

## **Derived Minimal Effect Levels (DMELs): Shortcomings one year after the REACH registration deadline**

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*[http://www.auva.at/mediaDB/861114\\_DMELs\\_Defizite\\_ein\\_Jahr\\_nachher.pdf](http://www.auva.at/mediaDB/861114_DMELs_Defizite_ein_Jahr_nachher.pdf)  
([www.gefahrstoffe.de](http://www.gefahrstoffe.de)).*

*Deviations from the original paper are italicised and marked with asterisk.*

### **Summary**

Derived Minimal Effect Levels (DMELs) have no basis in the REACH Regulation. Their character as risk-based exposure limits for the genotoxic effects of substances and their derivation is recommended only in the guidance documents of the European Chemicals Agency (ECHA). Nevertheless they are required to be supplied when a substance is registered for which no toxicological threshold mode of action is to be assumed, and therefore no Derived No Effect Level (DNEL) can be established (cf. REACH, Annex I.1.4.1). According to ECHA's Dissemination Portal, 293 of 3,572 substances have been registered as proven carcinogens or mutagens (pC/Ms) (as of 7-Sep-2011). 70 % of these registrations do not include even one exposure limit value for pC/M substances, while DMELs are given in of 8.6 % of registrations of pC/M substances; Derived No-Effect Levels (DNELs) are given erroneously in 21.4 % of registrations of pC/M substances. DNELs are reserved for substance effects with a threshold mode of action. Several known pC/M substances have not been registered as such. On the other hand, in several registrations of substances without pC/M properties, DMELs have been provided. Checks of form and content revealed that most limit values are implausible and/or mutually inconsistent. The cancer risk on which the DMEL is based is not stated. Comparisons show that in some cases DMELs correspond to a working lifetime risk of up to 1.8 %. These findings underline that it makes no sense to leave it to the registrant to choose the cancer risk on which a DMEL is based. What is in fact necessary is the definition of a uniform Europe-wide acceptable risk. The currently registered exposure limit values for pC/M substances appear to be neither comprehensible nor reliable and in most cases useless.

### **1 Introduction and problem**

In protecting human health from risks due to chemicals, the REACH Regulation [1] essentially relies on a health-based protection level. This means that human exposure to chemicals shall be reduced to a level that health is not harmed. In the REACH Regulation, the associated maximum exposure level is expressed as the "Derived No-Effect Level" (DNEL). In the case of substances with genotoxic carcinogenic or mutagenic action, this approach is not applicable since, on the basis of present knowledge, even the slightest exposure to these substances entails a cancer risk. For these substances, the REACH Regulation therefore contains only qualitative provisions for the protection of human health. To render these not

directly applicable provisions practicable, the European Chemicals Agency (ECHA) has developed the concept of DMELs (Derived Minimal Effect Levels) [2; 3] in so-called guidance documents. DMELs are risk-based limit values for substances for which no toxicological threshold mode of action is to be assumed. The derivation of a risk-based limit value demands two elements: (i) an exposure–risk relationship, essentially a finding of toxicological research; and (ii) the definition of a cancer risk level that must not be exceeded [3; 4]. However, in its guidance documents for deriving DMELs [2; 5], ECHA does not recommend any specific risk level, but refers merely to the political character of this provision. This means that the DMEL approach is not applicable in practice for registrants. Other weaknesses of the DMEL approach and scope for improvement have been indicated and discussed in the literature [3] and at a Europe-wide workshop [6–8].

As of 1 December 2010 at the latest, all carcinogenic substances imported to the European Economic Area (EEA) or produced in an EEA state by the actor in question in a quantity exceeding 1 tonne (t) per year have had to be registered with ECHA [1]. For substances manufactured or imported in quantities of 10 t or more per year per manufacturer or importer, registrants have to additionally submit a chemical safety report in which, inter alia, exposure estimations for all exposure scenarios have to be undertaken and documented.<sup>1)</sup> The “risk characterisation”, which also has to be submitted, consists of a comparison of the exposure level with the exposure limit value. Only if the exposure remains below this limit value (DNEL) is the risk “adequately controlled” and the exposure scenario permits the application in question.

In contrast to health based DNELs, risk based DMELs for genotoxic substances are not envisaged in REACH. There is no uniform EU-wide acceptable cancer risk<sup>2)</sup> as a basis for their derivation. Therefore considerable problems and confusion among registrants were to be expected in advance [3]. The far-reaching decision on an acceptable cancer risk as a precondition for deriving DMELs is shifted to the various registrants and may become the subject of marketing considerations, since the magnitude of the DMEL is a factor affecting the scope for usage and sale of the substance. Only very few of the 30 EEA states have discussed and approved guidelines on the societally acceptable cancer risk from chemical substances [3]. Since, owing to the lack of an acceptable risk, registrants are unable to responsibly derive a DMEL, companies are advised to apply the 4 : 100,000 acceptable risk of the German “traffic light model” [4] or not to give any DMEL values at all [9] until agreement is reached on a uniform European acceptable risk and until the DMEL concept has been thoroughly revised [3]. A workshop [6] initiated by the German Federal Institute for Occupational Safety and Health (BAuA) proposed the provisional adoption of this acceptable risk of 4 : 100,000 until consensus is reached across Europe [10].

The goal of the present study is to determine whether and how the DMEL concept has been applied in the registration of proven carcinogens and/or mutagens (**pC/Ms**) and for which of these substances which limit values have been published.

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<sup>1</sup> For carcinogenic, mutagenic or reprotoxic (CMR) substances, the associated deadline was 1 December 2010. Since this date, the associated safety data sheets have had to be accompanied by exposure scenarios.

<sup>2</sup> [This footnote only was relevant for terminology in German language.]

## 2 Data basis and methods

### 2.1 Data basis for the DMELs

According to Article 119 of the REACH Regulation, ECHA has to make the DNELs for all registered substances publicly available over the Internet (along with other details). This is done – albeit incompletely – on the subpage\*) called the Dissemination Portal [11] at the ECHA homepage. ECHA publishes the data from the submitted registrations unchecked, as supplied by the registrants, and does not accept liability for their correctness [12].

\*) In the relaunch of the ECHA webpage the Dissemination Portal is entitled “Registered substances”.

The present study is based on the Excel list entitled “Publishable substances registered as of 7-Sep-2011” [11]. This list contained 3,838 substances (as part of a total of 5,065 substances registered by this date) whose registration ECHA has deemed publishable.\*\*) The list only contains substance name, CAS number, EC number (or a provisional “list number”) and registration status; **Table 1** characterises these data. Not contained in the list are those substances that have been registered in accordance with the Dangerous Substances Directive 67/548/EEC since September 1982 (“new substances”), unless registered under REACH, and substances whose identity may be kept confidential pursuant to a decision of ECHA.

\*\*) As of 5-June-2012 the list contains 4,268 publishable substances (as part of a total of 5,479 substances registered by this date).

**Table 1. Assignment of initial data and identified proven carcinogens or mutagens (pC/Ms) to EC numbers and registration status.**

	EC or List number		Total	Dossier disseminated <sup>a</sup>	Registered as <sup>b</sup>		
					Full <sup>c</sup>	TII <sup>d</sup>	OSII <sup>e</sup>
<b>Total</b>		<b>Registered substances thereof carcinogenic<sup>f</sup></b>	<b>3838</b>	<b>3791</b>	<b>2483</b>	<b>1515</b>	<b>982</b>
		<b>“Endpoint summary”<sup>f,g</sup></b>	<b>293</b>	<b>293</b>	<b>126</b>	<b>191</b>	<b>114</b>
			<b>111</b>	<b>111</b>	<b>103</b>	<b>60</b>	<b>37</b>
Substances with EINECS number	from 200-001-X	Registered substances thereof carcinogenic <sup>f</sup> “Endpoint summary” <sup>f,g</sup>	2721 244 108	2707 244 108	1964 117 100	1103 166 59	703 91 36
Substances with ELINCS number	from 400-010-X	Registered substances thereof carcinogenic <sup>f</sup> “Endpoint summary” <sup>f,g</sup>	96 1 0	96 1 0	56 0 0	37 1 0	7 0 0
No longer polymers	from 500-001-X	Registered substances thereof carcinogenic <sup>f</sup> “Endpoint summary” <sup>f,g</sup>	57 1 1	57 1 1	57 1 1	57 1 1	3 1 1
Others <sup>h</sup>	from 600-001-X <sup>h</sup>	Registered substances thereof carcinogenic <sup>f</sup> “Endpoint summary” <sup>f,g</sup>	964 47 2	931 47 2	406 8 2	371 23 0	268 22 0

a “Indicates that at least one registration dossier for this substance has been processed, confidential information removed, and the resulting ‘filtered’ dossier published on the Dissemination Portal” [11].

b The registration is entered in [11] as “full” and/or “TII” and/or “OSII”.

c “Indicates complete substance registration under REACH Article 10 as a full dossier.”

d “Indicates complete substance registration under REACH Article 18 as a transported isolated intermediate (TII).”

e “Indicates complete substance registration under REACH Article 17 as an on-site isolated intermediate (OSII).”

f pC/Ms excluding ‘complex coal- and oil-derived substances’ in CLP Annex VI (see text); without or with Endpoint Summary (see text).

g Endpoint Summary for substances of footnote f if the summary contains at least one limit value. Several Endpoint Summaries may exist for a single substance.

h For these substances (often reaction mixtures and residues) are only given ECHA-internal processing numbers (“list numbers”).

For the substances named in the list, there is occasionally more than one REACH registration. The main reason for this is to be found in violations of the REACH principle of “*One substance, one registration*” [13]. In addition, REACH allows for a deviation from this principle under certain conditions.

The Dissemination Portal [11] therefore comprised 4,416 entries (registrations) as of 7-Sept-2011.

The actual data published with each registration can be found with the aid of the database search mask [11]. The database entries accessible in this way contain up to 70 subcategories within the categories *General information; Classification and labelling; Manufacture, use & exposure; Physical and chemical properties; Environmental fate and pathways; Ecotoxicological information; Toxicological information; Guidance on safe use and Reference substances*. However, the categories and subcategories are often very incomplete or devoid of data entirely.

If provided, DNELs and DMELs are contained in the category *Toxicological information*, subcategory “*Toxicological Information*”. However registrants are not obliged to enter data into this subcategory named “Endpoint Summary” in the input mask of IUCLID. The “completeness check” conducted by ECHA before publication therefore does not cover the Endpoint Summary. In numerous cases, then, DNELs and DMELs cannot be found on the Dissemination Portal<sup>3</sup>). We have evaluated the data searchable in the Endpoint Summary (**Figure 1**). According to the understanding of ECHA Guidance Chapter R.8 [2], usually 15 DNELs or DMELs are to be given for each substance. The IUCLID user interface for registration in fact contains 18 DN(M)EL values in the Endpoint Summary, as can be seen from **Table 2**. The Endpoint Summary is an Internet subpage that shows only the assigned limit values for the up to 18 endpoints (Table 2).

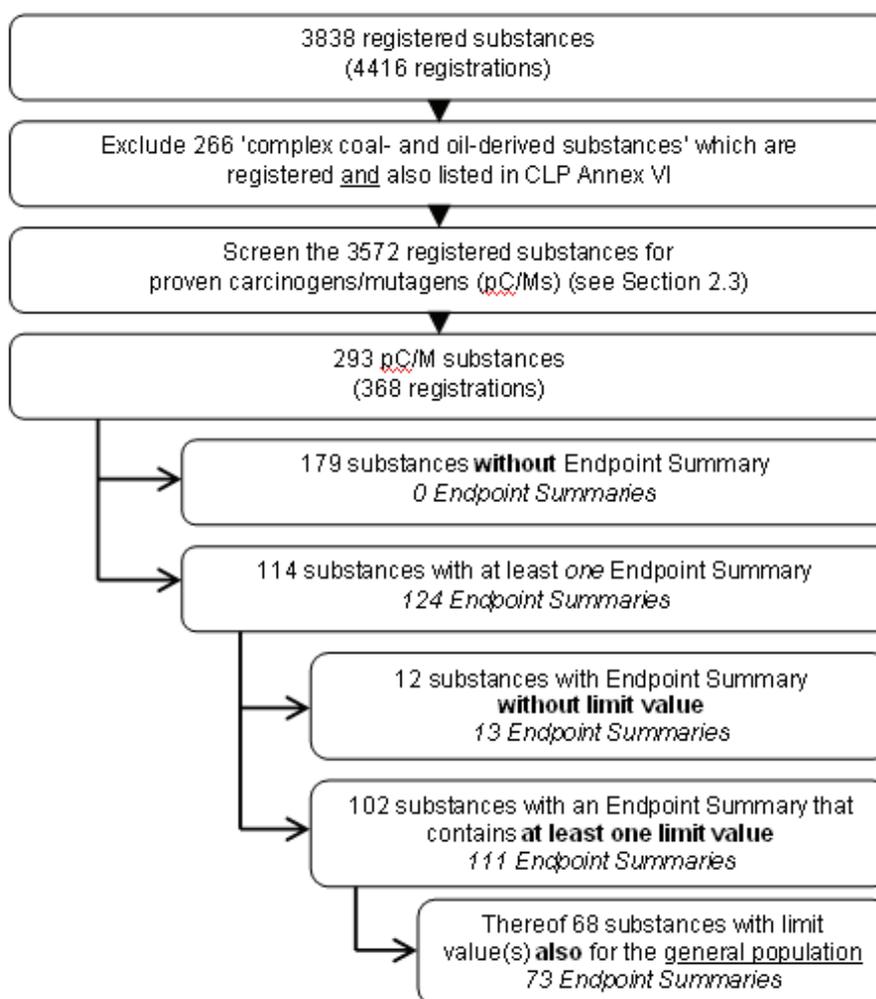
## **2.2 Restrictions relating to complex coal- and oil-derived substances**

Since the pC/M properties of distillation, extraction, reformation, coking, cracking and hydrogenation products of mineral oil and coal (that constitute 701 ‘*complex coal- and oil-derived substances*’ in Annex VI of the CLP Regulation [14]) usually depend on their content of benzene, butadiene or benzo[a]pyrene, these products – assuming they appear among the registered substances – have been excluded from the systematic analysis (Figure 1). Nevertheless, certain observations about these substances are presented in the results section (see below).

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<sup>3</sup> The obligation of REACH Article 119 to make DNELs publicly accessible has therefore only been partially complied with. A complete evaluation of the details missing at the Dissemination Portal would require examination of the various registration dossiers. Apart from the fact that this process would be extremely laborious, the registration dossiers are only available on request to the national competent authorities.

**Figure 1. Quantity framework and procedure for the study.**



**Table 2. Endpoints for which the IUCLID input mask envisages the registration of DNEL/DMEL values, and the abbreviations used in this article.**

Endpoint		Abbreviation
Workers – Acute / short-term exposure – systemic effects	Dermal *)	W-A-S-d
	Inhalation	W-A-S-i
Workers – Acute / short-term exposure – local effects	Dermal	W-A-L-d
	Inhalation	W-A-L-i
Workers – Long-term exposure – systemic effects	Dermal	W-C-S-d
	Inhalation	W-C-S-i
Workers – Long-term exposure – local effects	Dermal	W-C-L-d
	Inhalation	W-C-L-i
General population – Acute / short-term exposure – systemic effects	Dermal *)	G-A-S-d
	Inhalation	G-A-S-i
	Oral *)	G-A-S-o
General population – Acute / short-term exposure – local effects	Dermal	G-A-L-d
	Inhalation	G-A-L-i
General population – Long-term exposure – systemic effects	Dermal	G-C-S-d
	Inhalation	G-C-S-i
	Oral	G-C-S-o
General population – Long-term exposure – local effects	Dermal	G-C-L-d
	Inhalation	G-C-L-i

\*) This endpoint is not envisaged in Guidance Chapter R.8 [2], Table R.8-9 “DN(M)ELs that normally may need to be derived”.

## 2.3 Database search

At the Dissemination Portal [11], we ascertained in a first step in the category *Classification and labelling/DSD-DPD* whether a substance was registered as a proven carcinogen (formerly Carc.Cat. 1 or 2, now “Carc. 1A” or “Carc. 1B” according to the CLP Regulation) or proven mutagen (formerly Muta.Cat. 1 or 2, now “Muta. 1A” or “Muta. 1B”). Suspected carcinogens or mutagens (formerly Cat. 3, now “2”) were disregarded. 14 cobalt, nickel and cadmium compounds registered without pC/M properties where it can be assumed that the toxic metal ion is bioavailable were included as pC/M (e.g. Co octanoate, Cd nitrate, Cd carbonate).

Included in the evaluation as pC/M were therefore substances that were registered with the pC/M classification, or are pC/M substances according to the harmonised classification (Annex VI of the CLP Regulation [14]) or, as mentioned above, are to be considered pC/Ms owing to the bioavailable metal ion.

In a second step, we checked the presence of the Endpoint Summary in the category *Toxicological information* and evaluated any data found therein.

## 3 Results and assessment

### 3.1 Qualitative findings concerning proven carcinogenic or mutagenic substances

Among the registered substances ( $n = 3,838$ ), 293 proven carcinogenic and/or mutagenic (pC/M) substances were identified<sup>4</sup>). For 43 pC/M substances, there was more than one registration (maximum: 8 registrations for methyl oxirane); so a total of 368 registrations were evaluated (Figure 1). Therefore in the present study, a distinction is often made between “substances” and “registrations”. Each registration may (but does not necessarily) contain *one* Endpoint Summary.

It should be noted that many substances known as pC/Ms [15–17] were not registered under REACH (e.g. auramine, benzidine, diazomethane, 1,2-dibrom-3-chloropropane, diglycidyl resorcin ether, nitrosamines, polycyclic aromatic hydrocarbons, certain epoxy compounds, several metal salts, several aromatic amines). Active substances of pesticides and biocides are not to be found among the registered substances because according to REACH Article 15 these are regarded as being registered.

For seven substances there were two Endpoint Summaries and for one substance even three. For four substances, two limit values were registered for the same endpoint in each case; however, only in one case the limit values were identical; the others differed by factors of 69, 3 and 1.5. Only for one substance (hydrazine), for which incidentally a DNEL<sub>long-term</sub> is registered, were tests (for W-C-S-i and W-C-L-i; see Table 2 for abbreviations of the end-

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<sup>4</sup> In this process, 266 pC/M ‘complex coal- and oil-derived substances’ were disregarded, since they were excluded as explained in Section 2.2. On the other hand, among the registered substances were about 25 pC/M substances from oil and coal processing that were not mentioned in the CLP Appendix VI; these were not disregarded, but included.

points) proposed because of the insufficient data basis <sup>5</sup>). On the other hand, the evaluated Endpoint Summaries contain the entry “*no dose-response information available*” 365 times without toxicity tests being proposed. Since this phrase is given in the dropdown menu of the IUCLID input mask, no more importance should probably be attached to this entry than to the roughly 5,600 DMEL/DNEL input fields that were left blank.

### **3.1.1 Availability and type of registered limit values**

No Endpoint Summary was available for 179 of the 293 pC/M substances. Since any registered DNELs or DMELs are only publicly accessible via the Endpoint Summary, this means that no information on limit values was to be expected from the outset for 61 % of the pC/M substances (Figure 1). In several cases, a reason for the lack of a DMEL or DNEL could be partial exemption from the obligation to register (certain intermediates, substances used in research and development) or exemption from the obligation to supply a chemical safety report for substances below the 10 t threshold. However, even for 23 % of the pC/M substances with a “full registration” no limit value is supplied.

For 114 pC/M substances, we were able to find 124 Endpoint Summaries (Figure 1). Only for 102 substances <sup>6</sup>) did the pertaining 111 Endpoint Summaries contain at least one limit value. The Endpoint Summaries for the remaining 12 substances were empty or only contained standard phrases from the input mask like “*no dose-response information available*”, “*Exposure based waiving*” (see below), etc.

In 70 % of all Endpoint Summaries for pC/M substances that contained at least one limit value (or for 72 % of the pC/M substances with at least one limit value), exclusively DNELs (or, conflicting with the concept, DNELs mixed with DMELs) are registered. Since, according to present knowledge, genotoxic substances do not have a threshold mode of action, one would have expected DMELs to be given at least for long-term effects. It is conspicuous that DNELs were given for long-term effects as well as DMELs for acute effects. In many cases DNELs and DMELs seem to be used arbitrarily.

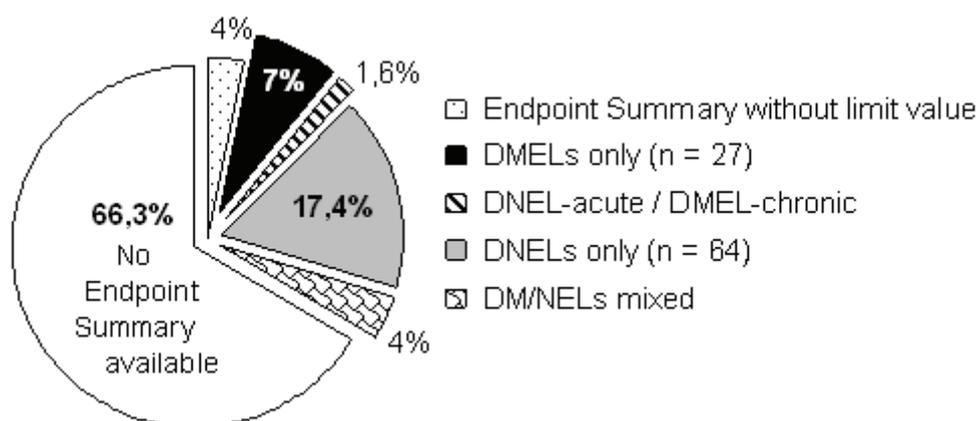
**Figure 2** shows the Endpoint Summaries found in all 368 registrations for the pC/M substances, broken down into “types”. “DMELs only” means that exclusively DMELs are given in this registration for acute and chronic effects. Where “DNELs only” is shown, only DNELs are registered. The type “DNEL-acute/DMEL-chronic” refers to the fact that Guidance Chapter R.8 [2] recommends deriving DNELs for effects with a threshold mode of action – acute effects of carcinogens may belong to these effects. In the registrations of this type, DNELs were always assigned to the acute effects and DMELs always to the long-term effects. However, this understandable usage of the concept could have occurred accidentally, since the terms “DNEL” and “DMEL” seem to have been assigned at random to

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<sup>5</sup> If the registrants had intended the derivation of a risk-based limit value for carcinogenic hydrazine, they could have found data on the hydrazine-related cancer risk in the Carcinogenic Potency Database (CPDB) <http://potency.berkeley.edu>.

<sup>6</sup> For eight of these substances, the list mentioned in Section 2.1 stated that no full registration under REACH Article 10 was available (but one for “transported intermediates” under Article 18).

the various endpoints (Table 2) in 12 % of the registrations with limit values given (“DM/NELs mixed”).



**Figure 2. Distribution of the 368 registrations (for 293 pC/Ms) among the various “types” of limit values found (explanation in text).**

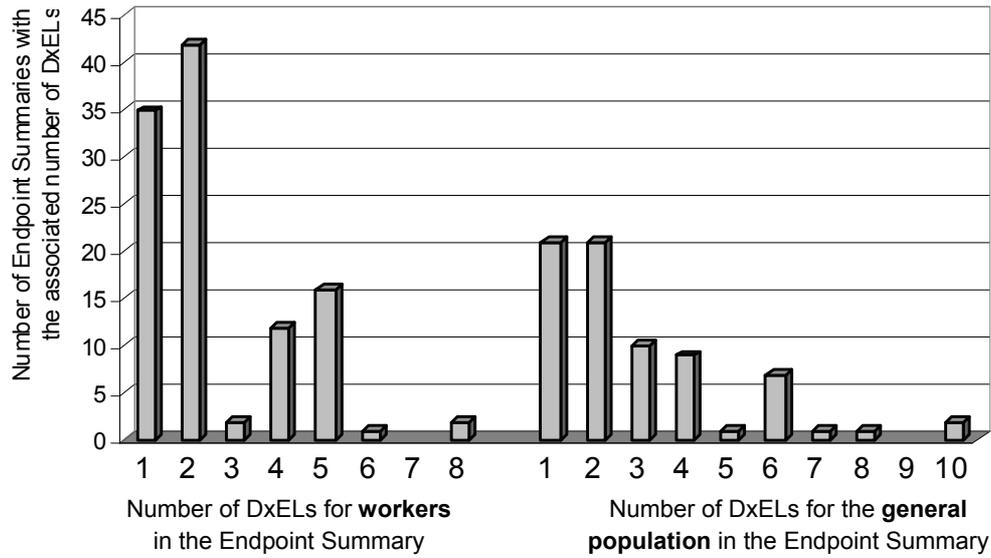
By applying form- and content-based criteria and by searching for an internal context for the registered values, it was not possible to conclude whether the term “DNEL” was used instead of “DMEL” for the long-term effect of a pC/M substance by mistake, due to lack of knowledge or understanding, or because of the lack of a uniform acceptable cancer risk – or if this was done according to a strategy and with deliberation. For statements concerning the chronic effects of pC/M substances, DMELs and DNELs are therefore treated as equivalent in the following. As the case may be, in the present article, we will use the term “**DxELs**”.

For some substances, the registration is inconsistent regarding the classification. For instance, raw tetrachloromethane has been registered by two large companies (who are named in the registration) as a “proven carcinogen”, although DNEL values were given for it. The DNEL for inhalative long-term exposure is, by the way, twice as high as the health-based workplace limit value under Technical Rule (TRGS) 900.

### **3.1.2 Distribution of limit values among groups and endpoints**

As can be seen from Table 2, the IUCLID registration software envisages per registration the statement of eight limit values for work-related exposed persons (‘workers’) and ten limit values for the general population. All 111 Endpoint Summaries containing limit values included at least one DxEL for workers, while only 66 % of these Endpoint Summaries included one (or more) values for the general population as well.

**Figure 3** shows the number of DxELs given in the different Endpoint Summaries, separately for workers and the general population. Most frequently the Endpoint Summaries showed two DxELs for workers and one or two DxELs for the general population. Two Endpoint Summaries provided values for all 18 endpoints.

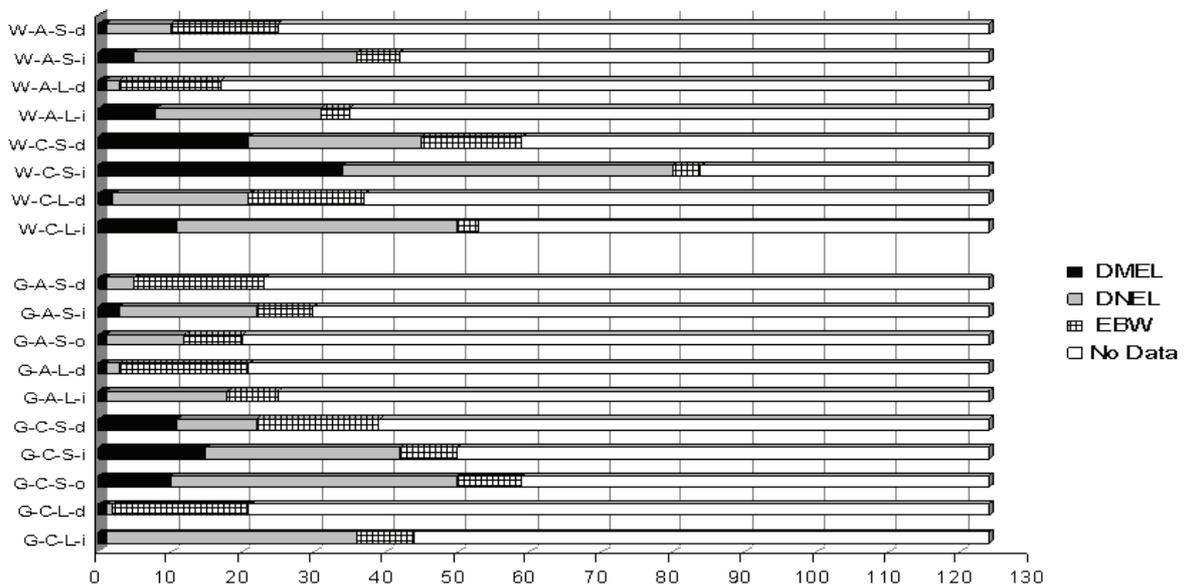


**Figure 3. “Density” of DxELs in the Endpoint Summaries (n = 111) containing DxELs. For workers, all 111 Endpoint Summaries, and for the general population, 73 Endpoint Summaries contained at least one DxEL.**

*Example: Looking at the 111 Endpoint Summaries (containing at least one DxEL) given for workers, 12 Endpoint Summaries contained 4 DxEL, 42 Endpoint Summaries contained 2 DxEL, etc.*

**Figure 4** illustrates the ‘frequency’ with which DxELs are provided for the endpoints named in Table 2. As mentioned, it should be borne in mind that more DxEL data sets exist for workers than for the general population. DxELs were most frequently assigned for chronic-systemic inhalation effects among workers. **Table 3** presents the figures.

**Figure 4. Number of DMELs and DNELs and the “exposure based waiving” (EBW) entry in the 124 Endpoint Summaries registered for the 293 pC/M substances, broken down according to endpoints (for abbreviations see Table 2).**



**Table 3. DMEL/DNEL and EBW entries in the 124 Endpoint Summaries for pC/M substances (EBW: exposure based waiving).**

Abbreviation (see Table 2)	DMELs	DNELs	Number of EBWs
W-A-S-d	1	9	15
W-A-S-i	5	31	6
W-A-L-d	1	2	14
W-A-L-i	8	23	4
W-C-S-d	21	24	14
W-C-S-i	34	46	4
W-C-L-d	2	19	16
W-C-L-i	11	39	3
Total W	83	193	76
G-A-S-d	1	4	18
G-A-S-i	3	19	8
G-A-S-o	1	11	8
G-A-L-d	1	2	18
G-A-L-i	1	17	7
G-C-S-d	11	11	17
G-C-S-i	15	27	8
G-C-S-o	10	40	9
G-C-L-d	1	1	19
G-C-L-i	1	35	8
Total G	45	167	120

### 3.1.3 Exposure Based Waiving (EBW)

According to Annex XI.3 of the REACH Regulation, registrants are permitted to waive certain toxicity tests and the derivation of the associated exposure limit values if they can prove that “no or no significant exposure” of humans arises from any use of the substance (“exposure based waiving”). The distribution of EBW entries can be seen in Figure 4. Of the 196 EBW entries (Table 3), some relate to the irrelevant skin absorption of gaseous substances. Others claim that, for instance, the intake of inorganic Cd compounds through the skin does not pose a risk. The EBW entries do, however, include problematic examples: The entry of “EBW” in the Endpoint Summary for methylhydrazine assumes that neither acute nor chronic exposure to this substance can occur at the workplace. This conflicts with the following data in the same registration: vapour pressure 50 mbar at 20 °C (comparable to ethanol), labelling as “fatal in contact with skin or if inhaled”, and several identified uses in which the possibility of human exposure is explicitly included (PROC 2, 8b, 9).

In the case of acrylonitrile, the EBW entry implies that there is no possibility of short-term inhalation of this substance at the workplace; and this despite registration as “toxic if inhaled”, a vapour pressure of 116 mbar and identified uses that implicate human exposure.

### 3.2 The magnitude of the DMEL or DNEL

In the following, observations about the magnitude of the registered DxEL values are reported. This is only possible to a limited extent, as the registered limit values and their

interrelationships show an extremely heterogeneous picture and the derivation of values, if at all, would only be comprehensible with access to the publicly inaccessible registration dossiers.

### 3.2.1 Comparison with the elaborated derivation method conforming to BekGS 910

After years of debate in the Federal Republic of Germany, a recognised standard for the derivation of risk-based limit values for airborne genotoxic substances is now available in the shape of BekGS 910 (Announcement on Hazardous Substances) [4]<sup>7</sup>). Its purpose is to reduce exposure to pC/M agents to such an extent that (after an introductory phase) the cancer risk in relation to working lifetime is not higher than 4 : 100,000 (equivalent to 1 : 25,000). **Table 4** compares DxELs from the Dissemination Portal specifically to those derived in conformity with BekGS 910.

It becomes clear that the cancer risk implicit in the respective DxEL value, but not numerically expressed, is up to 440 times the German acceptable risk of 1 : 25,000. In extreme cases, this means a working lifetime cancer risk of 1.8 %.

**Table 4. Comparison of DxEL values from the Dissemination Portal [11] with risk-based values conforming to the German BekGS 910 [4].**

	DxEL: Workers – long-term systemic – inhalation [mg/m <sup>3</sup> ]	BekGS 910: Concentration with acceptable risk 1 : 25,000 [mg/m <sup>3</sup> ]	DxEL is higher by the factor of ...	Working lifetime cancer risk associated with the DxEL
Acrylamide	DNEL 0.07 mg/m <sup>3</sup>	0.007 mg/m <sup>3</sup>	10	1 : 2.500
Acrylonitrile	DNEL 2.7 mg/m <sup>3</sup>	0.026 mg/m <sup>3</sup>	104	1 : 245
1,3-Butadiene	DMEL 2.21 mg/m <sup>3</sup>	0.05 mg/m <sup>3</sup>	44	1 : 57
Trichlorethene	DNEL 54.7 mg/m <sup>3</sup>	3.3 mg/m <sup>3</sup>	17	1 : 295
4,4'-Methylene dianiline	DMEL 0.0148 mg/m <sup>3</sup>	0.007 mg/m <sup>3</sup>	2,1	1 : 11800
Ethylene oxid	DMEL 1.6 mg/m <sup>3</sup>	0.02 mg/m <sup>3</sup>	80	1 : 315
Benzene *)	DMEL 3.2 mg/m <sup>3</sup>	— [0,02 mg/m <sup>3</sup> ] *)	— [160] *)	1 : 240 ... 1 : 760 <sup>a</sup>
Nickel monoxide	DNEL 0.05 mg/m <sup>3</sup>	—	—	1 : 450 <sup>a</sup>
Cadmium **)	DNEL 0.004 mg/m <sup>3</sup>	— [16 ng/m <sup>3</sup> ] **)	— [250] **)	1 : 110 ... 1 : 320 <sup>a</sup>
Vinyl chloride	DMEL 7.7 mg/m <sup>3</sup>	—	—	1 : 80 ... 1 : 1030 <sup>a</sup> 1 : 370 <sup>b</sup>
Pentazinc chromate octahydroxide	DNEL 0.05 mg/m <sup>3</sup>	—	—	1 : 380 ... 1 : 2200 <sup>c</sup>

a Determined with the assumption of a linear relationship based on the exposure-risk data in [18], corrected to a working lifetime of 40 years.

b According to [19], converted to a working lifetime of 40 years.

c According to [20], Pigment Yellow 36 [CAS 49663-84-5]. If the “DNEL” were applied directly to chromium(VI), the risk would range from 1 : 36 to 1 : 200.

\*) It should be mentioned that the German Committee on Hazardous Substances (AGS) recently has endorsed a limit value of 0.02 mg/m<sup>3</sup> based on the acceptable cancer risk of 1 : 25,000.

\*\*) It should be mentioned that the German Committee on Hazardous Substances (AGS) recently has endorsed a limit value of 16 ng Cd/m<sup>3</sup> based on the acceptable cancer risk of 1 : 25,000.

<sup>7</sup> Of the 30 EEA states, besides Germany only the Netherlands apply a risk quantification model [3].

The DMEL for benzene and that for vinyl chloride obviously copy the EU's binding occupational exposure limit, which is definitely not a risk based value. This suggests a way of thinking that Guidance Chapter R.8 [2] aims to overcome. The DxELs for acrylonitrile, trichloroethene and ethylene oxide seem to be based on the tolerance concentrations of BekGS 910. Concentrations in the magnitude of the tolerance risk of 1 : 250 certainly cannot be accepted in the longer term and call for immediate protection and control measures. The DMEL for vinyl chloride is even considerably higher than the former Technical Guidance Concentration (TRK) of 5 mg/m<sup>3</sup>, and that for acrylamide above the former TRK of 0.03 mg/m<sup>3</sup>.

### **3.2.2 Examples of substance groups: nickel, cadmium and cobalt**

A DNEL (instead of a DMEL) has been provided for chronic inhalation (W-C-S-i) of 13 nickel compounds. It amounts in all cases (with two minor deviations) to 50 µg/m<sup>3</sup>. Although poorly water-soluble Ni compounds (e.g. Ni oxides, Ni sulfides) are much more carcinogenic than readily soluble Ni compounds [21] owing to differences in their action mechanisms, toxicokinetics and elimination, the DNEL for both groups of Ni compounds is of the same magnitude. The same is true for the general population (G-C-S-i and G-C-S-o).

Since the formula weight of the Ni compounds concerned (based on the Ni atoms in the formula unit) differ by a factor of 4.6, the identical DNELs result in a 4.6-fold variation in the 'permissible' Ni exposure.

Although inorganic Ni compounds are hardly absorbed through the skin, the DNELs for long-term skin exposure (W-C-L-d), expressed in µg/cm<sup>2</sup>, but without exposure duration, vary arbitrarily by a factor of 3,000 without any recognisable consideration of molecular mass or solubility.

A DNEL (W-C-S-i) for workers of always the same value (4 µg/m<sup>3</sup>) is given likewise for cadmium and seven Cd compounds, although the formula weights vary within a 1.9-fold range. Applied to elemental cadmium, the given air limit value corresponds to a working lifetime cancer risk of ~0.6 %. Three Cd compounds were registered without being classified as "carcinogenic" (see Section 2.3).

For the 13 registered Co compounds, the limit values (W-C-L-i, G-C-S-o, G-C-L-i only), on the other hand, take into consideration the formula weights of the substances, albeit with one extreme deviation.

### **3.2.3 Example of a substance group: complex oil-derived substances**

For the majority of those oil-derived products for which DxELs have been provided for workers and the general population, the values for the general population are higher than those for workers. For instance, a DMEL<sub>worker</sub> (W-C-S-i) of 3.25 mg/m<sup>3</sup> compares to a value of 14.7 mg/m<sup>3</sup> for the general population. This observation is also true for numerous complex coal- and oil-derived substances excluded in Section 2.2 that were randomly sampled (e.g. EC Nos. 265-198-5, 270-662-5, 270-737-2, 265-193-8, 271-013-9, 309-939-3, 271-260-2,

308-773-0). If one assumes a demand for an equally low cancer risk level for workers as for the general population [3], an inhalation concentration twice as high would be expected for workers (because of the respiratory volume of 10 m<sup>3</sup>/8 h for workers versus 20 m<sup>3</sup>/24 h for the general population), and not vice versa.

However, the maximum dermal or oral exposure per kg bodyweight (bw), which always relates to 24 hours, should be the same for workers and the general population. This requirement is not met by the registrations mentioned: a DMEL (W-C-S-d) of 23.4 mg/kg bw-day compares with a DMEL (G-C-S-d) of 42.2 mg/kg bw-day. If one additionally considers the Endpoint Summaries in which DMELs and DNELs appear to have been arbitrarily mixed, even higher excess exposure of the general population occurs than for workers.

### **3.2.4 Comparison: Workers versus the general population**

For corresponding endpoints for which DxELs are given both for workers and the general population, 142 pairs of values were formed. These were based on 63 substances, with more than one pair of values being available for 33 of these substances. 48 value pairs concerning acute effects were excluded, as Guidance Chapter R.8 [2] recommends deriving DNELs and (not DMELs!) for effects with a toxicological threshold mode of action – and these may include *acute* effects of carcinogens. Furthermore, 16 pairs were excluded that envisaged a higher exposure for the general population than at the workplace.

The ratios  $\text{DMEL}_{\text{worker}}/\text{DMEL}_{\text{gen.pop.}}$  ( $n = 18$ ) showed a range of 1 to 3,800 (mean value = 350). The analogous result for  $\text{DNEL}$  ratios ( $n = 25$ ) differs only insignificantly from this: range 1 to 4,000 (mean value = 470)<sup>8</sup>. This finding is further evidence that the systematic difference between DMELs and DNELs was ignored in the course of registration. A comparative evaluation for acute endpoints yields a similarly inconsistent picture.

In the case of chronic intake of a certain substance, it can be expected according to Guidance Chapter R.8 [2] that the ratios  $\text{DxEL}_{\text{worker}}/\text{DxEL}_{\text{gen.pop.}}$ , calculated separately for dermal and inhalative exposure, will equal approximately the ratio of 1 : 2 (**Figure 5**). This demand was only satisfied in one of nine cases (trichloropropane).

### **3.2.5 Consistency between dermal and inhalative DxELs**

According to the standard model of Guidance Chapter R.8 [2], there is a relationship between the dermal or oral intake on the one hand and the inhalation limit value (DMEL or DNEL) on the other hand. For workers (10 m<sup>3</sup> respiratory volume in 8 hours of light work), 1 mg/kg bw-day of dermal or oral exposure corresponds with an inhalation concentration of 7 mg/m<sup>3</sup>, whereas for the general population (20 m<sup>3</sup>/24 h) this figure is 3.5 mg/m<sup>3</sup>. A body weight of 70 kg and 100 % absorption are assumed. The ratio  $\text{DxEL}_{\text{dermal}}/\text{DxEL}_{\text{inhalative}}$  must

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<sup>8</sup> Here, 23 Ni and Co compounds that each showed the same quotients were only included once for chronic-systemic and chronic-local effects. Otherwise the mean value based on 60 value pairs is 1,180.

	Workers (W)	General Population (G)
dermal, oral	$a \cdot r_{d,W} \cdot w \text{ mg/kg b.w.} \cdot d$ $(W_d)$ ↓ *70 kg b.w./person $70 \cdot a \cdot r_{d,W} \cdot w \text{ mg/person} \cdot d$ ↓ ÷ 10 m <sup>3</sup> /d 	$a \cdot r_{d,G} \text{ mg/kg b.w.} \cdot d$ $(G_d)$ ↓ *70 kg b.w./person $70 \cdot a \cdot r_{d,G} \text{ mg/person} \cdot d$ ↓ ÷ 20 m <sup>3</sup> /d 
inhalative	$7 \cdot a \cdot r_{i,W} \cdot w \text{ mg/m}^3$ $(W_i)$	$3,5 \cdot a \cdot r_{i,G} \text{ mg/m}^3$ $(G_i)$

$$\frac{W_d}{G_d} : \frac{W_i}{G_i} = \frac{a \cdot r_{d,W} \cdot w \cdot 3,5 \cdot a \cdot r_{i,G}}{a \cdot r_{d,G} \cdot 7 \cdot a \cdot r_{i,W} \cdot w} = \frac{1}{2} ; \quad \frac{W_d}{W_i} : \frac{G_d}{G_i} = \frac{1}{2} \quad *)$$

**Figure 5. Relationship between the limit values (DNELs or DMELs, long-term) for a certain substance according to the standard model of the Guidance [2].** The rate of absorption is assumed by default to be 100 %, as long as the absorption rate cannot be shown to be lower. In the case of the low chronic exposures considered, deviations between workers and the general population are improbable ( $r_{d,W} = r_{d,G}$ ;  $r_{i,W} = r_{i,G}$ ). On the other hand, the rate of dermal absorption (for workers and the general population) could differ from that for inhalative intake ( $r_{d,W}/r_{i,W} = r_{d,G}/r_{i,G} \neq 1$ ). With a factor of  $w > 1$ , workers would be burdened with a higher permissible exposure than the general population. As the equation shows, the factors  $r$  and  $w$  cancel and therefore have no effect on the quotient  $(W_d/G_d) / (W_i/G_i)$ .

\*) In the original paper, erroneously, this result was given with 2 instead of 1/2. The analysis in Section 3.2.5 is not affected by this mistake. It was correctly done independently from the wrong typing in Figure 5.

therefore be half \*\*) as high for workers as the corresponding ratio for the general population (Figure 5). Deviations could arise from absorption rates differing between the two groups of persons, which, however, is very unlikely in view of the low concentrations involved.

17 such relationships for the chronic-systemic effects were found and investigated. In only three cases did the registered DxELs show approximately the required relationship. In five cases, the two ratios had the same value, which conflicts with the standard model. In the other cases, the most curious constellations and contradictions occurred; e.g. for 1,2-dibromoethane (volatile like isobutyl acetate) a  $DMEL_{\text{dermal}}$  was provided that was 140 times higher than according to the standard model, and the same registration confirms skin absorptivity and nevertheless withholds data on dermal toxicity on the grounds of “exposure based waiving”.

\*\*) The wording “twice as high” in the original paper has to be replaced by “half as high” in order to correct the mistake indicated in the footnote to Figure 5. Further amendments are not necessary because the analysis was correctly done independently from the wrong typing in Figure 5.

### **3.3 DMELs for non-carcinogenic substances**

The ECHA Guidance [2; 5] envisages the derivation of risk-based DMELs only for proven genotoxic substances.

Nevertheless, substances that are not suspected of having a pC/M effect are registered with DMELs in the Dissemination Portal. For example, DMELs are provided partly or exclusively for the following substances in the Endpoint Summary: acetone, o- and p-xylene, styrene, cumene, 2-phenylpropene, di-tert-butyl cresol, tert-butyl benzoic acid, trichloroacetic acid, peracetic acid, fumaric acid, methyl tert-butyl ether, tin sulphate and diallyl phthalate. None of these substances is classified as pC/M in its own registration or in the harmonised classification. Furthermore, substances which are only classified as suspected carcinogens have been registered with DMELs (e.g. dichloromethane, vinylpyrrolidone). In many of these Endpoint Summaries, the DMELs, often mixed with DNELs, are scattered among acute and chronic effects, among workers and the general population. The fact that for some of the cited substances values qualified as “DMELs” appear which are numerically identical to the workplace limit values of TRGS 900 suggests that further confusion among the users of the Dissemination Portal has to be expected.

## **4 Discussion and conclusions**

### **4.1 Qualitative flaws and shortcomings**

For two thirds of the registered pC/M substances, not a single limit value is accessible<sup>9</sup>). DxELs are given only for one third of the substances; and for the vast majority of these cases only one or two values (Figure 3) are given, these by no means always being values for systemic long-term effects. The lack of a long-term value might mislead users of the portal to refer to the limit value relating to the acute effect as an ‘alternative’.

Where DMELs would be expected in accordance with the concept published by ECHA, predominantly DNELs have been registered (Figure 2). In the practice of registration, there is hardly any evidence of the principle of the ECHA concept, namely that DMELs are risk-based limit values whereas DNELs are health-based limit values. For the pC/M property of certain substances, there may be a non-genotoxic mechanism and a threshold mode of action. Whether the registration of these data as DNELs was prompted by this assumption is not apparent at the Dissemination Portal.

In many cases, the impression of an arbitrary muddle predominates, e.g. where a mix of DMELs and DNELs is given for varying endpoints or where DMELs are provided for substances (e.g. xylenes) that are not pC/M according to present knowledge. The presented deviations from the formal relationships between the DxELs for different endpoints and, for example, the use of DNELs to describe the long-term toxicity of mineral oil products contain-

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<sup>9</sup> See Figure 1. Most registrants will probably have welcomed the fact that the information given in the Endpoint Summary is voluntary. Some registrants may have gone by the fact that the ECHA Guidance – and specifically the derivation of DMELs – is not binding [22] or, in the event of a lack of a uniform acceptance risk, complied with the request not to derive a risk-based limit value. The reasons for blank entries are not given in the Endpoint Summary, and this considerably limits the usefulness of the portal.

ing benzene or butadiene also suggest that many registrants have neither understood nor applied the DMEL approach. In some cases of multiple registrations of the same substance, the DxELs differ considerably from registration to registration.

The described flaws gain practical significance from the fact that the Dissemination Portal is designed to make it easy to find data that have to be made publicly available under REACH Article 119. Unlike the author of the present paper, those interested in DMELs for a certain substance will not conduct systematic evaluations and will assume the published data to be correct while only a comparative analysis would prove these data to be nonsensical, dubious or incorrect. Navigation and access are additionally hampered by poor user-friendliness, formal and content-related confusion (e.g. 18 DNELs or DMELs per substance), mutilated data (such as the lack of parameter identifier or measurement units) and the pronounced frequency of omitted categories and blank entries.

The nature of the limit values and the assumptions on which their derivation is based are not disclosed in the Dissemination Portal [11]. The fields *Assessment factor*, *Dose descriptor starting point*, *Most sensitive endpoint* und *Justification for (no) DN(M)EL derivation / applied assessment factors* envisaged for registration provided in the IUCLID input mask shown at the portal although – as long as they are not blank – they could be useful for portal users for an initial plausibility check. The genuine registration dossiers that might contain such details are not accessible to the public. It is hard to understand why the derivation of exposure limit values is subject to confidentiality.

A third of the DxELs are referred to as “acute/short-term exposure” values, but no details of the duration of this “short-term” exposure are given.

ECHA’s statement that “*companies have the obligation to provide accurate and up-to-date information*” [12] has so far been realised only fragmentarily. The opportunities for correcting the registered data are obviously not made use of. An initial general evaluation that the author conducted on an earlier database version in 2010 revealed exactly the same shortcomings for the same substances.

REACH does not provide for an effective tool for a mandatory elimination of these flaws. The substance evaluation that will be undertaken by the member states as of 2012 and that consists of an inspection evaluation of selected registered data is intended to cover 30 to 40 substances per year of the total quantity of currently about 5,000 registered substances (which will be joined by many more in 2013 and 2018), without there being any focus in general on carcinogenic substances. Nor does it seem to be decided whether and in what way any mistakes discovered in the registration dossiers will be corrected.

*Rouw* [23] conducted a study of 33 registrations for 27 substances with declared DMEL<sub>worker</sub> and had the opportunity to evaluate the registration dossiers. In 61 % of cases, he found that DMELs were derived in accordance with the Guidance, while, in the remaining cases, DNELs had been erroneously derived, existing limit values had been copied, or “creative and doubtful interpretations” had been given. For 23 dossiers, he was able to determine associated risk levels that were not always explicitly identifiable. The lifetime cancer risk was 1 : 1000 or higher in 39 % of cases; for 17% it was (1 to 5) : 10,000, and for a further 39 % it was (1 to 5)

: 100,000 – the latter corresponds to the long-term German acceptable risk – and for 4 % it was lower. *Rouw* concluded that not all registrants have sufficient grasp of the DMEL concept.

## **4.2 The risk basis**

The cornerstone for a risk-based limit value is the risk on which its derivation is based. For the registered DMELs (that are frequently incorrectly given as “DNELs” in the Endpoint Summary), the cancer risks on which they are based – assuming they were taken into consideration at all – are not given. Table 4 illustrates that DxELs may be associated with intolerably high working lifetime cancer risks: for example, statistical risks from which it can be concluded that 1 in 57 or 315 exposed persons will contract cancer.

In many cases, existing or former limit values (e.g. TRKs = German Technical Guidance Concentrations) have simply been relabelled DxELs. The conjecture expressed in an earlier paper [3], that for a substance several DMELs with assigned different cancer risks would be communicated “for selection” by the user, cannot be confirmed. In fact, the link between the limit value and risk level seems to have been ignored, brushed aside or masked by means of an inappropriate DNEL. The author is so far unaware of a single safety data sheet in which the risk level on which a DMEL was based has been communicated.

In connection with an amendment of BekGS 409 [24], there are plans in Germany to address the usability of DMELs for health protection at work. The planned amendment explicitly states that reference can only be made to a DMEL if the cancer risk on which it is based has been quantified and is declared. \*) In the light of the above findings, it can be assumed that DMELs will be of no significance in occupational safety and health even in the medium and long term due to the missing declaration of the risk level on which their derivation had been based. On the other hand, many carcinogenic substances have been registered with DNELs<sup>10</sup> (see above). In view of these numerous incorrect registrations, it might be more appropriate to subject also DNELs to closer scrutiny before resorting to them. Since ‘wrong’ DNELs (instead of DMELs) can also be expected to be widespread in safety data sheets, the problems arising from the currently impracticable DMEL concept will tend to increase.

*\*) Meanwhile, the amendment has been endorsed and published (see reference [24]).*

Likewise, no clear picture can be gained for the magnitude of DxELs for workers compared to the corresponding DxELs for the general population (Section 3.2.4). With regard to the so-called “linearised approach”, Guidance Chapter R.8 [2] suggests a planned(!) cancer risk for workers ten times higher than for the general population, which is unacceptable for ethical reasons and must be rejected [3; 8]. The “Large Assessment Factor approach”, also proposed in this Guidance, pretends doing without the choice of acceptable cancer risk. In fact, however, this model assumes an acceptable risk amounting to 1 % and envisages the application of certain substance-independent assessment factors. These factors do not necessari-

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<sup>10</sup> According to the REACH regulation, DNELs are health-based and may only be assigned for effects with a threshold mode of action. The misuse of “DNEL” constitutes a legal infringement that should be punished by the member states.

ly reflect the carcinogenic potency of the substance in question, are not comprehensible and are doubtful in some cases: for instance, the unsubstantiated claim that the working population is twice as resistant to carcinogens as the general population <sup>11</sup>). The assumption that the cancer risk from a certain carcinogen is only half as high for working people would yield DMELs twice as high as those for members of the general public.

An evaluation of Endpoint Summaries containing corresponding DxELs for long-term exposure shows (along with the frequently observed internal inconsistency of the data) the following: 19 % of the pairs of values imply higher exposure for the general population than for workers. This gives rise to the suspicion that the data were not reviewed before registration. A further 18 % of the value pairs present an approximately equal risk for workers and the general population; these would satisfy the cited ethical criteria. According to 22 % of the pairs of DxELs, the limit values intended for workers are more than twice to 12-fold that for the general population. The remaining 41 % of value pairs express limit values for workers by a factor of 30 to 4,000 higher than for the general population. These differences call for a fully substantiated explanation <sup>\*</sup>). The fact that the pairs of values last-mentioned (factor 30 to 4,000) mainly consist of DNELs underlines the misuse of the DNEL concept, because such huge differences would not be expected if health-based values were used.

*<sup>\*</sup>) When taking into account the different exposure times during a working life and during a whole lifetime and the higher inhalation volume at work, an exposure to a certain level of a carcinogen over the whole lifetime or to the six-fold concentration of the same carcinogen over a working life leads to approximately the same cancer risk. An exposure putting workers at a higher risk than the general population is ethically unacceptable.*

## 5 Outlook

The heart of the problem seems to lie in the lack of a uniform acceptable cancer risk on which the derivation of DMELs is to be based. The present findings underline the fact that leaving the choice of the acceptable cancer risk to companies themselves is no substitute for the necessary debate on and definition and communication of a uniform Europe-wide acceptable risk. The lack of a risk level based on social consensus seems to be an important reason for the non-application of the DMEL concept, as individual registrants do not have (and do not have to have) the necessary competence for deciding on the acceptability of cancer and taking the responsibility for it.

One possible solution was outlined at a European workshop [6] in May 2011: Until a political consensus will be reached, it was proposed [8, 10] to base the derivation of DMELs on the acceptable risk of 4 : 100,000 of the German traffic light model [4] throughout the EEA.

The alternative would be for the EU institutions to withdraw the DMEL concept for revision and supplementation [3].

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<sup>11</sup> The authors of the original version of this strategy (which was developed for a different purpose and did not differentiate between workers and the general population) explicitly stress that the factors that they had proposed require political discussion and social consensus before their application [3; 8].

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