdot 10^{-7}$ to $7.7 \cdot 10^{-5}$ (local), $1.3 \cdot 10^{-5}$ to $3.2 \cdot 10^{-3}$ (Japan), $2.2 \cdot 10^{-6}$ to $1.3 \cdot 10^{-3}$ (global) for air emissions.[42]

Lobsheid, et al. (2004)
Lobsheid and co-workers used the San Francisco Bay Area in the U.S. as a case study to evaluate the atmospheric source-to-dietary intake links for semi volatile organic chemicals (SVOC) with particular emphasis on locally grown and consumed foods. The chemicals studied were benzo[a]pyrene (BaP), 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) and fluoranthene. They used a combination of empirically derived values from outdoor and indoor concentrations and food residue data and calculations made by the model CalTOX to compare ingestion/inhalation ratios related to two levels of scale, the environmental reach of a SVOC and food distribution. For the scenario studied these two scales were on the same order of magnitude for the two PAHs, BaP and fluoranthene. For dioxin the local and regional pollution could not be differentiated, which implies that food exposure from dioxin can be adequately assessed by combining nationally averaged residue levels and intake data. The results indicated that the extent to which SVOC:s released to air can contaminate local foods depends on the chemical-specific properties of the SVOC. The concept of intake fraction was used in the study to evaluate the relative contribution of various exposure pathways for BaP and flouranthene. The results indicate that foods, especially fruits, vegetables and grains, are most likely the largest contributor to total intake of airborne emitted SVOC:s when compared to all other terrestrial routes of exposure. The derived intake fractions for ingestion were $1 \cdot 10^{-5}$ for BaP and $2 \cdot 10^{-7}$ for flouranthene emitted to air.[43]

The previously mentioned articles, except the one by Brauer and co-workers, which was a review of particulate exposure uses for science and policy, are summarised, to simplify comparison, in a table in appendix 2.

5.1 Summary and discussion of the article study

Most estimates of intake fractions have been derived using different kind of models, see appendix 2, where the dominating one has been the dispersion model CALPUFF. Other models used are CalTOX, IMPACT 2002, (S-R) matrix and a Mackay type level III multimedia fate model with a food-chain exposure model in succession. When measured ambient levels of chemicals were used, it was still necessary to use a model to calculate the amount of emission and to calculate how much the intake actually was from the ambient concentrations.[44]

In three articles, equations to determine intake fractions based on a few properties have been derived by using either CalTOX[45] or CALPUFF[46,47]. Important properties in determining intake fractions have been found to be, when using CalTOX, reaction half-life, K_{aw}, and K_{ow}. The CalTOX study was the only study where a multitude of different chemicals were studied. In one of the CALPUFF studies the pollutants $PM_{2.5}$, secondary sulphate and secondary nitrate were studied[48]. The other one looked at secondary

[42] Hirai, et al. (2004)
[43] Lobsheid, et al. (2004)
[44] Marshall, et al. (2003)
[45] Bennett, et al. (2002a)
[46] Levy, et al. (2002)
[47] Hao, et al. (2003)
[48] Levy, et al. (2002)

sulphate.[49] In the first study total population, mixing height, inverse stack height, relative humidity, temperature, the intake fraction of sulphate and wind speed were derived to be more or less significant depending on source emission, mobile sources or power plants, and studied pollution. Background emissions were not considered in this study and two other studies showed that the background ammonia concentration could have an impact on the results.[50-51]

In the other study, in which only power plants were studied, for secondary sulphate the only significant parameter was found to be population density. For the same chemical and source the first study found a correlation with total population living within 1000 km and also relative humidity. Both of the studies give quite similar results which implies that intake fraction could maybe be used for deriving generalisable equations, although the parameter of relative humidity suggest that certain characteristics of the location may have to be taken into consideration as for example meteorological conditions. Of course the similar relationship could also be due to the fact that the same model was used for both cases.

Measured exposure values used in the articles are expressed in TEQ, see appendix 1. The TEQ values for dioxins have been used to compare models applied to the U.S.[52], Western Europe[53] and Japan[54]. In the U.S. study the calculated intake fraction was directly calculated from TEQ, while in the European study the value was recalculated to take five selected congeners into considerations. In the Japanese study the value was recalculated to take all 17 different congeners, which contribute to TEQ, into consideration. This difference in calculation method makes it harder to compare the derived intake fractions. In the U.S. study an intake fraction of $2 \cdot 10^{-3}$ was derived, Japan derived intake fractions ranged from $2.8 \cdot 10^{-5}$ to $2.6 \cdot 10^{-2}$ and for Western Europe the intake fraction was approximately $1.4 \cdot 10^{-2}$. The different intake fractions are compared to the U.S. study in Table 2.

When instead comparing the individual intake fraction calculated from the amount of pollutant released and the estimated intake per day and person the difference is smaller which also can be seen in Table 2. The European study includes an interval where the endpoints of the interval are derived from measured minimum and maximum values which gives a certain hint about the range of the values.

Table 2: Comparison of individual and total intake fraction for the U.S., European and Japanese study.

	kg released per year	intake per day per pers.	iF_i (intake per ind. ·365 /TEQ emission)	Percent of iF_i compared with the U.S.	Percent of iF compared with the U.S.
U.S.	3.3	63 pg	$7.0 \cdot 10^{-12}$	100	100
Japan	7.5	116 pg	$5.6 \cdot 10^{-12}$	81	1.4-1300
Europe	3.7-6.5	65.1-210 pg	$6.4 \cdot 10^{-12}$-$1.2 \cdot 10^{-11}$	92-170	700

[49] Hao, et al. (2003)
[50] Levy, et al. (2003)
[51] Zhou, et al. (2003)
[52] Bennett, et al. (2002a)
[53] Margni, et al. (2004)
[54] Hirai, et al. (2004)

The intake fractions compared to the U.S. study also included in the table demonstrates that different approaches can give very different estimates of intake fraction although the initial measured TEQ values showed similar relationships. The European study also looked at spatial and a-spatial differences. The spatial model accounted for emission location, chemical distributions patterns and the relative locations of the agricultural production. However these had a limited impact on the intake fraction. This is more or less consistent with the result from the study by Lobscheid and co-workers that concluded that local and regional dioxin pollution could not be differentiated, which implied that food exposure from dioxin can be adequately assessed by combining nationally averaged residue levels and intake data.[55]

To see if bioaccumulation and persistency are associated with a high intake fraction, the intake fractions from the study by Bennett, et al. (2002a) of the known persistent and bioaccumulating chemicals, Aldrin, DDE, Chlordane, Endrin, and 2,3,7,8-TCDD were compared to those of Acetone, Methanol, Formic acid, Hydrocyanic acid, and Methyl acetate, which are not considered to be persistent and bioaccumulating.[56]

Table 3: Comparison of iF:s between different chemicals from Bennett, et al. (2002a)

Chemical Persistent, bioaccumulating	Tot. iF emission to air	Tot. iF emission to water	Chemical Non persistent, non bioaccumulating	iF emission to air	iF emission to water
Aldrin	$4.4 \cdot 10^{-5}$	$1.1 \cdot 10^{-3}$	Acetone	$1.8 \cdot 10^{-5}$	$5.5 \cdot 10^{-6}$
DDE	$4.1 \cdot 10^{-4}$	$5.3 \cdot 10^{-5}$	Methanol	$6.2 \cdot 10^{-6}$	$1.2 \cdot 10^{-6}$
Chlordane	$7.5 \cdot 10^{-5}$	$3.1 \cdot 10^{-4}$	Formic acid	$6.0 \cdot 10^{-6}$	$4.7 \cdot 10^{-7}$
Endrin	$1.6 \cdot 10^{-5}$	$7.1 \cdot 10^{-5}$	Hydrocyanic acid	$2.5 \cdot 10^{-5}$	$3.3 \cdot 10^{-5}$
2,3,7,8-TCDD	$6.0 \cdot 10^{-4}$	$1.3 \cdot 10^{-5}$	Methyl acetate	$2.8 \cdot 10^{-6}$	$1.7 \cdot 10^{-6}$

The known bioaccumulating and persistent chemicals intake fractions ranged from $1.3 \cdot 10^{-5}$ to $1.1 \cdot 10^{-3}$ and the non-bioaccumulating and non-persistent chemicals intake fractions range from $4.7 \cdot 10^{-7}$ to $3.3 \cdot 10^{-5}$, see Table 3. The biggest differences in intake fractions are seen for chemicals released to water, and the persistent and bioaccumulating chemicals seem to have a slightly higher intake fraction than the other chemicals, which would be expected. The whole intake fraction interval calculated by Bennett, et al. (2002a) ranged from $8.6 \cdot 10^{-9}$ (1-Naphtyl-n-methylcarbamate) to $9.1 \cdot 10^{-4}$ (Heptachlorodibenzofuran) for air and $1.9 \cdot 10^{-10}$ (Maleic anhydride) to $1.1 \cdot 10^{-3}$ (Aldrin) for water.

The discussion given above and the article by Brauer et al (2002) formed the base for determining further research needs. These are summarised in the following questions:

- What is required to use measured exposure for estimating and/or deriving relationships for intake fraction?
- Is it possible to find this type of data or does it always require some kind of modelling?
- Are there any limitations concerning chemicals for which intake fraction can be estimated and/or useful?

[55] Lobscheid, et al. (2004)
[56] Örn, U. (2004-10-22) pers. comm.

- When can a linear emission-to-intake relationship be assumed?

Questions relating specifically to models used to determine intake fraction:

- Which type of model is it?
- What is the objective of the model? / For which purpose was it developed?
- What is the endpoint of the model relevant for this study?
- How has the model been validated?

These questions are relevant to see if the model represents a sufficient simplification of reality and if modelled exposure estimates can be appropriate to use when relating intake fraction to a few parameters.

- Which input parameters are needed to use the model?

This question is relevant to examine how much effort is needed to use the model and also to see potential benefits with using only a few parameters to determine intake fraction.

- Are there any known limitations?
- Is the model appropriate for point or non point sources?
- How does the model handle spatial- and time variation?

Limits in the model will also be limiting the intake fractions calculated with the model.

- How is population density modelled?

Two studies[57,58] have found relationships were population density have been an important parameter. How this parameter is assumed can have an important impact on modelled intake fractions.

- Which parameters are known to contribute to uncertainty in the exposure estimate?
- Is the result especially sensitive to certain input parameters?

These questions are relevant for identifying parameters that have the potential to be important when attempting to determine an intake fraction based on a few properties.

In order to find answers to these questions the methods and models to determine intake fraction needed to be studied which is done in the following section, with the focus on the models used in the articles, with the exception of the (S-R) matrix which contains source receptor factors specific for the U.S. The model for risk assessments in Europe, EUSES was also included in the study since it is a model that is widely used by the authorities in the European Union.

[57] Levy, et al. (2000)
[58] Hao, et al. (2003)

6 Methods to determine Intake fraction

The intake fraction is the ratio of intake to emission. To determine an intake fraction requires that the total amount of emission and the human intake is known. In the figure below the main factors influencing intake fraction is illustrated. Human exposure can be determined either through modelling or by measurements.

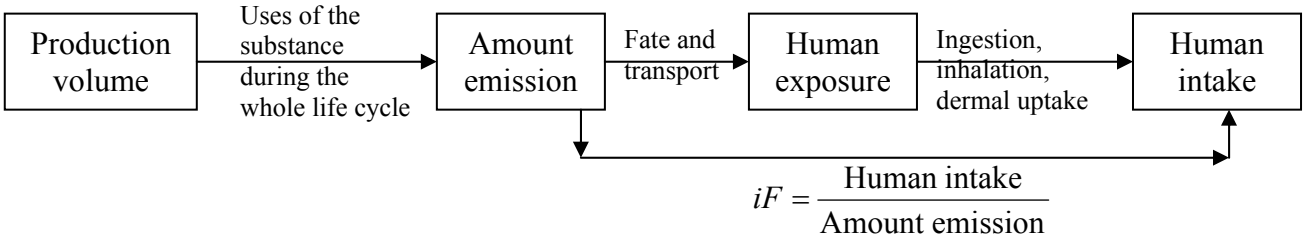

Figure 2: Intake fraction in relation to production volume, amount emission, human exposure and intake.

6.1 Amount emission

To determine the amount of emission of a chemical is a part of the exposure assessment. It is the aim of ESDs, *Emission Scenario Documents*, which are widely used for this purpose. [59] The documents describe the sources, production processes, pathways, and use patterns for chemicals and they are intended to provide information necessary to make estimates of emission into the compartment of the environment where release initially occurs.[60]

Amount of emission is also one of the outputs of the inventory part of a life cycle assessment. A life cycle assessment is a systematic approach to link a products impact on the environment during the whole life cycle of the product, from design to deposition. A life cycle assessment consists of three complementary parts: *inventory*, quantification of the energy and raw material requirements and environmental discharges, *impact*, characterisation of the effects on the environment and human health based on the inventory step and *improvement*, evaluation of the needs and opportunities to reduce the impacts on the environment and human health.[61]

6.2 Estimates from measured exposure

Measured values of direct exposure are the only way to really establish if, and to what extent individuals are exposed to a specific agent.[62]

Direct approaches to establish human exposure of chemicals include personal exposure monitoring, e.g. air monitors, duplicate portion samples and skin wipe samples, and biological markers e. g. breath, urine and blood.[63]

A problem with measured values, concerning the concept of intake fraction, is that a direct measurement does not in itself give any information about the sources of the

[59] OECD (2004-09-08)
[60] OECD (2000)
[61] Matthews, et al. (2002)
[62] Berglund, et al. (2001)
[63] WHO (2000)

emission or which amount of the substance that has been released prior to the measurement. Without establishing the amount of released substance it is impossible to determine an intake fraction. Another problem with direct measurements is that it is usually neither affordable nor practical to measure exposure for everyone in a population of interest.[62] There are however indirect approaches to derive exposure estimates using measured values. One way is to combine measured pollutant concentrations at fixed sites with information on rates of contact with these media. The rates can be estimated by using recorded data logs, diaries or time-activity surveys. A time-activity survey is used to find out people's activity patterns. That combined with people's eating and drinking habits and life style characteristics have been found to be, by past studies, crucial for achieving realistic estimates of actual human exposure.[64]

This type of studies on human exposure often introduces uncertainty due to that the studied individuals are not representative for the actual individuals under exposure, monitoring error or that the participating individuals not give accurate information.[65]

Measured human exposure is obviously not applicable for substances that have not been in use, since no exposure has occurred yet. To determine exposure for new substances always requires some kind of modelling.

6.3 Estimates from modelled exposure

Models are logical or empirical constructs, which uses certain input data to derive estimates of individual or population exposure parameters. The Scientific Committee on Toxicity, Ecotoxicity and the Environment has recommended six criteria that an exposure model should fulfil[66]:

1. *The model must be properly documented and analysed.*
2. *The model should have an appropriate time and spatial scale.*
3. *The applications range of the model and other limitations must be complied with.*
4. *The mathematical relations and the conceptual and theoretical background must be known.*
5. *The expected degree of uncertainty and the sensitivity of the model to input must be known.*
6. *There should be support for the assumptions made and for the values of the default parameters used.*

Models can generally be divided into three classes statistical, deterministic and practical or combinations of statistical and deterministic models.[64]

6.3.1 Statistical models

Statistical models are based on measured or calculated data and are in their simplest form numerical best fits of the collected data and potentially related factors. Usually it is the average outcome that is used for modelling but other values such as variance, percentiles or the median can also be used. Statistical models include multiple linear regression and analysis of variance (ANOVA). These two methods are closely related

[64] WHO (2000)
[65] Berglund, et al. (2001)
[66] IGHRC (2004)

and the only major difference is that for ANOVA all the independent variables are treated as if they were nominal (the data is measured by a numerical value e. g. concentration of a pollutant in the release medium)[65] whereas for multiple linear regression the independent variables can be nominal, ordinal (the data is measured by order or rank e. g. distance from the release site: within 0.5 km, 0.5-1 km, >1 km) or interval (the data is measured by proportions or number of observations in categories e. g. male versus female)[67] and any mixture is possible for the mentioned scales.[64]

Benefits with using models are that they make it possible to predict reduction in exposure for different types of regulation approaches and control strategies and that only limited data is needed. Disadvantages are that a certain amount of uncertainty is introduced into the models, which make the results less reliable[68] and before a statistical model can be used on populations and environmental settings besides those from which it was derived it has to be validated.[69]

6.3.2 Deterministic models

Deterministic models are based on logical expressions of the physical environment and the human behaviour in it. These types of models need to be validated with measured data before they can be assumed to reflect real exposure. They can be used in a more general way than statistical models but instead they lack accuracy and precision in the results. The deterministic approach uses single values, e. g. a concentration averaged over a given time period, to represent different exposure input variables and the result is expressed in a single estimate. Benefits with deterministic models are that they usually are simple, quick and inexpensive. Disadvantages are that they provide little information on how exposure or risk varies within studied populations or subgroups and that they can result in conservative or unrealistic exposure estimates.

To deal with the problem of accounting for the variability within populations a probabilistic approach can be used instead. Probabilistic models are often based on deterministic models but instead of a point estimate distributions for the input variables are used for the links in the chain that leads to exposure. This gives a more realistic population exposure distribution. The exposure distribution is commonly derived by using a mathematical sampling technique such as Monte Carlo simulation.[69] A Monte Carlo simulation samples values in a random fashion from the input distributions and propagates these to calculate the resulting exposures. This is done repeatedly and the results from the different trials are then used to estimate the exposure distribution.[70]

6.3.3 Practical models

Practical models are often a combination of both deterministic and statistical model components. Most of the developed models for describing fate of contaminants in the environment have been single-medium models, which only deal with a specific environmental medium e. g. soils or indoor air. To determine human exposure through more than one medium requires some kind of multimedia modelling. Multimedia models have been recognised to be sufficient to provide a screening level assessment of source to exposure/dose relationships of regional emissions and they can be used for

[67] Berglund, et al. (2001)
[68] Berglund, et al. (2001)
[69] WHO (2000)
[70] Kammen, & Hassenzahl, (2001)

priority setting since they enable comparison between the magnitudes of exposure likely to occur from different media.

All models for estimating human exposure have at least two features in common, firstly the movements of a chemical between different media, which is referred to as inter-media transfer factors, and secondly the rate and/or frequency of human contact with the different media, which is referred to as exposure factors.[69] The most widely used multimedia models are the Mackay-type compartmental models. [71]

Mackay type models
The Mackay-type model was developed to calculate the behaviour of chemicals in the environment as an answer to the societal need of having available methods for this purpose. This is essential for assessing or implementing remedial measures to treat already contaminated environments, or predicting the fate of new chemicals not yet on the market or the impact of increased quantities of chemicals already on the market.[72]

Mackay type models are mass conservative, which means that a chemical at a specific location has three possible outcomes, it can remain at the location, it can be carried elsewhere by transportation processes or it can be eliminated through transformation into a new chemical. To achieve accurate results for fate and transportation, an understanding of every process contributing to the mass balance of the chemical is required. The mass balance of a chemical can be expressed as:

Change in storage of mass = mass transport in - mass transport out + mass produced by sources - mass eliminated by sinks.[73]

The Mackay type model can be divided into four levels where the level I is the most simplistic one and level IV is the most sophisticated.[74] The models are most appropriate for determining the fate of low concentration chemicals emitted from non-point sources over a relatively long time and length scale. The different media are represented as separate compartments, which are assumed to be individually well mixed. Transport between the compartments occurs in response to gradients in chemical fugacity or concentration.[75] Fugacity measures the tendency of a chemical to escape from the phase it is in and it is expressed in units of pressure (Pa). Fugacity is sometimes also called *escape tendency* or *escape pressure*.[76]

The level I model simulates the equilibrium distribution of a fixed quantity of a non-reactive chemical, in a closed environment at equilibrium. No consideration is taken to degradation, advective processes or intermedia transport (transport from one media to another) processes e.g. sedimentation or wet deposition. The model is intended to establish the general behaviour of a new or existing chemical and to determine which media the chemical will tend to partition into. The results also give an indication of the relative concentration in each medium. Parameters required for modelling include amount of chemical, molecular mass, temperature, and for chemicals that partition into

[71] Hertwich, et al. (2001)
[72] MacKay, D. (2001)
[73] Hemond, et al. (2000)
[74] Canadian Environmental Modelling Centre (040812)
[75] Hertwich, et al. (2001)
[76] van Leeuwen, & Hermens (1995)

all media, it is necessary to determine water solubility, vapour pressure, octanol to water partitioning coefficient (log K_{ow}) and melting point. Involatile chemicals or chemicals with no or almost no solubility requires the input of partition coefficients. Environmental properties required are volumes and densities for the different media, organic carbon content and fish lipid content (only for the chemicals that can partition into all media).[74] The output of the level I model is the distribution of the chemical between the different compartments.[76]

The level II model is similar to the level one but assumes a constant input rate. Consideration is also given to advective in- and out- flow of the chemical and degradation reactions. The parameters required for level II are the same as for level I plus data for advective inflow rates, inflow concentrations, reaction half-lives in each medium, and the emission rate.[77] The output of the level II model is besides the distribution between different compartments also the environmental lifetime.[78]

The level III model assumes a steady state instead of an equilibrium state. Steady state refers to when the system's competing rates of input/uptake and output elimination are equal resulting in a constant chemical concentration over time.[78] The model also incorporates intermedia transfer. It requires the same parameters as level II with the addition of emissions and advective inflow rates and concentration to each medium and intermedia transfer rates, such as rain rate, aerosol deposition and sedimental burial.[77] The level III model gives a more accurate estimation of the output available from a level II calculation and the concentration of the chemical in the different compartments.[78]

The level IV model assumes a non-steady state. The necessary parameters are similar to those of the level III model. The outputs from the model are time related concentrations, as well as the time needed before steady state is achieved or the time required for the chemical to disappear when a discharge ends.[78]

The endpoint of the Mackay type models does not involve human exposure. This requires that further calculation and modelling are needed to determine human intake.

Human exposure models
Humans can be exposed to chemicals in their working place, through consumption and through the environment.[78]

The exposure can occur directly via inhalation (of air, dust, and aerosols), soil ingestion and dermal contact and indirectly via food products and drinking water.

The direct exposure is relatively simple to model. The concentrations in different media, calculated with dispersion models of e. g. the Mackay type models described above, can be used directly. The concentrations are then combined with the total daily intake of these media.

To estimate indirect exposure requires, besides determining the exposure in different media e. g. soil, groundwater, air and surface water, also determining the concentration in different food products and drinking water. Models used to estimate exposure through food products can be divided into two types, physiologically based models and

[77] Canadian Environmental Modelling Centre (040812)
[78] van Leeuwen, & Hermens (1995)

more simple models. The physiologically based models incorporate knowledge on the physiology of the species and kinetics of the studied chemical, while the more simple models uses estimated bioconcentration (BCF), biotransfer (BTF) and bioaccumulation (BAF) factors. These are defined as fixed ratios and are valid under the assumption of steady state. These types of models are often highly dependent on the K_{ow}.

A general formula for calculating the doses from drinking water, air, fish, crops, meat and milk is given. Dermal uptake probably contributes little to the total uptake and soil intake will only be relevant for heavily polluted soils or for extremely toxic compounds.

$$DOSE_{\text{medium x}} = \frac{C_{\text{medium x}} \cdot IH_{\text{medium x}}}{bw}$$

Dose is the total daily dose through a specific medium, C is the concentration of the chemical in the same medium, IH is the total daily intake of the medium and bw is the (average) human bodyweight.[79]

In the case of inhalation a correction factor accounting for bioavailability need to be incorporated, usually 0.75.[79]

There are several models which already incorporate both a dispersion model of Mackay type and a human exposure model, e. g. CalTOX and EUSES

CalTOX
CalTOX is a multimedia model based on the concept of fugacity.[80] It was developed to assist in health-risk assessments and the ultimate objective is to improve the quality of risk information incorporated in regulatory decision-making.

To use CalTOX requires the following inputs: *physical-chemical properties* including molecular weight, octanol-water partition coefficient (K_{ow}), melting point, solubility, Henry's law constant or vapour pressure, diffusion coefficients in pure air and water, intermedia distribution coefficients such as K_d and K_{oc}, and media specific transformation rates, *landscape properties* including meteorological data, hydrological data, and soil properties, *human exposure properties* including exposure duration and averaging time, anatomical and dietary properties, food consumption patterns, activity patterns and exposure times, household parameters, other human factors such as soil ingestion and breast milk intake, and parameters associated with food crops and food producing animals. In addition a number of partition factors need to be known to be able to calculate intermedia transfer factors.[81] The model is most appropriate for handling non-point sources.[82] Some limitations for the input parameters are that the model can not handle surfactants or volatile metals and great care should be taken when modelling partially ionized metals. The model is neither appropriate to use if water occupies more than 10 % of the surface area studied or on areas less than 1 000 m^2.[81]

Between emission and intake a linear relationship can be assumed. This is based on the assumption that the transportation processes, diffusion and advection, are linear with

[79] van Leeuwen, & Hermens (1995)
[80] Bennett, et al. (2002a)
[81] The University of California (1994)
[82] Hertwich, et al. (1999)

concentration and that transformation processes, such as photolysis, hydrolysis and biodegradation can be well approximated as linear and first order. This is a simplification but efforts made to evaluate the model against environmental data have shown that the model yields reasonable estimations.[83] However the approximations limits the application range of the model in the sense that it is only suitable for low concentrations of a substance (the results are e. g. not valid if the substance concentration exceeds the solubility limit in any phase) and for long time scales, from several months to decades, and must be used with caution for time periods less than a year.[84]

Key assumptions in the model are that the atmosphere is modelled as a single compartment, a uniform volume source in the release medium is used, the landscape parameters are considered to be uniform and also the population density is considered to be uniform. The endpoint of the model is a source-to-intake relationship expressed as a dose.[85]

CALPUFF
CALPUFF is a multi-layer, multi-species non-steady-state puff dispersion model. The model was developed as a part of a study to develop and design a generalised non steady state air quality modelling system for regulatory use.[86]

It simulates the effect of time- and space-varying meteorological conditions on pollution transport, transformation and removal.[87] The modelling system consists of three main components: CALMET, which is a diagnostic 3-dimensional meteorological model, CALPUFF, an air quality dispersion model and CALPOST, a post processing package.[88]

The input required to CALMET includes surface and upper air meteorological data (e. g. wind speed, wind direction, temperature, cloud cover, vertical profiles of wind speed) and geophysical data, which include gridded fields of terrain elevations and land use categories. If the modelling involve transportation over water additional information is needed on the air-sea temperature difference, air temperature, relative humidity and the mixing height at one or more stations over water. [89]

The CALPUFF part is a Lagrangian and multilayer gridded non-steady state puff dispersion model. It can simulate the effects of temporally and spatially varying meteorological conditions on pollutant transport, removal of pollutants by dry and wet deposition processes, and transformation of pollutants through chemical reactions. Input data required include gridded three dimensional hourly meteorological data from the CALMET model and emission sources. The modelling system can handle both varying and constant emissions from point, line, volume and area sources.[86] The emission is modelled as continuous puffs emitted into the ambient wind flow.[89] The endpoint of the model is the concentration at different predefined locations. An Intake fraction can be calculated directly from these concentrations by using the following equation:

[83] McKone, T. E. (2004-09-04) pers. comm.
[84] The University of California (1994)
[85] Bennett, et al. (2002a)
[86] Scire, et al. (2000)
[87] U.S. EPA (040819)
[88] Earth Tech (040819)
[89] Elbir, T. (2003)

$$iF = \frac{I}{Q} = \frac{\sum_{i=1}^{n} \Delta C_i \cdot P_i \cdot B}{Q}$$

Where I is the intake rate, ΔC_i is the average concentration increment caused by emissions, P_i is the population, B is the average breathing rate and Q is the emission rate.[90]

IMPACT 2002
IMPACT 2002 (IMPAct Assessment of Chemical Toxics, version 2002) is a multiple exposure pathway model. The model consists of a common fate model and two effect modules, one for human health and one for ecosystems.[91] Only the fate model is relevant for this study. It links a chemicals concentration in the atmosphere, soil, surface water, and vegetation to human intake through the inhalation and ingestion routes and the endpoint is an intake fraction.[92]

The model was developed to understand the true relevance and limitations of eco- and toxicological indicators in comparative applications such as Life Cycle Assessment (LCA). [93] It is designed specifically for comparative assessment and it estimates the cumulative impacts linked to a mass emitted, e. g. one kg, compared with a reference substance.[92] The model exists in two versions; one is an a-spatial version where no consideration is taken to where the emission occurs and the other version has spatial resolution where consideration is taken to the relationships between the location of food production, water supply and where population cohorts live relative to location of the emission source.[94]

Parameters that need to be known to use the model include: half life and release rate to different media, partition coefficients, pK_a, bioconcentration factors and biotransformation factors, bulk plant soil concentration ratio, Henry's constant or K_{aw}, log K_{ow} and if the chemical is degradable or non degradable.[95]

The geographical area used in the model is Western Europe and the population is estimated to 420 million. The substances that the model can be used for include organic substances as well as inorganic substances and metals.[96]

EUSES
The European Union System for the Evaluation of Substances (EUSES) was developed for assessing risks according to European legislation and is based on the EU technical guidance documents for existing and new substances. It is a tool for supporting decision-making and it is intended more for initial and refined risk assessments than comprehensive assessments.[97] It covers in principle the whole life cycle of a substance

[90] Hao, et al. (2003)
[91] Jolliet, et al. (2004-10-12)
[92] Jolliet, et al. (2003)
[93] Apitz & Butler (2004-10-12)
[94] Pennington, et al. (2004)
[95] Pennington, et al. (2003)
[96] GECOS. (2004-09-20)
[97] European chemicals bureau (2004-08-19)

and includes exposure assessment, effects assessment and risk characterisation for environmental populations and humans. This study focuses on human exposure assessment and therefore only this component was further studied.

Three modules of EUSES is relevant for this purpose: the emission module, the distribution module and the exposure module.

The emission module uses emission factors for a given substance that is taken from a database. The database emission factors are based on industry category documents and expert determined default values. The model is designed to be able to account for a broad range of different chemicals. Emission factors are mainly developed for the industrial uses. For most of the private use and the waste management the emission factor has to be estimated manually.[98]

The distribution model consists of a regional multimedia model of Mackay type level III and local models. The local models are, among others, a sewage treatment plant simulation model, an air distribution model, surface water dilution and sorption model and a one-compartment soil model.

The exposure module estimates intake levels related to human exposure through consumer products, exposure at the workplace and exposure through the environment by inhalation of outdoor air and consumption of food and drinking water.

Three different spatial scales are considered: personal, local, and regional. The personal scale concerns the individual exposure of workers and consumers. On the local scale a large point source is considered. It is not an actual site but a hypothetical one with predefined environmental characteristics adapted to reflect the European Union. The regional scale assesses the risk due to all releases in a large region (4 000 km^2 with 20 million inhabitants) assuming the same environmental characteristics as for the local scale. A fourth continental scale is also available that summarises the exposure for all of the EU member states. This scale is however not used for the final risk characterisation. In a new version of the model (EUSES 2.0) also three overlying global scales (moderate tropic and arctic) can be included and they are neither included in the final risk characterisation.[99]

Different time scales are considered depending on local or regional and continental exposure. For the local scale the exposure through the environment is considered to be averaged over a long time period and derived from average emission rates. For consumers and workers the exposure is considered to be acute, sub-chronic or chronic. On the regional and continental scale the emission is regarded as diffuse and continuous, leading to steady-state environmental concentrations. The steady-state concentrations can be considered to be estimates of long-term average exposure levels.[100]

In the model exposure through the environment can occur through drinking water, food consumption, and inhalation of air. The dermal route and ingestion of soil are not taken into consideration since those routes are not considered to be appropriate for a generic

[98] Fischer, S. (2004-11-24) pers. comm.
[99] EC (2004)
[100] Vermeire, et al. (1997)

exposure scenario. For the local scenario all food products are derived from the vicinity of one point source and, for the standard assessment, the highest country-average intake rate is used. In the regional scenario all the food products are instead taken from the regional model environment and the highest country-average intake is used.[99]

The minimum of parameters needed to run EUSES relevant for human exposure are molar mass, vapour pressure, log $K_{ow,}$ degradability, and solubility. Henry's law constant and BCF for fish is also required but can be estimated by the model.

The result of EUSES relevant for the exposure of humans is a risk estimation in the form of a Risk Characterisation Ratio (RCR), which is the ratio of the dos-response assessment and the estimated exposure. [101]

The models described above are summarised, in a table in appendix 3, in an attempt to answer the questions from the discussion in section 5.1.

6.3.4 Reliability of modelled exposure estimates

Models always represent a simplification of reality. Before conclusions are drawn based on the result from a model it is important that the model reliability is understood and how the input parameters influence the results.

To determine if a model gives an accurate representation of reality some form of model validation is required. This can be done by comparing predicted values with measurements or it can be done by comparing the results from different assessment methods or modelling approaches.[102] Model validation should be viewed as an iterative process where the model's predictive performance is evaluated, the results are used to refine the model and then the model is evaluated again.

The modelled results are also highly influenced by uncertainties in the input parameters. These uncertainties can be separated, based on the type of source from which it arises, into the following groups according to Morgan and Henrion:

- *Statistical variation,* arises from random error in direct measurement of a quantity.
- *Subjective judgment,* arises from systematic error from biases in measuring apparatus and experimental procedure.
- *Linguistic imprecision,* arises when using imprecise language when referring to events or quantities.
- *Variability,* refers to quantities that vary over time and space.
- *Inherent randomness,* refers to a quantity for which no known pattern or model can account for its variability.
- *Disagreement,* arises from different technical interpretations of the same available scientific literature.
- *Approximation,* arises from simplification of the real world system.

[101] Vermeire, et al. (1997)
[102] WHO (2000)

The mentioned uncertainty sources are valid for input parameters that represent measurable properties of the real world system. Generally these types of parameters are the most usual in risk analysis models.[103]

To analyse the effects on the result of the uncertainties in the input parameters a sensitivity analysis, uncertainty propagation or uncertainty analysis can be performed. The sensitivity analysis is performed to compare how changes in input affect modelled predictions. Uncertainty propagation is performed for calculating the uncertainty in the model output induced by the uncertainties in the model inputs and uncertainty analysis is performed for comparing the importance of the input uncertainties in terms of their relative contributions to uncertainty in the output.[104]

The uncertainty in environmental fate and effect models is most often determined by Monte Carlo analysis. This analysis method can help to determine the uncertainty from chemical properties, landscape properties and emission data. Uncertainty in emission data can be very high and is often difficult to estimate and if included in the uncertainty study it often plays a significant role. Otherwise the parameters that have been found to contribute the most to the variance of the estimated output are the chemical properties, especially half-lives. This is due to the fact that it is the parameter that usually has the highest standard deviation.[105]

Uncertainty and validation status of the studied models
All of the models mentioned in section 6.3.3 have been validated to a certain extent.[106,107,108,109,110,111] Available validation studies showed that all of the models seem to be able to, at least to a certain extent, predict sufficiently accurate exposure for regulating chemicals, although some of them have been identified to require further validation.[112-113]

Some of the models have been found to underestimate exposure, e. g. EUSES [114,115] and CALPUFF.[116] One of the reasons of the underestimation has been thought to lie in difficulties in estimating amount of emission.[116,117,118]

The model IMPACT2002 has been used to compare spatial and a-spatial resolution. It was found that the spatial model estimated slightly higher intake fractions compared to the a-spatial version and that the spatial models estimations were closer to monitored values.[119] Another study compared the two different versions with monitoring data for

[103] Morgan, & Henrion (1990)
[104] Morgan & Henrion (1990)
[105] Webster & Mackay (2003)
[106] Dor, et al. (2003)
[107] Elbir, T. (2003)
[108] Honaganahalli & Seiber (2000)
[109] Margni, et al. (2004)
[110] Pennington, et al. (2004)
[111] Jager, T. (1998)
[112] Dor, et al. (2003)
[113] EC (2004)
[114] Jager, T. (1998)
[115] Kawamoto, et al. (2001)
[116] Elbir, T. (2003)
[117] Kawamoto, et al. (2001)
[118] Honaganahalli, & Seiber, (2000)
[119] Margni, et al. (2004)

PeCDF (2,3,4,7,8,-Pentachlorodibenzofuran) to investigate when spatial resolution is needed and when the more simplified version is sufficient. This study showed that spatial distinction may not improve the reliability of predicted estimates pertaining to PeCDF. However the same study also compared calculated intake fractions for several representative organic, non-dissociating chemicals for the different versions. The chemicals were selected to reflect plausible differences in partitioning behaviour, dominant human exposure pathways, overall environmental persistence and long-range characteristics. The results indicated that the intake fractions predicted with the a-spatial version were typically lower than those of the spatial version. The difference was less than a factor of two for air (probably due to a low air grid resolution) and ten for soil emission scenarios. For emission to water the difference could be as high as three orders of magnitude (probably due to variation in volume and residence time between lakes and rivers).[120]

Parameter uncertainty has been studied using the model CalTOX. The parameters that contribute the most to the variance of the exposure estimate were determined by using a sensitivity analysis. The variance was found to be mostly due to the uncertainty in chemical-specific input parameters, especially half-lives. For chemicals with dominant exposure through indirect routes, certain exposure factors were seen to be important such as fish intake and the source of drinking water. Landscape characteristics were of minor importance. The uncertainty in the exposure estimate, defined as the ratio of the 95th to the 5th percentile, was typically about one order of magnitude, although it varied from ½ to 3 ½ orders of magnitude.[121]

A sensitivity analysis has also been performed on EUSES, by implementing a spreadsheet version. The sensitivity analysis was carried out for the polycyclic musk fragrance HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-[g]-2-benzopyrane) and the predicted environmental concentration in the surface water. The study came to the conclusion that only 15 % of all EUSES parameters influenced the regional and local water concentrations. The modelled results were always sensitive to emission rates. For the regional scale, sensitive parameters were the fraction of people connected to sewage treatment plants and the regional area. For the local scale, sensitive parameters were dilution factors and the number of inhabitants discharging into the one plant. The study only dealt with variability in the input parameters and did not include other types of uncertainty. The study also compared two different scenarios where the chemical was classified as readily biodegradable and not biodegradable. The results of the first scenario were sensitive to degradation rate while the other scenario results were more sensitive to vapour pressure, water solubility and K_{ow}.[122]

6.4 Summary and discussion of methods to derive iF

To determine intake fractions by using measured exposure involves some difficulties. The total intake of the exposed population need to be measured and measured exposure does not in itself give any information about the sources of the emission or which amount of the substance that has been released prior to the measurement . Exposure can quite easily be measured on an individual level but requires some kind of extrapolation to represent the whole exposed population. This introduces further uncertainty in an estimate that already contains uncertainty from e. g. measurement error.

[120] Pennington, et al. (2004)
[121] Hertwich, et al. (1999)
[122] Schwartz, et al. (2000)

Most of the studied models were developed for helping with priority setting and regulation of chemicals and all of the models require that several different input parameters are known. The model that requires the least is EUSES, which can estimate human exposure based on only five parameters (molar mass, vapour pressure, K_{ow}, degradability and solubility. The rest of the necessary parameters can be estimated by the model or are default values that reflect Europe, however the model is complex and requires that the user have a certain expertise to correctly interpret the results and to determine when more data is necessary.

Models offer a much easier task to calculate relationships for estimating intake fractions compared to measured exposure since often the modelled results can be divided, without requiring much extra effort, with the emission input of the model and it is also not necessary to know the real exposure. A problem with this is that models already contain a certain degree of uncertainty and performing e. g. multiple linear regressions on modelled intake fractions introduces even further uncertainty in the exposure estimate.

The model's limitations will also directly affect and limit intake fractions calculated with them. All of the models, except the air dispersion model CALPUFF, are based on the Mackay type model and assume that media are represented as separate individually well mixed compartments. The Mackay type models are most appropriate for modelling low concentrations, for long time and spatial scale and they are not suitable for point sources. Some of the Mackay type models are not appropriate for modelling surfactants, volatile metals, partially ionized metals and non-dissociating substances of intermediate lipophilicity.

7 Determinants for human exposure

A lot of factors influence the behaviour and fate of chemicals. Is it realistic to find a few properties that can be used to determine exposure?

To illustrate the many factors that actually have the potential to influence exposure, a list was compiled. This list is by no means complete and not all of the properties mentioned affect the exposure of all chemicals but it shows the magnitude of potential parameters that could be studied when e. g. performing a multiple linear regression analysis.

The parameters have been compiled from the sources: van Leeuwen and Hermens (1995), Hemond and Fechner-Levy (2000) and parameters affecting exposure identified in appendix 3,

The parameters have been grouped into five categories that affect exposure: properties of the source, properties of the chemical, media characteristics, transformation processes and factors that specifically influence human intake.

Source factors
Emission data: emission rate, yearly production volume, geographical location, stack height, volumetric exhaust rate, temperature of exit gases.

Physico- chemical properties
Molecular weight/mass, water solubility, acid dissociating constant (pK_a), vapour pressure or Henry's law constant (partition coefficient usually defined as the ratio of a chemical's concentration in air to water at equilibrium), water solubility, K_{ow}, melting point, half-life.

Media characteristics
Air:
Meteorological conditions: wind speed and direction, atmospheric stability or atmospheric turbulence, mixing height, temperature, solar radiation or cloud cover, precipitation, terrain data; roughness, length, land use.

Water:
Velocity, system geometry, hydrology, flow volumes, river depths, rainfall, entering streams and non-point source flows, ground water flows, evaporation rates, wind speed, suspended particle and sediment loads, dissolved organic carbon content, pH, temperature,

Soil:
Soil density, porosity, moisture content, organic matter or organic carbon content, pH, cation or anion exchange capacity and redox potential, aquifer depth and width, chemical input coordinates, hydraulic conductivity and hydraulic gradient, vertical dispersivity and withdrawal rates of pumping locations.

Transformation processes
Gas-particle partition and deposition parameters, photochemical degradation rate, reaction rate with OH-radical and other reactive chemical species, biodegradation.

Human intake factors
Anatomical and dietary properties, soil ingestion, efficiency of drinking water treatment processes, breast milk intake, total daily intake of meat, milk, air, drinking water, fish, and crops, bioconcentration (uptake from the surrounding aqueous phase), bioaccumulation (uptake from the environment via any possible pathway), biomagnification (uptake via the food web), bulk plant soil concentration ratio, people's activity patterns, and population density.

7.1 Summary and discussion of determinants for human exposure

A multitude of different factors have the potential to affect the human exposure of chemicals, however some of the mentioned parameters have the potential to affect the exposure estimate more than others. Some of these parameters have been identified to include emission data, fish intake, drinking water source, chemical properties; especially half-life, vapour pressure, water solubility and K_{ow}, see appendix 3.

A previous study has also showed that landscape characteristics have a low influence on the exposure estimate[123] and two studies have showed that source characteristics can be of minor importance.[124,125]

The mentioned parameters have been identified mainly through the use of uncertainty analysis or sensitivity analysis to have a high influence on the exposure estimate. One problem with these types of analyses is that the results are dependent on how the uncertainties in the input parameters are defined and also which uncertainties that are considered. If uncertainties in some parameters are omitted this can highly influence the result, making it difficult to generalise results from this type of studies.

Another study that also might imply that only a few parameters could be used for estimating a relationship for intake fraction was a sensitivity analysis, which only considered variability, performed on EUSES. The study showed that only a few parameters were important for estimating the concentration for the considered media.[126]

Parameters that already have been used to derive emission-to-intake relationships include population density, K_{ow}, K_{aw}, half-lives, and when only considering air emission; mixing height, inverse stack height, relative humidity, temperature, the intake fraction of sulphate and wind speed.

These parameters could be used as a starting point if attempting to find potential parameters to estimate intake fractions from a few parameters.

[123] Hertwich, et al. (1999)
[124] Levy, et al. (2002)
[125] Hao, et al. (2003)
[126] Schwartz, et al. (2000)

8 Discussion

Intake fractions for a variety of chemicals have been calculated ranging from $1.9 \cdot 10^{-10}$ (Bennett, et al. (2002a)) to $1.1 \cdot 10^{-2}$ (Margni, et al. (2004)).

This wide range implies that differences in exposure between chemicals could vary significantly since emission of 1 000 tonnes of one chemical with an intake fraction of $1 \cdot 10^{-9}$ could potentially result in the same intake as emission of 1 kg of a chemical with an intake fraction of $1 \cdot 10^{-3}$. This implication is valid if the estimations are accurate and if a linear relationship between emission and intake can be assumed.

This assumption has been assessed to be a reasonable estimation when validating multimedia models against measurements.

The possibility of calculating intake fractions based on a few properties has the potential to reduce the time and effort needed to perform human exposure assessments. Derived relationships for estimating intake fractions could be used as an initial screening step. A low estimate (compared to the results of the dose-effect/dose-response assessment) would imply that no further examination of the chemical would be required and a high estimate would imply further examination using a more accurate estimation method.

This requires that the estimated intake fraction be based on a worst case scenario to not underestimate exposure. Several of the models have been found to underestimate exposure compared measurements, see appendix 3. One potential reason for this underestimation has been thought to lie in an incorrect estimate of the emitted amount of the chemical.

The importance of accounting for population density need to be further investigated. Several studies have shown that for dioxins the assumption of a uniform population density can be a sufficiently approximation but for other chemicals this parameter could be important.[127,128] A study that has not been published yet has looked at the dependence of intake fraction due to release location and the conclusion in that study is that the locations of population and food production relative to sources of chemicals are important variables that should be considered in human health assessments. The results show that the use of continentally averaged parameters for population density and food production provided an accurate estimate of the median intake fraction calculated for emissions in individual regions; however, the intake fraction could range from this median by up to 3 orders of magnitude, especially for chemicals transferred through foods.[129] When comparing spatial and a-spatial model prediction with measurements the spatial model was seen to predict higher concentration that was closer to monitored values.[130] This indicates that a spatial model should be used to not underestimate intake fractions.

This implies that the intake fractions, and the intake fraction interval ranging from as much as 10^{-10}-10^{-3}, calculated by Bennett et al. (2002) using CalTOX (which assumes a

[127] Lobscheid, et al. (2004)
[128] Pennington, et al. (2004)
[129] MacLeod, et al. (2004)
[130] Margni, et al. (2004)

uniform density) needs to be re-evaluated. The authors did not expect the estimate to be more accurate than within one order of magnitude but considering the results of the more recent studies given above, the results cannot be assumed to be more accurate than within 3 orders of magnitude.

The same study also derived empirical relationships for predicting intake fraction based on half-life, K_{ow}, and K_{aw}. These parameters are some of the parameters that have been found to have a high contribution to the uncertainty in exposure estimates, see appendix 3, especially half-life which is the parameter that usually has the highest standard deviation and thus is the most uncertain parameter.

Another uncertain parameter that has been found to cause problems when validating models is estimating the correct amount of emission. This is a crucial parameter when calculating intake fraction. Combined with the uncertainty when determining half-lives it makes it questionable if the concept of intake fraction is appropriate for simplified human exposure assessment, at least with the data that is currently available.

However intake fraction as a concept offers several benefits when presenting and comparing results. It gives an immediate understanding of a chemical's potential human uptake, simplifies determining if the calculated exposure estimate is realistic and it is easy to comprehend but is highly dependent on assumptions made when calculating it and a certain caution should be taken when comparing results.

Few parameters are required to estimate relationships for determining intake fractions and the simplification is transparent, the user is not deceived into believing that the concept is not a big simplification. The concept would also be easy to use and save time compared to using more complex models, making it suitable for estimating benefits when implementing risk reduction measurements.

Simple relationships for estimating intake fraction could also be used as a first screening step. The calculated intake fraction could be compared to the estimate from a dose-response assessment in the risk characterisation step. To be able to perform this type of comparison requires that there are no dependencies of the health effect on intake dosage rate, no threshold effects between dose and effect, and the health effects have to be proportional to cumulative exposure.

If the chemical fulfils these criteria and the expected intake is low compared to the intakes known to cause a significant effect, this could imply that no further examination of the chemical would be required. If on the other hand the estimate is high in comparison this would imply that further examination is needed using a more accurate estimation method.

Before this is possible to apply, however, further research is required. It is recommended to initially focus on how the intake fraction is affected by population density and the location where food is produced relative to the emission source location. This is also necessary to see if there is really such a wide range of more than seven orders of magnitude between intake fractions for different chemicals. If a similar range still exists calculated intake fractions could be used for priority setting, identifying chemicals that potentially lead to high human exposure although the emission volume is low.

Another big limitation for the possibilities of using this concept lies in the lack or uncertainty of available data. It is questionable if half-life is a good parameter for calculating intake fractions since it is usually the most uncertain parameter. The amount of emission is another highly uncertain parameter, but this would be of less importance if estimated intake fraction relationships were based on values calculated with models since a linear relationship can be assumed between emission and intake. This type of relationships would be model dependent but it could still serve as an appropriate tool for identifying chemicals that potentially would lead to a high exposure.

Other alternatives to developing relationships for estimating intake fraction for simplified human exposure assessments could be to require more actual monitoring of exposure, or to require a higher expertise within the industry that would make it possible for them to use more complex tools.

8.1 Conclusions

The relationships that have been used so far for estimating intake fractions for a multitude of chemicals cannot be used for simplifying exposure assessments for new chemicals as they exist today. Further research is recommended to initially focus on determining the relevance of population density, the relevance of where food is produced relative to emission source and lack and uncertainty of available data. The relationships are based on K_{ow}, K_{aw} and half-life. Half-life is one of the most uncertain parameters used in multimedia modelling and it is questionable if relationships based on this parameter are useful since they must be highly uncertain.

A high total production volume of a chemical does not necessarily result in a high human exposure since the exposure is dependent on several factors including production processes, transport, metabolism, and use patterns. However, the higher the volume of a chemical emitted into the environment, the higher the exposure of humans will be. This is based on that chemical exposure can be considered to be linear with concentration when considering chemicals that are released to the environment. This assumption has been seen to be a good approximation when validating multimedia models.

However differences in exposure between chemicals could vary significantly since emission of 1 000 tonnes of one chemical with an intake fraction of $1 \cdot 10^{-9}$ could potentially result in the same intake as emission of 1 kg of a chemical with an intake fraction of $1 \cdot 10^{-3}$, although how big this span between chemicals actually could be requires further research

Intake fraction could then potentially be used to identify chemicals that can result in a high human exposure although they are not produced or imported in high volumes. This requires that calculated generalisable intake fractions are available for a multitude of chemicals.

It is important to remember that exposure can occur not only through the environment but also through more direct ways in the form of consumer products and the working environment. It is possible to calculate intake fractions for these scenarios also, but the generalisability and usefulness of these calculations would need to be further investigated.

The applicability of the concept for risk assessments will furthermore be limited in the way that it is most appropriate for chemicals, whose effects on human health show no dependencies on intake dosage rate, no thresholds between dose and effect and proportionality to cumulative exposure.

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Glossary of terms and abbreviations

BAF	Bioaccumulation factor. Bioaccumulation refers to uptake from the environment via any possible pathway.
BCF	Bioconcentration factor. Bioconcentration refers to uptake from the surrounding aqueous phase.
BMF	Biomagnification factor. Biomagnification refers to uptake via the food web.
Congener	Chemicals that are chemically related compounds that are formed during the same process.
Exposure	The contact of a biological, chemical, or physical agent with the outer part of the human body, such as the skin, mouth or nostrils.
Half-life	The time required for the amount of a reactant to decrease to half its initial value.
Henry's law constant	Partition coefficient usually defined as the ratio of a chemical's concentration in air to water at equilibrium
Human exposure	The contact of a biological, chemical, or physical agent with the outerpart of the human body, such as the skin, mouth or nostrils.
Human capital	The knowledge, skills, abilities and capacities possessed by people.
K_{aw}	Air-water partition coefficient.
K_{ow}	Octanol-water partition coefficient.
Mixing height	The height above the earth's surface where the air is well mixed caused by the turbulence from the earth-atmosphere interaction, this normally identified by the base of an inversion
Pathway	e. g. eating contaminated food, breathing contaminated workplace air, touching residential surfaces
QSAR	Quantitative Structure Activity Relationship. Models used to predict properties of chemicals based on their molecular structure
Route	Inhalation, dermal contact, ingestion, multiple routes.
SVOC	Semivolatile organic compound.

TEF	Assigned to congeners in relation to the most toxic one.
TEQ	Toxic equivalents. The amount of each congener multiplied by their respective toxic equivalence factors (TEF)
WTP	Willingness to pay. The amount a consumer is willing to pay for a particular quantity of a good or service.

Appendix 2
Summary of studied articles

Article:	Chemical studied:	Model:	Measures:	Scenario:	Release medium	Aim of the study:	Range of calculated iF:s
Bennett, et al. (2002a)	308 organic chemicals	CALTOX	dioxin	U.S.	air, water, soil	calculate iF, derive relationships	air: $8.6 \cdot 10^{-9}$-$9.1 \cdot 10^{-4}$ water: $1.9 \cdot 10^{-10}$-$1.0 \cdot 10^{-3}$ measured: $2 \cdot 10^{-3}$
Levy, et al. (2002)	$PM_{2.5}$, secondary sulphate, nitrate particles	CALPUFF	-	U.S.	air	derive relationships	$PM_{2.5}$: $2.2 \cdot 10^{-6}$-$9.1 \cdot 10^{-6}$ sec. sul: $1.8 \cdot 10^{-7}$-$2.2 \cdot 10^{-7}$ sec. nit: $3.1 \cdot 10^{-8}$-$3.5 \cdot 10^{-8}$
Nishioka, et al. (2002)	$PM_{2.5}$, secondary sulphate, nitrate particles	Regression equations derived by Levy et al.	-	U.S.	air	show how reduced energy use can save lives	-
Zhou, et al. (2003)	particulate matter, sulphur dioxide, sulphate, nitrate	CALPUFF	-	China	air	calculate iF, sensitivity of results	$PM_{2.5}$: $1.5 \cdot 10^{-5}$ sul. diox: $8.4 \cdot 10^{-5}$ sulphate: $6.0 \cdot 10^{-6}$ nitrate: $6.5 \cdot 10^{-6}$
Marshall, et al. (2003)	carbon monoxide, benzene	microenvironmental	ambient concentrations	California's South Coast Air Basin	air	calculate iF	car. mon: $4.6 \cdot 10^{-7}$ benzene: $4.8 \cdot 10^{-7}$
Levy, et al. (2003)	$PM_{2.5}$, secondary ammonium sulphate, ammonium nitrate particles	CALPUFF, (S-R) Matrix	emission from 7 power plants	Georgia, U.S.	air	Compare models	a. nitrate: CALPUFF $6.4 \cdot 10^{-8}$, (S-R) matrix $2.5 \cdot 10^{-8}$ const. ammonia conc. (S-R) matrix $4.1 \cdot 10^{-8}$ unlimited ammonia conc. a. sulphate CALPUFF $1.6 \cdot 10^{-7}$, (S-R) matrix $1.7 \cdot 10^{-7}$ $PM_{2.5}$ CALPUFF: $6.2 \cdot 10^{-7}$, (S-R) matrix $5.3 \cdot 10^{-7}$

Appendix 2
Summary of studied articles

Article:	**Chemical studied:**	**Model:**	**Measures:**	**Scenario:**	**Release medium**	**Aim of the study:**	**Range of calculated iF:s**
Hao, et al. (2003)	sulphur dioxide	CALPUFF	180 samples from emission sources	Hunan Province, China	air	Derive mult. regression equation, calculate health damage cost.	$1.17 \cdot 10^{-6}$-$3.16 \cdot 10^{-6}$
Margni, et al. (2004)	dioxin	IMPACT2002	TEQ values	Western Europe	air	evaluate model	estimated $3.5 \cdot 10^{-3}$ monitored ~$1.4 \cdot 10^{-2}$ pred. spatial $1.1 \cdot 10^{-2}$ pred. a-spatial $3.9 \cdot 10^{-3}$
Hirai, et al. (2004)	17 PCDD:s/DF:s, 12 CoPCB	Mackay type level III multimedia fate model, food-chain exposure model (in succession)	TEQ values, Composition of TEQ	local, Japan and the northern Hemisphere (excl. Japan)	air, soil, water, only air for measured values	evaluate model	measured $2.8 \cdot 10^{-5}$-$2.6 \cdot 10^{-2}$ for emission to air: local $3.7 \cdot 10^{-7}$-$7.7 \cdot 10^{-5}$ Japan $1.3 \cdot 10^{-5}$-$3.2 \cdot 10^{-3}$ global $2.2 \cdot 10^{-6}$-$1.3 \cdot 10^{-3}$
Lobscheid, et al. (2004)	SVOCs: benzo[a]pyrene (BaP), 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD), fluoranthene	CALTOX	-	San Francisco Bay Area	air	evaluate source-to-dietary intake links	BaP $1 \cdot 10^{-5}$ fluoranthene $2 \cdot 10^{-7}$

Appendix 3
Summary of studied models

Model:	**Type of model/ Model objective**	**Required input**	**population density**	**Limitations**	**Validation findings.**	**Parameters that pot. contribute to uncertainty/sensitivity**	**Model endpoint (relevant for this study)**
Mackay type Level I … Level II … Level III … Level IV …	Multimedia model, calculates the behaviour of chemicals in the environment	Emission data of chemical, molecular mass, temp. Water solubility, vapour pressure, log K_{ow} and melting point or partition coefficients. Volumes & densities of media, organic carbon content & fish lipid content. … + advective inflow rates, inflow conc., media reaction half-lives. … + emissions and advective inflow rates, conc. to each media, intermedia transfer rates, e. g. rain rate, aerosol deposition and sedimental burial. … similar to level III	Human exposure not included in the model	For low conc. of chemicals, non-point sources, long time and length scale. Media repr. as separate individually well mixed compartments	Depending on model.	Often difficult to estimate emission data, chemical properties, especially half lives	Level I: distribution between compartments Level II: distribution between compartments, environmental life time Level III: Environmental conc. Level IV: time related concentrations
Human exposure	Models to estimate human intake of chemicals	Conc. in media total daily intake of media, Physiology of species and kinetics of the studied chemical or bioconcentration (BCF), biotransfer (BTF) and bioaccumulation (BAF) factors.	?	?	?	?	Human dose

Appendix 3
Summary of studied models

Model:	**Type of model/ Model objective**	**Required input**	**population density**	**Limitations**	**Validation findings.**	**Parameters that pot. contribute to uncertainty/sensitivity**	**Model endpoint (relevant for this study)**
CalTOX	Multimedia model, developed for health-risk assessments	molecular weight, K_{ow}, melting point, solubility, Henry's law constant or vapour pressure, air/water diff. coeff., intermedia distr. coeff.(K_d and K_{oc}), media specific transformation rates, meteorological data, hydrological data, soil properties, exposure duration, averaging time, anatomical and dietary properties, food consumption patterns, activity patterns, exposure times, household parameters, soil ingestion, breast milk intake, parameters associated with food crops and food producing animals, partition factors.	Uniform population density assumed	Non-point sources, not for surfactants or volatile metals great care if partially ionized metals. Not appropriate if water occupies more than 10 % of surface area or areas less than 1 000 m^2	Showed good correlation of predicted and measured exposure. Transfer to food pathway contain high uncertainty. Further research concerning the reliability is requested generally for multimedia models.	chemical-properties especially half-lives, for some: fish intake, drinking water source. General lack of reliable chemical property values. uncertainty ½ to 3 ½ orders of magnitude.	Human dose
CALPUFF	Air quality model developed for regulatory use	Emission sources, surface and upper air meteorological data (e. g. wind speed, wind direction, temperature, cloud cover, vertical profiles of wind speed), geophysical data. Air-sea temperature difference, air temperature, relative humidity and the mixing height (if over water)	Human exposure not included in the model	both varying and constant emissions from point, line, volume and area sources. Only for air modelling.	Problems: modelling major buildings and street canyons,	Biggest uncertainties seems to lie in finding appropriate input data, e. g. inaccurate source estimation, erroneous observed conc., insufficient meteorological data, results sensitive to distribution of primary particles and background pollutant conc.	concentration at different predefined locations

Appendix 3
Summary of studied models

Model:	**Type of model/ Model objective**	**Required input**	**population density**	**Limitations**	**Validation findings.**	**Parameters that pot. contribute to uncertainty/sensitivity**	**Model endpoint (relevant for this study)**
IMPACT2002	Multimedia-multipathway model. Spatial and a-spatial version. Developed for comparative applications such as (LCA)	Half life & release rate to different media, partition coefficients, pKa, bioconcentration factors, biotransformation factors, bulk plant soil concentration ratio, Henry's constant or K_{aw}, log K_{ow} degradable/non degradable	Uniform pop. assumed. (a-spatial) Consideration to population density taken. (spatial)	both spatial and a-spatial resolution. For organic substances, inorganic substances and metals. Appropriate for Western Europe.	soil module slightly underestimated monit. conc., model exposed and unexposed produce, pred. conc. in sea fish underest. considers. spatial model slightly closer to mon. values compared with a-spatial.	No information found.	Intake fraction
EUSES	Emission module, distribution module (Mackay type level III, a sewage treatment plant, air distribution model, surface water dilution and sorption model, soil model.) and exposure	Minimum: molar mass, vapour pressure, log $K_{ow,}$ degradability, and solubility. Henry's law constant & BCF for fish (can be estimated)	consumer & worker scale: considers individual exposure local scale: no consideration to pop. density regional scale: uniform population density	Adopted after European Union legislation, not for: persistent, non-dissociating substances of intermediate lipophilicity	conservative; the release estimation (deviation 1-1000), biodegradation (deviation 0.1-100), the exposure scenario, workplace exposure (deviation 0.1-1000) Median: partition coefficients,	emission rates, degradation half-lives, and lack of data on advective inflow of contaminants in air, vapour pressure, water solubility & K_{ow}. Regional scale: fraction of people connected to sewage treatment plants and the regional area. Local scale: dilution factors and the number of inhabitants discharging into the one plant.	Human dose

Appendix 3
Summary of studied models

Model:	Type of model/ Model objective	Required input	population density	Limitations	Validation findings.	Parameters that pot. contribute to uncertainty/sensitivity	Model endpoint (relevant for this study)
	module. Assessing risks according to European legislation				BCFs. Optimistic: regional distribution model		