ISES Europe Training Series

DoE 3: Exposure Modelling

Module 3: Human Exposure Modelling for the General Population

Hello, everybody. This is module 3 of the domain of expertise 3, exposure modelling. This is part of the ISES Europe training series on exposure modelling that will be held by me and Wouter Franzmann. First of all, again some disclaimers and where we are. Module 3 is about human exposure modelling for the general population.

My name is Natalie von Goetz. I am working as a project leader at the Swiss Federal Office of Public Health, and also I am lecturing at ETH Zurich, the Federal Institute of Technology, where I was previously leading a group on human exposure modelling research. My education background is chemistry, and I have a PhD in natural sciences, where I already did some exposure modelling.

Again, some disclaimers. And now the learning objectives. By hearing this module, we want you to understand the principles and the context of exposure modelling, we want you to understand the formula and the necessary parameters, describe tiered approaches for the general population exposure modelling, and also be able to explain how exposure models can be validated by using human biomonitoring. The content of today is first some introductory words, then I will lead you from key factors for product exposure assessment to the assessment of overall exposure and some methods and the tiered approach. And then last but not least, uncertainty assessment and validation.

So let me start again by some definitions. We are talking today, well, I am talking today about the modelling for the general population. And this includes all exposures that are not workplace related. In module 2, you have heard from Wouter more about how to model occupational exposure. Now this module is all about non-occupational exposures, which come from environmental media and from consumer exposure. Sometimes the term general population exposure modelling is used to describe only environmental exposure. But here I am using it as a general term that includes both exposure from environmental sources and from consumer products. And there is also some confusion around the term environmental exposure because this is used both to describe human exposure from environmental media and on the other hand, exposure of environmental organisms. And therefore, it is also very important to explain what you mean and easiest would be if the term environmental exposure would not be used in the context of human exposure.

Then, since you have heard now a lot about occupational exposure, it is important to stress the differences. In worker exposure assessment, you have already quite a diversity of workplaces and also scenarios where the persons work in, but this is even more diverse for the general population. We have so many different ways of handling products that have to be taken into account in the

exposure assessment. Then a good thing is that exposure is normally at lower concentrations compared to the worker exposure because the dangerous substances should not be used in the context of consumer products. And then another feature, which you may have heard in the lecture on occupational exposure, that specifically inhalation and dermal exposure are very important.
For the consumer, on the other side, ingestion or oral exposure is much more important to look at because many of the substances that we are exposed to are, for example, contained in food. Therefore, different methods are being used for assessing general population exposure compared to occupational exposure and this is why we have two different modules in our domain of expertise on these two. And then also for general population, exposure modelling, at least in the past, was always more important because specific exposure monitoring is less often available than at the workplace.

So how do we start an exposure assessment? Risk assessment is normally about a single chemical substance. This has changed now a little bit, so that also mixtures are in the focus, but first of all, one has to focus on a single chemical substance. Therefore, also exposure assessment starts with single substance assessment, and we have several models that are available to do this. For example, we can do this with CONSEXPO or ECETOC-TRA, but also we have equations, mathematical equations that one can just use without any tool behind.

And the key factors to think about are then, first of all, how does my product look like? A consumer product is a sum of chemical substances. This is mostly not only one substance. The substances are tied together by chemical and physical forces. Products are meant for a specific use by specific people. And when we are doing risk assessment for a product, we have to select on what we want to focus because doing it for all the different substances is quite complex. There are several features on which we could focus first. One is the highest percentage in a product, highest toxicity or highest release rate. And then if you think of release from a product, for example, when you have consumer products like a carpet containing phthalates, which are only solved in the carpet, we have to think about how the substance is released and how easily it is released.

This depends obviously on the matrix, whether the product is a liquid like in pesticide solutions, shampoo, household cleaner, et cetera, or whether it is solid, for example, a pesticide, granules, furniture, or whether it is a polymer. And specifically for a polymer, we have different ways on how the substances can be tied into the polymer. We have, on the one hand, physical bonds only. For example, you have the plasticizers, which are introduced into a plastic to make it soft, and these are just solved into this otherwise solid product. But you also have the polymer themself, which is a substance that is tied together by chemical bonds and these bonds are much stronger. These are covalent bonds or hydrogen bridges and they are not so easily broken. Therefore, substances that are tied into a product by chemical bonding are much less frequently released.

And then the next consideration we have to make that normally we don't have only one product. We are still thinking of only one substance, but we have several products that could contain the substance. And there we have the direct sources like food, dust, cosmetics, textiles, among the most important direct sources. These can be taken up into the body by oral uptake or inhalation or dermal uptake, which are here denoted by the different colours. But originally, these are not planned to be in these indirect sources. If we are, for example, thinking of a contaminant like PFAS or dioxins or PCBs, they are normally not contained in the food. They come there from somewhere else. And these are then the indirect sources. And these can enter the food by processing, agriculture, packaging, but also from the environment, which is not mentioned here.

For dust, the indirect source or the primary source where it is primarily introduced by the manufacturing process could be furniture, carpets, cleaning chemicals, and these chemicals end then up in the dust. The same for cosmetics: These could be different primary sources, e.g. personal care products, sunscreens. And then also for textiles, we have to think on how the different components of the textile have been treated before becoming textiles. On the one hand, we have agriculture, for example, for cotton planting or textile finishing, so that we have a textile that is not eaten up by moths. Also, often we are using pesticides and preserving.

And now it is interesting to think about which substances are used in the different sources. We have the substance classes, additives, pesticides, migrating compounds, for example, for the processing. We have here biocides, flame retardants, et cetera, in furniture, carpets, preservatives in cosmetics, pesticides, biocides, et cetera, in agriculture. These are then the substance classes that we have to think of when we are thinking about what can be in our different products. And then to make it even a bit more interesting and complicated, we have these different substance classes in different sources. The pesticides cannot only be in food, they can also be in the textiles. And biocides often or at least sometimes the same substance as a pesticide. Then also the dust or other textile processing aids can contain biocides. And then, if it comes to cosmetics, the preservatives, these can also be sometimes the same substances as biocides. So all of these substance classes might have to be considered when we want to assess how high the exposure to a substance is altogether. And when we are doing this, when we are considering the exposure from multiple products, we are calling this aggregate exposure. I will come back to this in a minute.

I am now at chapter two, assessment of overall exposure, where I want to show you how we do this, how and with which equations we can assess the overall exposure. First of all, we need to think of the different levels of summing up exposure. Firstly, we have the different routes of exposure and we have one substance that can enter the body by oral exposure, by inhalation, and by ingestion. And then we have different sources of exposure that we have discussed just now, the different products, which could be consumer goods, food, environment, and so on, and which all have to consider for aggregate exposure. And then another step further would be a mixture assessment for different substances, but this would be one step further from the one substance assessment.

So on this basis, there are also different definitions that we have to keep in mind. Aggregate exposure is the exposure to one agent from different exposure sources. Here, one agent means one substance and different exposure sources by a different exposure pathways and/or exposure routes. But it doesn't mean that I'm taking always all sources into account. So one could say I'm aggregating exposure only for the food sector, then it would be an aggregate food exposure. We could also do an aggregate exposure over different cosmetic ingredients, but then we could also aggregate food and cosmetic exposure. And then we come to the second definition, which is total exposure. And this then relates to all routes and sources that are possible. So if all routes and sources really have been considered in the aggregate exposure assessment, then the aggregate exposure is equivalent to the total exposure. But oftentimes, our knowledge is not complete enough and total exposure can really only be assessed by human biomonitoring, which integrates the exposure over all pathways. And then the next step is that we can do a total or aggregate exposure for multiple chemicals or stressors and this is then called cumulative or combined exposure. Hence, looking more into the details of aggregate exposure, we have single substances, a single substance across multiple sources, multiple routes, multiple pathways. And the reason why we have a lot of

discussion at the moment about doing aggregate exposure also via different sectors, because normally for one legislation, say, for example, food, an aggregate assessment is only done in this specific sector. As an example EFSA, the European Food Safety Agency, oftentimes only does the aggregate exposure over all food sources. But this is a problem when it comes to the risk, because it obviously can be underestimated if all sources and routes are assessed separately. There are also quite some efforts at the moment to join occupational and non-occupational assessment, because these have oftentimes been conducted separately in the past. In the framework of the one substance, one assessment regulation that has just been accepted by the European Union, aggregate exposure assessment is more in the focus. Currently there is no harmonized methodology, but the different agencies on the European level are working on this.

In research, there are already some examples where aggregate exposure modelling has been done and it is also not a big problem to do in terms of methodology because all you have to do is you think of all the different products where the substance can be contained. You are thinking of all the different intake routes that can be concerned and then you are doing a calculation that involves the concentration of a substance in the source and the quantity of the substance that is taken up. You divide this by the bodyweight and multiply by an uptake fraction that accounts for the different uptake fractions. For example, when you have an uptake via skin or via inhalation, via skin you have a much lower uptake than by inhalation. I think you have heard this already in module two. And then the aggregate exposure is just the sum of all the different contributions of the different sources added up. And just a side note, an exposure pathway is defined by the combination of an exposure source with an intake route.

Now, this is quite some work to be done to think of all the different sources and routes and to combine them all and come up with parameters for all. Therefore, you have to consider whether it is really necessary to do an aggregate exposure. And obviously, it is more important to do an aggregate assessment when you have small contributions by many different products. But there you have then also the problem that if you have many products that have been assessed by a worst case approach, so a tier one approach, then you might end up with very unrealistic exposures. So here it is most important also to think of the methodology you have to use.

Therefore, I would like to give you a better overview now about the methods that can be used in exposure modelling and the tiered approach. You have to be very aware regarding the choice of methods, which key questions you want to answer and what the problem formulation is. So which population are you interested? Which endpoint, which hazard is the one you need to correlate your exposure with and these different things. And then also you have to consider which parameter values you have at hand and which modelling method is then suitable to be used with this database. Because these two have to match regarding complexity: If you have only very little data available, it doesn't make sense to use a very sophisticated modelling method, because the result will not be much better than with a less sophisticated method. So in the end, we also here

Therefore, in the end we depart from a tier one and this is an example here of a decision tree introduced by EFSA on how to decide whether you want to stop with your exposure assessment or what you can do to refine. So first of all, you are doing a tier one standard screening assessment with upper bound parameters, and then you look whether you exceed the acceptable level. If not, then it's the end of the assessment and the product or the substance is allowed on the market. If you exceed the acceptable level, then you have to look for the options of refinement of the assessment.

And there are several ones that I will not read out, you can read them later. And if then you have an adequate certainty of acceptable exposure or risk, then you can end your assessment. If not, you have to do another round or maybe you cannot allow this product on the market. And then these refinement, they are commonly referred to as tier 2 or tier 3 methods.

In exposure modeling, standard tiers are the deterministic assessment. This is also called sometimes the screening approach, where you're using point values for the exposure equation here. You would select then a very high concentration or the upper limit concentration in a product. You would combine this with an upper limit quantity that is taken up and then come up with an upper bound for the exposure estimate. If you have to do a more refined assessment, you can either do a probabilistic assessment, where you represent each parameter with a distribution instead of a point value, or you can also do an individual-based assessment, which includes co-exposure.

And I will give you now a small overview on these two methods, probabilistic assessment and individual-based assessment. A probabilistic modelling with the Monte Carlo approach has the following principle: You consider the equation that you want to model your dose with and for each of the parameters, you are selecting a probability distribution. Then the numerical method selects for each step one parameter value based on the probability that this parameter has in the distribution. And then in the next step, it does this again. So you see the cross is at a different place. It's a different parameter combination and we obviously then also have a different dose and you do this not only three times, like I have depicted here, but for example, ten thousand times, and then you have a more or less stable distribution for your dose.

You can choose different distribution types for your input distributions. Very often, for example, for concentrations, log-normal distributions are used. If you know less about a parameter, if you know, for example, only the most probable value, you can pick a triangular distribution. And if you know even less about a parameter, you only know the upper and the lower bound, and you don't know anything about how probable the parameter values are in between, you can choose a uniform distribution.

And then coming to the other method, which is individual-based exposure modelling, there you have data, behavioural data, for single individuals. So you know the quantity, for example, of a food that they take in. And then you can model for each of the individuals separately the exposure. And you can depict this either with the probability distribution to the left or with the cumulative distribution function to the right. The advantage over the Monte Carlo method or the probability distribution based method is that you can also consider the co-exposure to multiple products because it was shown that for some products you have a higher probability that they are used together. And this you cannot mirror with a separate distribution in the other method. For example, lipstick is used together with eyebrow pencil or something like this. Or noodles are often used together with ketchup.

One example I would like to give you for individual-based modelling is the PACEM model that is also available in a web-based version. Meanwhile, this has been developed by RIVM, also in collaboration with ETH. And here we had assessed the behavioural data of 516 individuals and put this all into a database and combine this with the substance information to yield a population aggregate exposure distribution. And how do these surveys look like? What you are most interested in is the frequency, how often do you use a shampoo, but also the amount, obviously.

And in this survey we used pictures, but you can also do this differently by weighing. For example, you weigh the shampoo before you use it and after, or you weigh the shampoo and then two weeks later you weigh it again and then you know how much the person has used in these last two weeks.

What you also can do very nicely with individual-based modelling or probabilistic modelling is that you can compare different substances here. This is one example for the bisphenols, BPA, BPF, and BPS. And if you want, you can then also combine this to a cumulative exposure assessment.

Now coming to some example models, tools for consumer exposure modelling, if you want to do it yourself. As said, you can always construct your own model, but there are also tools available that you can use, which makes it easier. There is guidance on exposure modelling in the Technical Guidance Document on Risk Assessment from the European Union and also the REACH guidance chapters. And there are models like ECETOC-TRA, CONSEXPO, and so on that can be used. In the introductory course, I have also said that in Schlueter et al. 2020, we have made an overview of existing models that can be used.

Then another important part is the selection of parameters for the consumer exposure modelling. And just to give you a bit an idea on where you could get these values from: For concentrations, for example, you could use total diet studies with representative sampling. You could, for cosmetics, use SCCS opinions, non-food sources national surveys, and always it is important to do some literature search. For the exposure quantities, behavioural surveys are important, and also the EPA Exposure Factors Handbook is a great resource, as well as the ExpoFacts database, the database for European data, which soon will be replaced by another more extensive database. Then for uptake fractions, there are in vitro models available where you can get some information, but oftentimes also conservative default values are used. For example, for skin uptake, for cosmetics, in case no in vitro studies are available, oftentimes 50% is being used. Regarding bodyweight, there are some legislations that have included a default value, like for the deterministic assessments by SCCS and also by EFSA.

This should have been a brief overview on how you can do exposure modelling. But for modelling, it is always very important to also assess the uncertainty around the modelling. Since we have to be generic, we have to consider many different possible scenarios, there's always also uncertainty. There's uncertainty in the model that we are using and also in the parameter selection. And it is clear that we cannot report ever the true value. But this is why we have to report always the uncertainty around the parameters or the model, hence the overall uncertainty involved in the exposure modelling.

And another thing that can be done also to test whether the exposure modelling is in the right order of magnitude, you can test the method with an alternative assessment method, which for source to dose modelling is the human biomonitoring. This comes then from a different side: with the source to dose modelling, you start with the model at the source, you are thinking about the concentrations of the substance in the source, and you are calculating how this ends up in the body. With the biomonitoring, you're doing it the other way around: You have concentrations in your body and by the help of a pharmacokinetic model, you are calculating what the total dose is, because neither the

blood nor the urine also gives you the correct value. For example, the urine concentration only refers to what is excreted. This is why you need a pharmacokinetic model to calculate from there the total dose.

And then you can make the comparison, like, for example, what has been done in the EFSA opinion on bisphenol A. There were exposure models that had been used for food and non-food, and there were high uncertainties, which was why two different scenarios were assessed, one average and one high internal exposure scenario. And this was then compared to biomonitoring. And you see that for the high internal exposures, there is a nice match between the different values, specifically for the toddlers, the children, and the women. But for the average internal exposure, one sees that the exposure calculation is still quite conservative. But it's the same order of magnitude, which proves that the source-to-dose modelling, here named the forward modelling, is more or less accurate.

In summary, aggregate exposure modelling is very important to consider, to reach a correct risk assessment, and there all routes and sources of exposure have to be considered. Oftentimes, an aggregate exposure spans several different legislations, which makes it difficult because they have different requirements, then it is important to keep in mind that for exposure modelling, a tiered approach is followed, as is frequently done in risk assessment, also in other areas of the risk assessment (that are not exposure science). And that validation of models is important, but oftentimes very difficult.

The next modules are environmental exposure modelling and validation. And with this, I would like to thank you for your participation and hope that you will also listen to the other modules of our domain of expertise in exposure modelling.