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New aspects in the assessment of skin exposure in the workplace

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Occupational exposure limits (OEL) for dangerous substances have yet been practically solely set for the inhalation of workroom air. Where studies have shown that dermal exposure may cause systemic effects, a skin notation is added as an alert to the OEL of the chemical. With the introduction of the EU REACH-directives, separate exposure limits were derived for dermal exposure such as the $DNEL_{dermal,\ local}$ or the $DNEL_{dermal,\ systemic}$. Has this new attention lead to new tools to assess dermal exposure in the workplace? This was discussed in the symposium, which was organized by the NVT-Section Occupational Toxicology and the Contact Group of Health and Chemistry (CGC). A summary of the symposium is given below. The presentations are available on the websites of the NVT (www.toxicologie.nl) and CGC (www.arbeidshygiene.nl).

SysDEA, systematic analysis of dermal exposure to hazardous chemical agents in the workplace: overview and experimental concept

Gudrun Walendzik, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA), Dortmund, Germany

The first speaker of the symposium was Gudrun Walendzik. In justifying the contribution of dermal exposure to toxic chemicals in the overall occupational health risk, she told that there is a high need to improve and standardise the assessment of occupational dermal exposure. The need arises from the facts that: dermal exposure monitoring methods are still not harmonized; studies on evaluating the significance and applicability of these methods are missing; the available methods do not take into account physical and chemical properties of the toxic substances; and there are no systematic studies available on comparing the quality and validity of the different methods. Hence, to meet partly these needs, the BAuA[3] is developing a new tool with the purpose to generate more data on dermal exposure in a reliable and consistent way: the SysDEA. The project is divided in five phases:

1) literature search on current dermal exposure measurement methods,
2) literature analysis and developing the experimental design,
3) measurements of potential dermal exposure in test rooms,
4) data analysis and evaluation, and
5) reporting and promoting SysDEA.

At the moment experiments are performed on dermal exposure in the test rooms. Walendzik expects that the final report will be finished in spring 2018.

Regarding phase 3, Walendzik explains that three techniques are used to sample the toxic substances: the interception (patches, gloves), removing (wiping, rinsing), and in-situ techniques (UV-fluorescence detection by video imaging). Quantification of dermal exposure is assessed by taking into account the type of substance, job tasks (dumping, pouring, rolling, surface spraying, handling immersed objects, handling contaminated objects), and ambient conditions (room temperature, humidity, atmospheric pressure, ventilation conditions). Furthermore, special test rooms were developed to be able to perform the exposure assessments under standardized conditions. Based on viscosity, three types of substances have been selected (high or low viscosity liquid, and a dusty solid). According to Walendzik, these test substances are not harmful for the volunteers. Unfortunately it is too early to show the results.

One of the meeting participants wonders whether individual differences between the volunteers will be taken into account, such as the length of the arms. Walendzik confirms that personal factors are partly taken into account. She also replies that TNO is developing software to take physical characteristics of the substances into account, such as the octanol-water partition coefficient. Another meeting participant asks why cleaning activities are not included in the job tasks. Walendzik explains that a maximum of five tasks could be chosen, and that the final choice is based on the most commonly reported tasks, and tasks which are mentioned in the REACH regulations.

Dermal exposure modelling

Jody Schinkel, TNO innovation for life, Zeist

Jody Schinkel summarizes that the first instruments on measuring dust and vapour in the air became available in the nineteen-fifties, whereas personal air sampling techniques became available in the nineteen-sixties. Also modelling techniques were developed as an alternative in measuring exposures at locations. Nowadays a variety of exposure models has been developed. Schinkel explains that dermal exposure may lead to a variety of local and systemic effects, and may induce infec-

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tion diseases when the skin is damaged during exposure. For low-volatile substances, dermal exposure is supposed to be the main route of exposure. In modelling dermal exposure, various generic models were developed, such as the BROWSE model (deterministic, for neurotoxic low-volatile pesticides, aggregated exposure, agriculture sector), ECETOC TRA (cumulative exposure), RISKOFDERM (ROD, partly based on the control-banding approach in COSHH essentials), BEAT (biocides, Bayesian integration), DREAM (conceptual and observational models), and the dermal Advanced REACH Tool (dART, will be online at the end of summer 2016, conceptual model, low-volatiles, comparing DNELs). The question is how well these models predict dermal exposure. Schinkel explains that this is not really known, due to limitations in model validation caused by limited availability of quantitative exposure data. At the moment TNO is validating the ECETOC TRA (dermal) model.

Various reasons may account for the difficulty in modelling dermal exposure, such as the complexity of the exposure process, the use of different sampling techniques, uncertainty on the most relevant exposure metric, use of protective measures, maximum loading of the skin, etc. Schinkel believes that reliable exposure modelling will become possible, by starting a conceptual framework of dermal exposure, linking all the initiatives which already have been introduced, using SysDEA, and by identifying knowledge and data gaps.

Schinkel continues with explaining the conceptual dART model for complex dermal exposure. A main difference between inhalation and dermal exposure is that there is only one source of inhalation exposure (the air), whereas various sources may be detected for dermal exposure (deposition, splashes/impaction, surface contact, etc). So all these sources need to be taken into account. To calibrate the model, a uniform collection of data is needed (SySDEA, contextual information), and data on DNELs for dermal exposure. The next steps will be the aggregation of the potential exposure (including inhalation, ingestion and dermal exposure), followed by assessing internal exposure (by internal-external exposure modelling using interactive PBPK models).

A participant comments that a DNEL for dermal exposure is actually in many cases based on data from oral exposure studies. So he questions the usefulness of DNELs in dermal exposure modelling. Another participant asks whether in the models a fourth source of dermal exposure is taken into account, namely direct penetration of vapour. Schinkel confirms this. Regarding questions on the most relevant sampling techniques, Schinkel emphasizes that it is very difficult to obtain consistent exposure results, since it is not clear what the best site on the body is to monitor dermal exposure.

How to measure dermal exposure? Experiences with the dermal assessment of VOCs

Jeroen Vanoirbeek, Centre for Environment and Health, Catholic University of Leuven, Belgium

Dermal exposure has often been perceived as being less relevant than inhalation exposure. Thus, dermal OELs are largely lacking, as well as validated analytical methods. However, there are cases in which the dermal pathway is at least as significant, *e.g.* the case of isocyanate-related occupational asthma. Figures from the US show that dermal illnesses are the largest category of non-fatal occupational diseases. The number of occupational diseases caused by skin absorption of chemicals is not known. Only recently, the WHO still concluded that there is currently no study design available to estimate dermal exposure in a wide range of circumstances, nor can a guide be provided to support selecting a proper method in specific cases.
While the previous presentation focused on modeling, Jeroen Vanoirbeek continued by presenting an overview of methods to measure dermal exposure. *Indirect* methods include sampling on surfaces other than human skin by means of wiping or tape-stripping, and human biomonitoring. The latter may be performed in blood, urine or - in order to estimate long-term exposure - hair. *Direct* methods include in-situ, removal, and interception techniques. A very illustrative method is video imaging. However, quantification is a challenge. Removal techniques include washing, wiping, or tape stripping of the exposed skin. Interception techniques catch the contaminants on alternative surfaces, such as gloves, patches, or coveralls. Detecting contaminants at the inside of gloves, or at patches placed under protective clothing, may provide information on the penetration of gloves or clothing by these contaminants. In addition, information may be collected on the deposited mass only (wiping, washing), on the deposited mass as well as the absorbed mass (tape stripping), or on the deposited, absorbed and - over time - desorbed mass (patches).

Vanoirbeek went on with describing experiments in which active charcoal patches were used to assess dermal uptake of benzene and toluene in a cohort of workers at a petrochemical plant. Both benzene and toluene were detected on the patches – and at very low concentrations in air – but it was concluded that the design of the patches needed to be improved to limit direct contact with the solvents. Further experiments at a shoe factory showed that these patches are a useful quantitative technique, although exposure appeared to be very low in this case.
Recently, experiments at the Catholic University of Leuven have been performed in order to develop a suitable quantitative method along with air sampling and biomonitoring, to assess the exposure concentrations of a range of 180 volatile organic compounds (VOC). A novel patch type (Permea-Tec) was used, which combined an active charcoal absorbing part with a qualitative colorimetric indicative patch. The colorimetric detection appeared not to be

useful, as it proved to be very insensitive. After extracting the charcoal part, quantitative GC-FID analysis was carried out. According the desorption efficiency (DE) from the patch, three groups of compounds were distinguished: apolar VOC with a constant DE approaching 100%, polar VOC with a constant DE ranging from 70 to 90%, and VOC with a concentration-dependent DE. Altogether, it was concluded that the results were very promising. Although additional testing is needed, the method may be useful to evaluate dermal exposure to 180 different VOC. Further research is needed on its limit of detection, precision, and storage stability, as well as the patch's validation in field studies. Regarding the latter, a first field study was performed at a chemical plant in which VOC were used for cleaning. Again, the colorimetric part showed a low sensitivity. Further results will be presented at the OEESC-conference in Manchester later this year. Additionally, studies will be set up on dermal exposure to isocyanates, using a different type of patch.

After a question from the audience it was concluded that there is not one 'best' dermal exposure metric. *E.g.*, one should take exposure duration into account, instead of simply taking the full dose on a specific patch surface. Biomonitoring may remain an alternative to get a picture of the 'total dose'. However, biomonitoring is rather complicated as kinetics and metabolism of the substance in question should be known in detail. Finally, it was remarked that variations in humidity and temperature may affect the performance of the patch, and that validation on these aspects is on its way.

Dermal occupational exposure limits: their use in risk assessment

Peter Bos, RIVM, Bilthoven

The discussion on developing dermal exposure limits (DOELs) has been going on for about 30 years now. Many factors determine dermal uptake of chemicals. Three phases are involved: penetration into the skin, permeation trough the skin, and resorption into tissues or blood. Two measures for the dermal absorption are the flux or permeation rate, which is seldom available, and the absorbed fraction. Factors affecting dermal absorption (-rate) include molecular weight (< 500 D or g/mol), exposed skin surface area, skin integrity, exposure duration, formulation of the substance, temperature, humidity, occlusion, and the log K_{ow} of the substance. Generally, substances with a log K_{ow} between -1 and 4 are regarded as penetrating, with a peak at log K_{ow} 1-2.

In 2001, the Health Council of the Netherlands evaluated several options for developing dermal exposure standards, such as DOELs or biological limit values (BLVs), and qualitative 'skin notations'. Currently, the 'skin notation' in the Netherlands is assigned to substances which contribute for more than 10% to the total body burden, at an exposure duration of 1 hour of a specific surface area.

First attempts to develop a concept for the derivation of DOELs were done in 1998. DOELs may be set at an internal exposure level (BLVs), the level on the skin surface, or the level on other surfaces in the workplace. Unfortunately, dermal toxicity studies are rarely available. Alternatively, DOELs may be based on a maximum internal dose which is derived from data on other (*e.g.*, oral) exposure routes. One of the challenges in extrapolating the data is the fact that the relative dermal uptake may decrease with increasing external dose on the skin: a too high dose on the skin cannot be absorbed in a limited time period. If the flux is known, the internal dose after skin absorption depends on the maximal flux, exposure duration, and exposed surface area. Thus, for a given time period (*e.g.*, 8 hours), the DOEL may be expressed as a 'maximum allowable exposed skin surface area'. If the flux is not known, a DOEL may be derived from a substance's absorption percentage, which in turn depends on the dermal dose per unit area. For estimating the dermal absorption percentage, a tiered approach is used: the default is set at 100%. If the molecular weight is less than 500 D, or the log K_{ow} is < -1 or > 4, the absorption percentage is set at 10%.

Within the framework of REACH, dermal DNELs are set for both systemic and local effects. Specific guidance on how to derive these DNELs, *e.g.*, on which safety factors to use, is available at the website of the ECHA. The European Scientific Committee on Occupational Exposure Limits (SCOEL) has developed guidance on deriving qualitative standards ('skin notation') as well as BLVs. Finally, ECETOC has developed guidance on the evaluation of systemic health effects following dermal exposure, using a stepwise approach: derivation of a health-based reference value, initial risk assessment, and refined risk assessment. In the initial assessment a default of 100% absorption is used, while in the refined assessment more detailed data on exposure, absorption and biomonitoring data are generated. Again, the 'skin notation' approach is used as a risk management tool.

In conclusion, Bos stated that dermal exposure can be a relevant route, but risk assessment is still challenging, which is partly due to the many factors determining dermal absorption. Qualitative approaches (skin notations) are still frequently used. Quantitative approaches (DOELs, DNELs or BLVs) are often based on toxicological information from other routes of exposure. This leaves us with uncertainties about the relevance of 'first pass effects', rate of entry, exposure scenarios, and relevant dose metrics.

General Discussion

Frans Jongeneelen

In the general discussion several questions were proposed to the participants. One was the question who in the public is assessing or had assessed dermal exposure in the workplace, and what methods were used for the assessment. Examples of the participants were the use of

wearing a second glove for substance sampling, and the use of a fluorescent agent in paints to raise awareness among painters.

Another question was what the road is that lays ahead for quantitative dermal exposure assessment: how will colleagues in 2040 cope with dermal exposure? The most likely scenario according to some participants is that dermal exposure models will still be used by that time, because of existing regulations. However, regarding these models, these must be optimized by bringing forth more data and by improving measurement techniques. Furthermore, it should be clearly defined what is actually meant by dermal exposure, for instance internal or external dermal exposure.

The next question was whether it is too early for a guideline for workers' dermal exposure assessment (EN 689-like)? Most participants agreed that indeed it is too early for such a guideline.

The last issues was a statement 'The worker $DNEL_{dermal,local}$ and $DNEL_{dermal,systemic}$ make dermal risk assessment for the industrial hygienists easier'. Some participants replied that it could be helpful, but only when high quality and validated methods are available, and these are not. Also there was doubt whether the $DNEL_{dermal,systemic}$ was of relevance in case of high volatile substances. However, there was an agreement that DNELs can be valuable in the overall risk communication to the workers. Some participants argue that the value of a DNEL is a rather academic discussion, and that in practice, in the workplace, workers are better off with a skin notation.