A Comparison of REACH-Derived No-Effect Levels for Workers With EU Indicative Occupational Exposure Limit Values and National Limit Values in Finland

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ABSTRACT

The purpose of occupational exposure limit values (OELs) is to regulate exposure to chemicals and minimize the risk of health effects at work. National authorities are responsible for the setting and updating of national OELs. In addition, the EU sets indicative occupational exposure limit values (IOELVs), which have to be considered by the Member States. Under the new European legislation on chemicals (REACH), manufacturers and importers are obliged to establish derived no-effect levels (DNELs) for chemicals that are manufactured or imported in quantities >10 tonnes per year. Chemical safety data sheets must report both OELs and the DNEL values, if such have been set. This may cause confusion at workplaces, especially if the values differ from each other. In this study, we explored how EU IOELVs and Finnish national OELs [Haitallisiksi tunnetut pitoisuudet (HTP) values] correlate with worker inhalation DNELs for substances registered under REACH. The long-term DNEL value for workers (inhalation) was identical to the corresponding IOELV for the majority of the substances (64/87 cases). Comparison of DNELs with HTP values revealed that the values were identical or close to each other in 159 cases (49%), whereas the DNEL was considerably higher in 69 cases, and considerably lower in 87 cases. Examples of cases with high differences between Finnish national OELs and DNELs are given. However, as the DNELs were not systematically lower than the OELs, the default assessment factors suggested by REACH technical guidance had obviously not been used in many of the REACH registrations.

KEYWORDS: derived no-effect level; DNEL; occupational exposure limit values; OEL; REACH

INTRODUCTION

The purpose of occupational exposure limit values (OELs) is to regulate exposure to chemicals and thereby minimize the risk of health effects caused by chemicals at the workplace. Currently, different national authorities are responsible for the setting and updating of OELs in most industrial countries (Nielsen and Ovrebo, 2008; Ding et al., 2011). OELs are usually given as the time-weighted average (TWA) for 8 h and a 40-h work week. In addition, a 15-min value may be set as short-term exposure limit (STEL), for example, in the case of substances with irritating or narcotic effects. Ceiling limit values are exposure concentrations that should not be exceeded, even during...
very short exposure times (Nielsen and Ovrebo, 2008; SCOEL, 2009a; ACGIH, 2014).

In the EU, indicative occupational exposure limit values (IOELVs) have been given since 1991. The values are recommended by the Scientific Committee on Occupational Exposure Limits (SCOEL), agreed by Member States and adopted by the EC. They are health based and describe the air concentration of a chemical to which repeated and regular exposure throughout a worker’s working life does not cause harmful health effects. Values are given for 8 h or 15 min and are only given for substances whose threshold level of effects can be identified (SCOEL, 2009a). Each Member State of the EU has to take the IOELVs into consideration when setting their national limit values (EC, 1998). In addition to the IOELVs, a few substances also have binding occupational exposure limit values (BOELVs). BOELVs have to be applied as such or even more strictly in the Member States (EC, 1998). They are not only health based, but also socioeconomic and other aspects are taken into consideration when setting the values.

In Finland, the Ministry of Social Affairs and Health biennially confirms a list of Finnish OELs, called ‘concentrations of impurities in workplace air known to be hazardous’ [Haitallisiksi tunnetut pitoisuudet (HTP) values]. The criteria documents for the substances are prepared by experts from the Finnish Institute of Occupational Health and from the Ministry of Social Affairs and Health. The experts propose health-based values, which are calculated on a case by case basis, meaning that no fixed uncertainty/assessment factors have been set. There are not either any fixed acceptable risk levels for non-threshold substances (e.g. genotoxic carcinogens). The final decision on which value to propose for the Ministry is taken by a tripartite group, meaning in practice that usually the health-based values proposed by the experts are adopted as such, but socioeconomic issues may, in certain cases, have an impact on the HTP values. Currently, 562 chemicals or groups of chemicals have these values. They are intended to be taken into account when assessing the quality of workplace air, employees’ exposure, and the significance of the results of exposure measurements at Finnish workplaces, but compliance with the values is not a specific legal requirement. Susceptible subgroups such as atopic people or those with chronic diseases have not generally been taken into account when setting the Finnish HTP values. Until the middle of the 1980s, the values very often based acute effects following inhalation (e.g. respiratory tract irritation). For example, carcinogenic properties have only systematically been taken into account as critical endpoints for HTP values since 1987. Compared to many other countries, the number of substances on the HTP list is relatively high (Schenk et al., 2008a).

Under the EU legislation on chemicals (REACH), manufacturers and importers are obliged to establish derived no-effect levels (DNELs) for all chemicals that are manufactured or imported in quantities >10 tonnes per year (EC, 2006b). This means that DNELs will be available for an enormous amount of substances, for which no EU or national OELs have been set. As regards OELs, the DNELs can be calculated on the basis of human or animal health hazard data. The European Chemicals Agency (ECHA) has published detailed guidance on how to derive DNEL values. A preferred approach is to base the calculations on the identification of no observed adverse effect levels (NOAELs), which are then converted to DNELs by applying different assessment factors, depending on the type and quality of the study reports. Also other starting points such as lowest-observed-adverse-effect level or benchmark doses can be utilized (ECHA, 2012). DNELs are given for workers and the general population, for acute and/or long-term exposure via inhalation, oral and/or dermal routes (EC, 2006b). DNEL values describe the exposure concentrations below which there should be no health risks. In the REACH registration of substances classified for their health effects, the registrants have to report all uses in exposure scenarios and have to demonstrate that the exposures are below the DNEL concentrations in the specific scenarios (EC, 2006b).

Safety data sheets, which are distributed when selling a chemical, have to report both the OEL and DNEL values, if such have been set (EC, 2010). It has been acknowledged that confusion may occur at workplaces if the safety data sheet presents national OELs and DNEL values that differ from each other (RPA, 2012), as it is not very clear for the workplaces what is the difference between the two types of values.

Although the idea behind the derivation of the OELs and DNELs is quite similar, differences in values may still exist. This was indicated in the paper of Nies et al. (2013), who checked the correlation
between German OELs and DNEL values and also briefly presented data on EU IOELVs versus DNELs. These may derive from either the selection of critical study and NOAEL or differences between the calculations of the OEL/DNEL from the same NOAEL. ECHA guidance has defined the assessment factors that should preferably be used, unless the registrant can justify the use of substance-specific assessment factors (ECHA, 2012). Most national authorities and the SCOEL have no default assessment factors for OELs. Where the need for assessment factors is identified they are set case by case using the expert judgement of an independent scientific committee (Nielsen and Ovrebø, 2008). Schenk and Johanson (2010) analysed 62 SCOEL summary documents published in 1991–2003, which presented recommendations for 75 IOELVs. No explicit uncertainty factor was stated for 31 of the IOELVs. A large variation in uncertainty factors was seen in the documents stating such values, the factors ranging between 1 and 50. When compared with the default assessment factors given in REACH technical guidance, the factors used by SCOEL were generally significantly lower (Schenk and Johanson, 2011).

For the setting of DNEL values, ECHA guidance offers the opportunity to use the IOELV as a DNEL for the exposure route and duration for which the IOELV has been given, unless new scientific data show that the IOELV is not valid as a DNEL. The ECHA guidance also makes clear that national OELs can be used as worker inhalation DNELs where the toxicological information and evaluation of health effects used for setting the national OEL are documented and available. (ECHA, 2012). However, currently only 121 substances/groups of substances have IOELVs. The numbers of national OELs varies markedly between different EU countries, being probably between 300 and 600 (Schenk et al. 2008a,b).

The aim of the current study was to obtain an understanding of how the EU IOELVs (EC, 2000, 2006a, 2009) and Finnish national OELs (HTP values) (STM, 2014) correlate with the worker inhalation DNELs of substances registered under REACH and to obtain an overview of the similarities and differences. Aspects related to DNEL values for the general population are not included in this paper. Throughout the paper, ‘DNEL’ refers to worker DNEL values for inhalation exposure.  

### METHODS

The first step of the study involved searching for REACH registration information on the ECHA dissemination website (http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances) by CAS number for all substances on the Finnish HTP list (n = 560). The original searches were performed in January 2012.

For the comparison of DNEL values with IOELVs, we checked whether the registered worker long-term and short-term DNELs were identical to the respective 8-h TWA IOELVs and 15-min STEL values. A DNEL value of 95–105% of the IOELV was considered identical to the IOELV. If one substance was given two different DNELs in two or more separate registrations, and at least one of those was different from the IOELV, then the substance was assigned into the category ‘different from IOELV’. All DNEL values for substances included at the IOELV list were re-checked upon submission of this paper (May 2014).

The substances for which long-term worker inhalation DNEL values were found were listed and the values were compared with the 8-h HTP values. The substances were thereafter grouped into three categories: DNEL similar to HTP, DNEL significantly higher, or DNEL significantly lower than the HTP value. A 1.9-fold or larger difference was selected as the criteria for significant difference. Substances with a <1.9-fold lower or higher DNEL value than the HTP value were classified as similar to the HTP value. A similar comparison was made for short-term DNELs and 15-min STEL values. It should be noted that acute DNELs are not necessarily calculated for 15-min exposure, although it is stated in the ECHA guidance that this is the most usual time length (ECHA, 2012). In cases where a substance had DNEL values for local, as well as for systemic long-term effects, the lower one of the values was selected for the comparison. The same applied for short-term DNELs as well.

A few of the substances whose DNEL and HTP values were significantly different, and which are common in occupational settings in Finland, were selected for further examination of their critical effects and justifications for the values. The information related to the DNEL values was obtained from the dossier information publicly available on the ECHA website, and the HTP value data from the criteria documents.
prepared for each HTP value (www.tyosuojelu.fi; only in Finnish).

RESULTS

Comparison of DNEL values with EU IOELVs

The current lists of IOELVs contain 115 substances identified by their CAS number. In addition, six groups of substances have no specified CAS numbers (EC, 2000, 2006a, 2009). In order to be able to compare the DNELs with the IOELVs, only those substances for which a CAS number was listed \((n = 115)\) were selected for the study. According to the ECHA dissemination site, 97 of these substances were registered (accessed 14 May 2014). For seven of the substances, no DNEL value was given (probably due to low tonnage band or the fact that they were registered as intermediates, when no DNEL is required), which means that 90 substances were selected for the final comparison between IOELVs and DNELs.

Eighty-seven out of 90 substances had either only an 8-h TWA IOELV or an 8-h value and 15-min STEL value. Three of the substances included in the IOELV list (chlorine, hydrogen bromide, and nitric acid) had a STEL value only and no 8-h value. For these, the STEL value was registered as an acute DNEL value for inhalation. In addition, these substances were also given long-term DNELs in the REACH registration.

The results presented in Fig. 1 show that for the majority of the registered substances (64 of the 87 substances; 73.6%) that have an 8-h TWA IOELV, the long-term DNEL value for workers (inhalation) was identical to the IOELV. Only for 18 of the 87 substances (20.78%) were the registered DNELs lower than the IOELVs. The largest differences between the long-term DNEL and the 8-h IOELV were seen for 2-ethoxyethanol, cresol, and 5-methylheptan-3-one, for which the long-term worker DNEL values were very low, only 1, 4, and 5% of the 8-h IOELVs, respectively. The substances with DNEL values lower than the IOELV are presented in Table 1. Among the registered substances, five cases (5.7%) showed DNEL values that were significantly higher than the respective IOELVs. The largest difference was seen for oxalic acid (4-fold difference). Table 2 shows all substances with DNELs higher than the corresponding IOELV.

EU STEL values have been set for 61 substances, and 54 of these substances were registered under REACH by the end of February 2013. Short-term DNEL values were given for 41 of the substances, meaning that no short-term DNEL was registered in 13 out of 54 cases, although the substances have EU STEL values. In some cases, this was explained by the fact that the substances were registered as intermediates, for which DNELs are not necessary. However, in most cases, the reason for not giving a short-term DNEL remained unclear, although the substances often had a classification for acute effects. Most likely, no threshold levels for short-term effects were identified, and therefore it was not possible to derive DNELs. Furthermore, if it can be shown that there is no potential for peak exposures, acute DNELs are not required. Comparison of short-term exposure DNELs with EU STEL values revealed that, in the majority of the registrations, the short-term DNEL was identical to the STEL (29/41 cases; 70.7%) (Fig. 2). Of the remaining substances, eight were given a short-term DNEL lower than the corresponding STEL (Table 3). As shown in Table 3, two registrations have been made for some of these substances, and different short-term DNELs were given. In four cases, the DNEL was higher than the STEL (Table 4).

We observed some cases of recent updates of the DNEL values. In these cases, the DNELs were originally higher than the IOELVs but are now identical with the IOELVs (e.g. cyclohexanone, which first upon registration had a long-term DNEL of 80 mg m\(^{-3}\), but now a DNEL of 40 mg m\(^{-3}\)). Furthermore, we found some cases where substances were first registered without any DNEL, but recently the dossiers have been updated and DNEL values included (e.g. cyanamide).
Comparison of DNEL values with Finnish HTP values

The newest version of the OEL list for Finland (HTP values) contains 562 substances or groups of substances (STM, 2014). When this part of the study was carried out, 392 of these substances (based on CAS number) had been registered under REACH (ECHA dissemination site, accessed 31 January 2012). In the registrations,

### Table 1. Substances with a long-term DNEL value lower than the 8-h IOELV

<table>
<thead>
<tr>
<th>Substance</th>
<th>CAS number</th>
<th>IOELV (TWA 8 h) mg m(^{-3})</th>
<th>DNEL (workers, long-term exposure) mg m(^{-3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium dihydroxide</td>
<td>1305-62-0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Chloroform</td>
<td>67-66-3</td>
<td>10</td>
<td>2.5</td>
</tr>
<tr>
<td>Cresol</td>
<td>1319-77-3</td>
<td>22</td>
<td>0.9</td>
</tr>
<tr>
<td>Cyanamide</td>
<td>420-04-2</td>
<td>1</td>
<td>0.35</td>
</tr>
<tr>
<td>1,2-Dichlorobenzene</td>
<td>95-50-1</td>
<td>122</td>
<td>10</td>
</tr>
<tr>
<td>1,4-Dichlorobenzene</td>
<td>106-46-7</td>
<td>120</td>
<td>46.1</td>
</tr>
<tr>
<td>Dimethylamine</td>
<td>124-40-3</td>
<td>3.8</td>
<td>1.027</td>
</tr>
<tr>
<td>(\varepsilon)-Caprolactam</td>
<td>105-60-2</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2-Ethoxyethanol</td>
<td>110-80-5</td>
<td>8</td>
<td>0.083</td>
</tr>
<tr>
<td>Ethylene glycol (ethane-1,2-diol)</td>
<td>107-21-1</td>
<td>52</td>
<td>35</td>
</tr>
<tr>
<td>Isopentyl acetate</td>
<td>123-92-2</td>
<td>270</td>
<td>20.8</td>
</tr>
<tr>
<td>5-Methylheptan-3-one</td>
<td>541-85-5</td>
<td>53</td>
<td>2.9</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>91-20-3</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>98-95-3</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>Phosphorus pentachloride</td>
<td>10026-13-8</td>
<td>1</td>
<td>0.87</td>
</tr>
<tr>
<td>Pyridine</td>
<td>110-86-1</td>
<td>15</td>
<td>2.5</td>
</tr>
<tr>
<td>Resorcinol</td>
<td>108-46-3</td>
<td>45</td>
<td>5.6</td>
</tr>
<tr>
<td>Xylene</td>
<td>1330-20-7</td>
<td>221</td>
<td>77</td>
</tr>
</tbody>
</table>

\(a\) Data source: ECHA dissemination site, accessed 14 May 2014.

### Table 2. Substances with a long-term DNEL value higher than the 8-h IOELV

<table>
<thead>
<tr>
<th>Substance</th>
<th>CAS number</th>
<th>IOELV (TWA 8 h) mg m(^{-3})</th>
<th>DNEL (workers, long-term exposure) mg m(^{-3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Aminoethanol</td>
<td>141-43-5</td>
<td>2.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>108-90-7</td>
<td>23</td>
<td>23/42.3(^b)</td>
</tr>
<tr>
<td>Heptan-2-one</td>
<td>110-43-0</td>
<td>238</td>
<td>394</td>
</tr>
<tr>
<td>Orthophosphoric acid</td>
<td>7664-38-2</td>
<td>1</td>
<td>1/2.92(^b)</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td>144-62-7</td>
<td>1</td>
<td>4.03</td>
</tr>
</tbody>
</table>

\(a\) Data source: ECHA dissemination site, accessed 14 May 2014.

\(b\) Two registrations giving different DNELs.
long-term DNEL values for workers (inhalation) had been proposed for 308 of the substances. As shown in Fig. 3, the HTP and DNEL values were identical or close to each other in 152 cases (49%), whereas they differed from each other in 156 cases (51%). A closer look at the substances with differing limit values showed that the HTP value was higher than the DNEL in 56% of the cases (87/156). In 69 of the 156 cases, the DNEL values were at least 1.9 times higher than the corresponding HTP values (Fig. 3). The substances with the largest differences between DNEL and HTP values are presented in Tables 5 and 6.

In the analysis of the data, 32 substances with a long-term DNEL value but no 8-h HTP value were identified. In addition, six substances had 8-h HTP values, but only acute and no long-term DNEL values.

Among the 308 substances for which data were collected, 23 cases were identified as substances with more than one DNEL value for worker exposure via the inhalation route. The values were either given within the same registration dossier or in more than one dossier.

### Table 3. Substances with a short-term DNEL value lower than the EU STEL

<table>
<thead>
<tr>
<th>Substance</th>
<th>CAS number</th>
<th>STEL (15 min) mg m⁻³</th>
<th>DNEL (workers, short-term exposure) mg m⁻³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia, anhydrous</td>
<td>7664-41-7</td>
<td>36</td>
<td>16/36&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cumene</td>
<td>98-82-8</td>
<td>250</td>
<td>100/250&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1,2-Dichlorobenzene</td>
<td>95-50-1</td>
<td>306</td>
<td>10</td>
</tr>
<tr>
<td>ε-Caprolactam</td>
<td>105-60-2</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Ethylbenzene</td>
<td>100-41-4</td>
<td>884</td>
<td>293/884&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5-Methylheptan-3-one</td>
<td>541-85-5</td>
<td>107</td>
<td>53</td>
</tr>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>127-19-5</td>
<td>72</td>
<td>36</td>
</tr>
<tr>
<td>Xylene</td>
<td>1330-20-7</td>
<td>442</td>
<td>289</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data source: ECHA dissemination site, accessed 14 May 2014.

<sup>b</sup>Two registrations giving different DNELs.

### Table 4. Substances with a short-term DNEL value higher than the EU STEL

<table>
<thead>
<tr>
<th>Substance</th>
<th>CAS number</th>
<th>STEL (15 min) mg m⁻³</th>
<th>DNEL (workers, short-term exposure) mg m⁻³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorobenzene</td>
<td>108-90-7</td>
<td>70</td>
<td>70/94&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>108-94-1</td>
<td>81.6</td>
<td>80/100&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dimethylamine</td>
<td>124-40-3</td>
<td>9.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Heptan-2-one</td>
<td>110-43-0</td>
<td>475</td>
<td>1516</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data source: ECHA dissemination site, accessed 14 May 2014.

<sup>b</sup>Two registrations giving different DNELs.
The years when the current HTP values were first given are included in Tables 5–7. We observed a general trend, showing that the HTP values given decades ago are in many cases markedly higher than the DNELs (Table 5). However, this is not the situation for all substances and some HTP values that are fairly new, such as the HTP values for 1,3-dioxolane and 4,4′-methylene-bis[2-chloroaniline] (given in STM, 2014), were also significantly higher than the DNELs.

The 23 substances listed in Table 7 were selected for further examination of the data and approaches used to derive the DNELs and HTP values. All substances selected for this part of the study were considered as interesting from an occupational exposure perspective in Finland, but no systematic criteria were applied for the selection of the substances to be examined. The information on the most sensitive endpoints and assessment factors were collected from the ECHA dissemination website, and the justifications for the HTP values were obtained from the HTP value background documents (Table 7).

As shown in Table 7, the overall assessment factor in the setting of DNELs was often 1, which might indicate that the DNELs were probably derived on the basis of human data. However, in practice, it may also be an indication of the registrant using an OEL or some other means to develop a DNEL (e.g. physiologically based pharmacokinetic modelling). In our study, we also found some examples of the use of higher assessment factors. The highest overall assessment factor reported for substances examined in this study was 25 (Table 7), which was applied in the DNEL derivation for turpentine, based on repeated dose toxicity. The DNEL set for turpentine (local effects after repeated exposure) was 0.77 mg m⁻³, which is significantly lower than the Finnish HTP value of 140 mg m⁻³. The reason for the low DNEL remains, however, still very unclear since the lowest NOAEL presented in the registration dossier was 25 ppm (140 mg m⁻³). Most likely also other factors, e.g. for allometric scaling, have been applied and presented in those sections of the registration dossiers which are not publicly available.

In some of the cases, the DNELs and HTP values differed from each other because the values were based on different critical endpoints or critical studies. For example, in the case of cobalt and its inorganic substances, repeated dose toxicity was selected as a critical endpoint for the worker inhalation DNEL, whereas the HTP value was based on irritation, observed in humans.

When looking at the dossiers and the DNEL values of two groups of substances, namely cadmium and cobalt and their inorganic compounds, it was clear that read-across approaches had been adopted for the setting of DNELs for individual compounds. However, cadmium and cadmium compounds were all given 0.004 mg m⁻³ as long-term DNEL values. Although it is not mentioned on the ECHA dissemination websites for these substances, it can be assumed that the values are given as corresponding to cadmium (mg cadmium m⁻³) and not as the concentrations of the substances as such. On the other hand, the different cobalt compounds were given DNEL values between 0.05 and 0.10 mg m⁻³ (Table 7). We calculated that each of these concentrations corresponds to 0.04 mg cobalt m⁻³, which is also the DNEL for cobalt metal.

**DISCUSSION**

In this study, we compared the DNEL values of substances registered under REACH with their EU IOELVs and Finnish HTP values, in order to see whether the values differ. Under REACH registration, deadlines vary depending on the quantities manufactured or imported. At the moment (June 2014), the registration deadline has passed for companies manufacturing or importing substances in volumes of ≥100 tonnes per year, as well as substances classified as carcinogenic, mutagenic or toxic for reproduction Categories 1 or 2 and which may cause long-term effects in the aquatic environment (EC, 2006b, 2008). The ECHA database on registered substances contains now information on ~12 500 unique substances (ECHA website http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances, accessed 17 June 2014). EU IOELVs and national...
OELs have mainly been given for high production volume chemicals and chemicals causing serious health effects. Therefore, almost all substances with an IOELV or a national OEL are already registered. The majority of substances on the Finnish HTP value list have also been registered.

In a recent paper (Nies et al., 2013), DNEL values were compared with IOELVs and German limit values. The authors concluded that in mid-2012, 75% of the DNELs corresponded to the IOELVs. Now in 2014, after the second REACH registration deadline has passed, the situation is very much the same. According to our results, 73.6% of the registered long-term DNEL values were identical with the 8-h IOELVs. The differences between the results of the two studies are, most likely, mainly due to the fact that we included only the CAS numbers.

### Table 5. Substances with largest differences (>10-fold) between DNELs and Finnish HTP values: DNEL lower than the HTP value

<table>
<thead>
<tr>
<th>Substance</th>
<th>CAS number</th>
<th>HTP (8 h) mg m⁻³</th>
<th>Year of HTP</th>
<th>DNEL (workers, long-term exposure) mg m⁻³</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Chlorotoluene</td>
<td>95-49-8</td>
<td>260</td>
<td>1981</td>
<td>3.52</td>
</tr>
<tr>
<td>Cresol</td>
<td>1319-77-3</td>
<td>22</td>
<td>1972</td>
<td>0.9</td>
</tr>
<tr>
<td>m-Cresol</td>
<td>108-39-4</td>
<td>22</td>
<td>1972</td>
<td>0.9</td>
</tr>
<tr>
<td>o-Cresol</td>
<td>95-48-7</td>
<td>22</td>
<td>1972</td>
<td>0.9</td>
</tr>
<tr>
<td>p-Cresol</td>
<td>106-44-5</td>
<td>22</td>
<td>1972</td>
<td>0.9</td>
</tr>
<tr>
<td>1,2-Dibromoethane</td>
<td>106-93-4</td>
<td>0.78</td>
<td>1998</td>
<td>0.0005</td>
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<tr>
<td>Dimethoxymethane</td>
<td>109-87-5</td>
<td>3200</td>
<td>1972</td>
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<tr>
<td>1,3-Dioxolane</td>
<td>646-06-0</td>
<td>310</td>
<td>2009</td>
<td>19</td>
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<td>Disulfiram</td>
<td>97-77-8</td>
<td>2</td>
<td>1981</td>
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<td>Diuron</td>
<td>330-54-1</td>
<td>10</td>
<td>1981</td>
<td>0.17</td>
</tr>
<tr>
<td>2-Ethylhexyl lactate</td>
<td>6283-86-9</td>
<td>42</td>
<td>2000</td>
<td>0.63</td>
</tr>
<tr>
<td>Formamide</td>
<td>75-12-7</td>
<td>19</td>
<td>1998</td>
<td>0.66</td>
</tr>
<tr>
<td>Glycidol (2,3-Epoxypropan-1-ol)</td>
<td>556-52-5</td>
<td>6.1</td>
<td>2000</td>
<td>0.145</td>
</tr>
<tr>
<td>Graphite</td>
<td>7782-42-5</td>
<td>2</td>
<td>2007</td>
<td>0.01/1.2b</td>
</tr>
<tr>
<td>4,4’-Methylenebis [2-chloroaniline]</td>
<td>101-14-4</td>
<td>0.11</td>
<td>2009</td>
<td>0.000776</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>98-95-3</td>
<td>1</td>
<td>2005</td>
<td>0.07</td>
</tr>
<tr>
<td>1-Nitropropane</td>
<td>108-03-2</td>
<td>92</td>
<td>1972</td>
<td>3.6</td>
</tr>
<tr>
<td>2-Phenoxyethanol</td>
<td>122-99-6</td>
<td>110</td>
<td>2002</td>
<td>8.07/3.84b</td>
</tr>
<tr>
<td>Pyrocatechol</td>
<td>120-80-9</td>
<td>22</td>
<td>1981</td>
<td>1</td>
</tr>
<tr>
<td>1,2,3-Trichloropropane</td>
<td>96-18-4</td>
<td>18</td>
<td>1981</td>
<td>0.007964</td>
</tr>
<tr>
<td>Tetraethyllead</td>
<td>78-00-2</td>
<td>0.075</td>
<td>1972</td>
<td>0.00058</td>
</tr>
<tr>
<td>Turpentine, oil</td>
<td>8006-64-2</td>
<td>140</td>
<td>2005</td>
<td>0.77/5.98b</td>
</tr>
</tbody>
</table>


Two registrations giving different DNELs.
numbers mentioned at the IOELV list, whereas Nies 
et al. (2013) included also those chemicals mentioned 
at a group level, without CAS numbers, in the IOELV 
list [such as 'Fluorides (inorganic)']. It is obvious that, 
in line with the ECHA guidance, the majority of regis-
trants have taken advantage of the opportunity to use 
the IOELV as a DNEL value as such. It can be assumed 
that at least in some cases, the DNEL would have been 
significantly lower than the IOELV if the default assessment 
factors published in the REACH guidance (ECHA, 
2012) had been applied. In the papers by 
ECETOC (2010), Kreider and Spencer Williams (2010), 
and Schenk and Johanson (2011), DNELs were calculated 
according to the REACH guidance documents. As 
an example, the theoretical calculations presented by 
Schenk and Johanson (2011) would result in a DNEL 
value of 2 mg m$^{-3}$ for triethylamine, but the registered 
DNEL value, which is identical to the IOELV, is 8.4 mg 
m$^{-3}$. For the substance ethanolamine (2-aminoethanol), 
the long-term DNEL value is 3.3 mg m$^{-3}$, and the IOELV 
is 2.5 mg m$^{-3}$; but when using the point of departure 
and total assessment factors suggested by Schenk and 
Johanson (2011), the DNEL value would be 0.5 mg m$^{-3}$. 
Kreider and Spencer Williams (2010) calculated DNEL 
values for styrene by following the recommendations in 
the REACH guidance. This substance does not have an 
IOELV, but the 8-h HTP value of 85 mg m$^{-3}$ is similar to 
the national values in, e.g. Austria, Germany, Spain, and 
Switzerland, as well as the recommendation of ACGIH 
in the USA (ACGIH, 2014; GESTIS, 2014). In line 
with the national values, the worker long-term DNEL 
for styrene (presented in the joint registration dossier) 
is 85 mg m$^{-3}$ (100 mg m$^{-3}$ in one individual submission), 
but according to the calculations presented in the paper 
by Kreider and Spencer Williams (2010), it should be as 
low as 1.7 mg m$^{-3}$.

When looking at substances for which no IOELVs 
have yet been set, but for which SCOEL has given 
its recommendations (which are likely to result in 
IOELVs in the near future), it was obvious that some 
of the registrants had noticed the SCOEL recommen-
dations. Examples of this are cadmium and sulphur 
dioxide. The DNEL value of 0.004 mg m$^{-3}$ for cad-
mium, cadmium chloride, cadmium oxide, cadmium 
sulphate, and cadmium sulphide is identical to the 
SCOEL recommendation (SCOEL, 2010) for an 8-h 
TWA of 0.004 mg m$^{-3}$ (respirable fraction) for cad-
mium and its inorganic compounds. As the justifica-
tions for the DNEL values are not publicly available, 
it was not possible to see whether they are specified

<table>
<thead>
<tr>
<th>Substance</th>
<th>CAS number</th>
<th>HTP (8 h) mg m$^{-3}$</th>
<th>Year of HTP</th>
<th>DNEL (workers, long-term exposure)$^a$ mg m$^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium sulphate</td>
<td>10043-01-3</td>
<td>1</td>
<td>1996</td>
<td>20.2/3$^b$</td>
</tr>
<tr>
<td>Barium chloride</td>
<td>10361-37-2</td>
<td>0.5</td>
<td>1972</td>
<td>8.8</td>
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<tr>
<td>Cyclohexane-1,2-dicarboxylic anhydride (hexahydrophthalic anhydride)</td>
<td>85-42-7</td>
<td>0.01</td>
<td>2005</td>
<td>7.05</td>
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<tr>
<td>Dimethyl phthalate</td>
<td>131-11-3</td>
<td>5</td>
<td>1972</td>
<td>293.86</td>
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<tr>
<td>Gallium arsenide</td>
<td>1303-00-0</td>
<td>0.0003</td>
<td>2012</td>
<td>0.02</td>
</tr>
<tr>
<td>Hexahydromethylphthalic anhydride</td>
<td>25550-51-0</td>
<td>0.01</td>
<td>2005</td>
<td>79.3</td>
</tr>
<tr>
<td>Phthalic anhydride</td>
<td>85-44-9</td>
<td>0.2</td>
<td>1993</td>
<td>32.2</td>
</tr>
<tr>
<td>Trimellitic anhydride (benzene-1,2,4-tricarboxylic acid 1,2-anhydride)</td>
<td>552-30-7</td>
<td>0.04</td>
<td>1993</td>
<td>17.5</td>
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</tbody>
</table>

$^a$Data source: ECHA dissemination site, originally accessed 31 Jan 2012. Values re-checked 14 May 2014. $^b$Two registrations giving different DNELs.
<table>
<thead>
<tr>
<th>Substance</th>
<th>CAS Number</th>
<th>DNEL (mg m(^{-3}))</th>
<th>IOELV (mg m(^{-3}))</th>
<th>HTP (mg m(^{-3}))</th>
<th>Year of HTP</th>
<th>Most sensitive endpoint/REACH registration</th>
<th>Critical effect/HTP</th>
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<tbody>
<tr>
<td>Acetic acid</td>
<td>64-19-7</td>
<td>25</td>
<td>25(^b)</td>
<td>13</td>
<td>2005</td>
<td>Irritation (respiratory tract); assessment factor not published</td>
<td>Irritation (respiratory tract); human and animal data</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>100-51-9</td>
<td>90</td>
<td></td>
<td>45</td>
<td>2009</td>
<td>Repeated dose toxicity; assessment factor not published</td>
<td>Shortness of breath, neurological effects; based on oral animal study</td>
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<tr>
<td>Cobalt (metal)</td>
<td>7440-48-4</td>
<td>0.04</td>
<td></td>
<td>0.02</td>
<td>2012</td>
<td>Repeated dose toxicity; assessment factor not published</td>
<td>Irritation (respiratory tract); human data</td>
</tr>
<tr>
<td>Cobalt carbonate</td>
<td>513-79-1</td>
<td>0.0807(^b)</td>
<td></td>
<td>0.02</td>
<td>2012</td>
<td>Repeated dose toxicity; assessment factor not published</td>
<td>Irritation (respiratory tract); human data</td>
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<tr>
<td>Cobalt dichloride</td>
<td>7646-79-9</td>
<td>0.0881(^b)</td>
<td></td>
<td>0.02</td>
<td>2012</td>
<td>Repeated dose toxicity; assessment factor not published</td>
<td>Irritation (respiratory tract); human data</td>
</tr>
<tr>
<td>Cobalt oxide</td>
<td>1307-96-6</td>
<td>0.0509(^b)</td>
<td></td>
<td>0.02</td>
<td>2012</td>
<td>Repeated dose toxicity; assessment factor not published</td>
<td>Irritation (respiratory tract); human data</td>
</tr>
<tr>
<td>Cobalt sulphate</td>
<td>10124-43-3</td>
<td>0.1052(^b)</td>
<td></td>
<td>0.02</td>
<td>2012</td>
<td>Repeated dose toxicity; assessment factor not published</td>
<td>Irritation (respiratory tract); human data</td>
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<tr>
<td>Cobalt sulphide</td>
<td>1317-42-6</td>
<td>0.0618(^b)</td>
<td></td>
<td>0.02</td>
<td>2012</td>
<td>Repeated dose toxicity; assessment factor not published</td>
<td>Irritation (respiratory tract); human data</td>
</tr>
<tr>
<td>Substance</td>
<td>DNEL (mg m⁻³)</td>
<td>IOELV (mg m⁻³)</td>
<td>HTP (mg m⁻³)</td>
<td>Year of HTP</td>
<td>Most sensitive endpoint/REACH registration</td>
<td>Critical effect/HTP</td>
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<td>-------------</td>
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<td>Cyclohexane</td>
<td>110-82-7</td>
<td>700</td>
<td>700</td>
<td>350</td>
<td>2005 Neurotoxicity, overall assessment factor 1</td>
<td>Irritation and neurological effects; human data</td>
<td></td>
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<tr>
<td>Gallium arsenide</td>
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<td>0.02</td>
<td>0.0003</td>
<td>2012</td>
<td>No information</td>
<td>Repeated dose toxicity, lung effects; animal data</td>
<td></td>
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<tr>
<td>Toluene</td>
<td>108-88-3</td>
<td>192</td>
<td>192</td>
<td>81</td>
<td>2009 Neurotoxicity, overall assessment factor 1</td>
<td>Developmental toxicity, neurological effects; human data</td>
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<tr>
<td>Tricobalt tetraoxide</td>
<td>1308-06-1</td>
<td>0.0545b</td>
<td>0.02c</td>
<td>2012</td>
<td>Repeated dose toxicity; assessment factor not published</td>
<td>Irritation (respiratory tract) and lung effects; human data</td>
<td></td>
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<tr>
<td><strong>DNEL lower than HTP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ethyl acetate</td>
<td>141-78-6</td>
<td>734</td>
<td>1100</td>
<td>1981</td>
<td>Irritation (respiratory tract); assessment factor not published</td>
<td>No information (old value)</td>
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<tr>
<td>Ethylbenzene</td>
<td>100-41-4</td>
<td>77 (joint submission) / 442 (individual submission)</td>
<td>442</td>
<td>220</td>
<td>Joint submission: repeated dose toxicity; overall assessment factor 3. Individual submission: no information</td>
<td>Irritation (respiratory tract); animal data</td>
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<td>Cadmium</td>
<td>7440-43-9</td>
<td>0.004</td>
<td>0.004a</td>
<td>0.02</td>
<td>1972 Repeated dose toxicity; overall assessment factor 1</td>
<td>No information (old value)</td>
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<td>Cadmium chloride</td>
<td>10108-64-2</td>
<td>0.004</td>
<td>0.004a</td>
<td>0.02</td>
<td>1972 Repeated dose toxicity; overall assessment factor 1</td>
<td>No information (old value)</td>
<td></td>
</tr>
<tr>
<td>Substance</td>
<td>CAS Number</td>
<td>DNEL (mg m(^{-3}))</td>
<td>IOELV (mg m(^{-3}))</td>
<td>HTP (mg m(^{-3}))</td>
<td>Year of HTP</td>
<td>Most sensitive endpoint/REACH registration</td>
<td>Critical effect/HTP</td>
</tr>
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<tr>
<td>Cadmium oxide</td>
<td>1306-19-0</td>
<td>0.004</td>
<td>0.004(^a)</td>
<td>0.02</td>
<td>1972</td>
<td>Repeated dose toxicity; overall assessment factor 1</td>
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<tr>
<td>Cadmium sulphate</td>
<td>10124-36-4</td>
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<td>0.004(^a)</td>
<td>0.02</td>
<td>1972</td>
<td>Repeated dose toxicity; overall assessment factor 1</td>
<td>No information (old value)</td>
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<tr>
<td>Cadmium sulphide</td>
<td>1306-23-6</td>
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<td>0.004(^a)</td>
<td>0.02</td>
<td>1972</td>
<td>Repeated dose toxicity; overall assessment factor 1</td>
<td>No information (old value)</td>
</tr>
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<td>Chloroform</td>
<td>67-66-3</td>
<td>2.5</td>
<td>10</td>
<td>10</td>
<td>2002</td>
<td>Repeated dose toxicity; overall assessment factor 10</td>
<td>Extrapolation from short-term effects; animal data</td>
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<td>2,2′-Iminodiethanol</td>
<td>111-42-2</td>
<td>1</td>
<td>2</td>
<td></td>
<td>2002</td>
<td>Repeated dose toxicity; overall assessment factor 1</td>
<td>Irritation (respiratory tract); human data</td>
</tr>
<tr>
<td>Turpentine, oil</td>
<td>8006-64-2</td>
<td>0.77</td>
<td>140</td>
<td></td>
<td>2005</td>
<td>Repeated dose toxicity; overall assessment factor 25</td>
<td>Irritation (respiratory tract) and neurological effects; human data; overall assessment factor 2</td>
</tr>
<tr>
<td>Xylene</td>
<td>1330-20-7</td>
<td>77</td>
<td>221</td>
<td>220</td>
<td>2002</td>
<td>Repeated dose toxicity; overall assessment factor 3</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)SCOEL proposal.  
\(^b\)Corresponds to 0.04 mg Co m\(^{-3}\).  
\(^c\)mg Co m\(^{-3}\).
as corresponding to the respirable fraction. In 2009, SCOEL recommended 1.3 mg m\(^{-3}\) as an 8-h TWA and 2.7 mg m\(^{-3}\) as STEL (15 min) for sulphur dioxide (SCOEL, 2009b). These values were also registered as DNELs for the substance.

In the second part of this study, we compared the values in the Finnish OEL list (HTP values; \(n = 560\)) with the respective DNELs. At the time when this part of the study was carried out, the deadline had passed only for companies manufacturing or importing substances in volumes of \(\geq\)1000 tonnes per year, as well as substances classified as carcinogenic, mutagenic, or toxic for reproduction Categories 1 or 2 and which may cause long-term effects in the aquatic environment. According to our findings, the DNELs were at a similar level to those of the HTP values in about half of the cases (49%) and significantly different in the other half. The DNEL was considerably lower than the HTP value in 87 cases (28%). In some cases, the difference between the values was very high, as shown in Table 3. The situation in Germany is very similar to that in Finland. When comparing national German workplace limit values (AGW) with DNELs, 6% of the DNEL values were more than a factor of 10 lower than the AGW, and 25% were lower than the AGW (by a factor <10) (Nies et al., 2013). In comparison, 21% of the DNELs were lower than the corresponding IOELVs. This means that at least for the substances registered so far, the concerns raised by ECETOC (2010), Kreider and Spencer Williams (2010), and Schenk and Johanson (2011), that the DNEL values will generally be far lower than the current national or EU OELs do not always lead to discrepancies in practice. Based on our findings, it is very likely that many of the registrants have used IOELVs or national OELs as DNELs rather than the default assessment factors presented in the ECHA guidance. Unfortunately, the detailed justifications for the DNELs, presented in the registration dossiers, are not (at least yet) publicly available. Furthermore, for many of the registered substances, the ECHA dissemination site does not provide information on the specific endpoint that was identified as the most sensitive for the derivation of the DNEL or on what assessment factors were applied. In some cases, the basis for the DNELs is probably not appropriate. For example, in the case of anhydrides (Table 6), a DNEL based on repeated dose toxicity is set although the substances are respiratory sensitizers, for which no health-based threshold for the effects can be identified. We do not know, however, whether this aspect has in some other way been taken into account for example in the exposure scenarios for these substances.

Expectations regarding the positive effects of REACH have been high. A study carried out at the University of Sheffield estimated that the numbers of asthma and chronic obstructive pulmonary disease cases in the EU would annually decrease by 40,000 and 10,000, respectively, as a result of REACH (Pickvance et al., 2005). Based on the results of our study, we suppose that the positive benefits are not likely to occur due to lowered exposures based on low DNEL values, and thus strict exposure scenarios. Instead, the highest benefit of DNELs may be related to limiting the exposure of workers (and by analogy the general public) to those thousands of substances that had no limit values before. Furthermore, the authorization process of REACH, which may limit the use of the most hazardous substances, is likely to be even more effective in reducing exposure. A recently published report on the benefits of REACH (RPA, 2012) concluded that ‘the information being provided on DNELs is useful for workplace safety assessment (as a substitute for an OEL) and can contribute to better targeted RMMs’. In addition, the stricter classification of chemicals, as an outcome of REACH registration, is likely to reduce potential health risks (RPA, 2012).

It has to be remembered that the DNEL values are not intended to be used exactly in the same way as OELs have traditionally been used (e.g. measuring exposure levels and comparing those with the OEL). Instead, the DNELs form the basis of the exposure scenarios and the risk management measures, in which safe use conditions are presented in detail. It is highly important that the DNELs are based on sound toxicological data, in order to protect the workers as they should. If industry manages to present the exposure scenarios in a clear and understandable way in the extended safety data sheets, the final outcome may in practice be decreasing exposure levels.

In situations in which the national OEL is higher than the DNEL, it might be wise to check the basis for the OEL and decide whether there is a need to update the OEL. Although the list of Finnish HTP values is updated every other year, many HTP values have still not been checked or updated for years or decades. It
should, however, be noticed that the DNELs should be strictly health based, whereas socioeconomic aspects may influence national OELs.

At workplaces, situations in which the DNEL values are higher than OELs are likely to be problematic. The exposure scenarios of the extended safety data sheet, and the risk management measures presented in the scenarios, show circumstances under which the exposure level will stay below the DNEL but may still be higher than the OEL level. Recognizing these types of situations may be challenging for employers. If, for example, national authorities are aware of such cases, they should spread the information. Labour inspectors should also be observant of such cases.

CONCLUSIONS
A comparison of registered DNELs with EU IOELVs and Finnish HTP values clearly showed that DNELs are not systematically lower than OELs. For the majority of substances with an IOELV, the DNEL is identical to the IOELV. This indicates that the option, presented in the ECHA guidance, on using IOELVs or national OELs as DNELs has been applied in many cases. In some cases, the DNELs are significantly higher than IOELVs and the Finnish HTP values. However, cases also exist in which DNELs are (considerably) lower than the OELs. The guidance on the use of default assessment factors in the setting of DNELs is obviously not followed in many cases. Since the justifications for the DNELs, given in the registration dossiers, are not publicly available, no further conclusions can be made on the methods followed for the calculations of the DNELs. Those Finnish HTP values that are significantly higher than the DNELs are often old and have not been updated for years. Based on our results, the exposure is not likely to decrease due to DNELs being lower than OELs. Instead, the highest benefit of DNELs created under REACH are likely to occur due to the fact that the exposure scenarios, created for thousands of substances for which no national OELs have been set, will restrict the conditions of use and thus also decrease exposure. In addition, the authorization process of REACH will limit the use of the most hazardous substances.

Based on the data of this study, national authorities setting OELs may use the ECHA database on registered substances in order to identify substances with low DNELs, for which there might be a need to check the basis for the OEL. Furthermore, workplaces should receive information on how to deal with substances with higher DNEL values than the OEL. In these cases, applying the risk management measures presented in the exposure scenarios of the extended safety data sheet may still result in exposures higher than the OEL level.

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