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Contents

Executive summary

The objective of this project is to identify substances toxic to reproduction (hereafter: 'reprotoxins') that are relevant for workers' exposure via inhalation at a considerable number of workplaces in Europe and thus for which an IOELV under the CAD might be suggested.

As a starting point, the terms 'reprotoxin' and 'relevance' are defined for their use in the context of the project. In addition, the conditions under which an OEL would be appropriate as a regulatory tool are reflected on. Then the methods applied for selecting reprotoxins and for assessing their relevance are detailed. In addition to the reprotoxins already included in Annex VI of the CLP regulation, further substances are considered to be future (or 'potential') reprotoxins if they meet certain conditions and are included in the analysis.

The main information sources utilised are the C&L Inventory, the REACH database on registered substances and compilations of substances included in various REACH processes, all available on the ECHA website.

The analysis resulted in the selection of 141 reprotoxins or groups of reprotoxins, divided into three categories of different levels of relevance. For 66 of them an IOELV under the CAD might be suggested.

In an Annex all selected reprotoxins, complemented by additional information for further refinement, are listed.

1. Introduction

1.1 Background to the project

In its resolution on the improvement of occupational health and safety in the European Union, adopted by the Executive Committee in December 2014, the European Trade Union Confederation (ETUC) called, among other things, for the inclusion of reprotoxic substances in the scope of the Carcinogens and Mutagens Directive (Dir. 2004/37/EC, hereafter: CMD), 'due to the severity and irreversibility of the health effects for workers (especially pregnant women) from exposure to these substances'. With this request, the ETUC intends to generalise the past decision of several EU Member States to include the area of reprotoxic substances in the scope of their national legislation concerning carcinogenic and mutagenic substances.

The proposal was made against the background of the decision of the Commission, announced in October 2013, to halt the revision of the CMD during its mandate as part of the so-called REFIT programme. One issue of the revision of the CMD was the extension of its scope to include reprotoxic substances. However, even before halting the revision process as a whole, the Commission had already separated the issue of including reprotoxic substances in the scope of the CMD from other issues, among them the derivation of binding OELs for about 25 carcinogens.

For many reprotoxic substances that do not also exhibit carcinogenic properties, effect thresholds have been identified below which no adverse effects occur. For them, health-based OELs – so-called indicative occupational exposure limit values (IOELVs) – could thus be derived under the CAD that would be protective for reproductive toxicity. We should observe, though, that certain reprotoxic substances might be identified as endocrine disrupting chemicals (EDs) without an effect threshold below which no adverse effects occur. Once a reprotoxic substance is identified as an ED, no IOELV should be derived for it. Instead, for such substances other regulatory approaches are warranted.

In contrast to BOELs under the CMD, however, when it comes to their implementation in national legislation, Member States have the discretion of introducing higher limit values that might not be protective for reproductive toxicity. Nevertheless, establishing IOELVs under the CAD for reprotoxic substances would be an important initial step in protecting workers from the health effects of reprotoxic substances.

1.2 Objectives and limitations

The objective of this project is the identification of substances toxic to reproduction (reprotoxins) that can be considered relevant in the sense that a considerable number of workers in Europe are affected by exposure to them via inhalation.

In order to do so, two terms need to be defined in the context of this project, 'reprotoxin' and 'relevance'. In addition, the exposure routes of the relevant reprotoxins identified have to be assessed, and reprotoxins that are relevant with regard to dermal exposure only are to be excluded.

1.2.1 Definition of 'reprotoxin'

In the context of this project, all substances or mixtures included in Annex VI of the CLP regulation (Reg. (EC) No 1272/2008) classified as R 1A, H360 or R 1B, H360 are considered to be reprotoxins.

Effects on fertility and development are communicated by different hazard statements: reprotoxins adverse to fertility are denoted by the hazard statement H360F; reprotoxins adverse to development by the hazard statement H360D; and reprotoxins adverse to both fertility and development by the hazard statement H360FD.

1.2.2 'Relevance' of a reprotoxin

From an occupational health and safety perspective, the relevance of a reprotoxin is based on:
– the number of workers exposed to it; and
– the extent of the exposure (level, duration and frequency).

Given that quantitative data for these factors were available, the number of workers could be determined for whom the exposure levels via inhalation were above any threshold for effects adverse to reproductive toxicity. Assessments of the relevance of individual reprotoxins could then be based on either the total number of workers exposed to them, or the number of workers exposed to them above their respective effect threshold, or a combination of both.

Because, however, the necessary data for the two former factors – that is, number of workers exposed and extent of exposure – are not available, and information on the existence of an effect threshold and its size have been determined for only a limited number of reprotoxins as yet, the relevance of a reprotoxin cannot be determined by this method. Instead, other criteria have to be employed.

1.2.3 Appropriateness of an OEL as a regulatory instrument

OELs are major tools for risk assessment of respiratory exposure. There, they serve two main functions:
(i) for the design of control measures, they define the minimum level of protection; and
(ii) for the assessment of the effectiveness of control measures applied, they are the yardsticks for the resulting exposure level and, thus, for the necessity of improving those control measures.

For dermal exposure, however, OELs might be of scientific and regulatory, but not of practical interest due to the absence of suitable instruments for monitoring dermal exposure at the workplace.

1.3 Method – general definitions

The process of identification and selection of 'relevant reprotoxins' as discussed in the previous section is done in two steps. First, both terms are specified: which substances should be considered to be *reprotoxins* in the context of this project, and what criteria should be employed to designate a reprotoxin as a *relevant* one? Second, specific selection criteria for both categories are defined that enable the final selection of 'relevant reprotoxins' and their allocation to different levels of relevance.

In this section, the first step is addressed: the general schemes for identifying reprotoxins and assessing the relevance of substances, respectively, are described, and the concrete combination of both pieces of information is presented.

1.3.1 Reprotoxins

Given the purpose of this report – to provide a list of reprotoxins for which IOELVs under the CAD should be established – substances selected should meet the definition specified in Section 1.2, above. For simplification, these reprotoxins will be denoted as '*actual* regulatory reprotoxins'.

Actual regulatory reprotoxins placed on the market can be identified via the publicly available database containing classification and labelling information on notified and registered substances (C&L Inventory) on the website of the European Chemicals Agency (ECHA) (http://echa.europa.eu/information-on-chemicals/cl-inventory-database).

In addition to the 'actual regulatory reprotoxins', in the context of this project additional substances are considered to be 'potential regulatory reprotoxins'. A substance will be considered to be such a '*potential* regulatory reprotoxin' if one of the following three conditions is met:

(i) a process of harmonised classification either as R 1A, H360 or as R 1B, H360 was initiated and resulted in adoption by the Committee for Risk Assessment (RAC) of the ECHA by September 2015, but either subsequent legal procedures have not been finalised or the resulting adaptation to technical and scientific progress (ATP) has not come into force yet; information on such processes is available in the 'Opinions of the Committee for Risk Assessment on proposals for harmonised classification and labelling' section of the ECHA website (http://echa.europa.eu/web/guest/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling);
(ii) a process of harmonised classification either as R 1A, H360 or as R 1B, H360 was initiated but not finalised by October 2015; information on such processes is available in the 'Registry of Intentions' section of the ECHA website, both in the part 'Current CLH intentions', (http://echa.europa.eu/web/guest/registry-current-classification-and-labelling-intentions) and in the part 'Submitted CLH proposals' (http://echa.europa.eu/web/guest/registry-of-submitted-harmonised-classification-and-labelling-intentions); or
(iii) a substance without a harmonised classification with regard to reprotoxicity has been notified to the ECHA by one or more manufacturers or importers either as R 1A, H360 or as R 1B, H360; information on such notifications is available in the C&L Inventory on the ECHA website (http://echa.europa.eu/information-on-chemicals/cl-inventory-database).

Whereas conditions (i) and (ii) have been checked systematically for all entries in the respective list, no such systematic check has been undertaken for condition (iii). Not only is the number of substances with such notifications – with more than 1,700 entries – rather large, but the criteria for the individual notification applied by the respective notifier (manufacturer or importer) are unknown to the public. Therefore, an outside observer is not in a position to assess whether such a notification is justified or not. Such ambiguities are underlined by the observation that for a number of substances only a single notifier or a minority of notifiers indicated a notification either as R 1A, H360 or as R 1B, H360, whereas other notifiers of the same substance indicated either no notification for reprotoxicity or a notification for suspected reprotoxicity (R 2, H361) only. As a conclusion, substances with a notification either as R 1A, H360 or as R 1B, H360 are included as 'potential regulatory reprotoxins' only if other supporting evidence has been found, such as the inclusion in the risk management option analysis (RMOA) (cf. the ECHA website: http://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/pact), the inclusion in the Community Rolling Action Plan (CoRAP) (cf. the ECHA website: http://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table), or the derivation of an OEL at national level.

The reason for considering 'potential regulatory reprotoxins' is the expectation that in the foreseeable future many of them will become 'actual regulatory reprotoxins' by inclusion in Annex VI of the CLP regulation classified as R 1A, H360 or R 1B, H360.

1.3.2 Relevance

In the absence of comprehensive knowledge of both the extent of exposure to the majority of reprotoxins at workplaces in the EU and the effect thresholds for reprotoxicity of many of them, surrogate signifiers have to be employed to assess the relevance of individual reprotoxins.

For substances placed on the market, an initial approach for approximating exposure information is to use information on production or import volume. Such information is publicly available via a database containing information on substances registered under REACH on the ECHA website (http://echa.europa.eu/information-on-chemicals/registered-substances) for reprotoxins above a production or import volume above one tonne per year. For the purpose of this report, the following information is of particular significance: registration status (full registration/registration as intermediate/no registration), and tonnage band (in case of full registration).

Included in that database are substances notified as new substances (NONS) under Dir. 67/548/EEC before REACH came into force. For them, less information is available than for substances registered under REACH. In particular, no information on production volume is publicly accessible.

For certain substances placed on the market, such registration information is not available, however. Active substances for use either in plant protection products or in biocidal products are regarded as being registered under REACH (cf. Art. 15 of the REACH regulation) and are therefore not necessarily contained in the above-mentioned database. In the further analysis they are considered to be relevant if they are listed either in the Annex to Commission Implementing Regulation (EU) No. 540/2011 implementing Regulation (EC) No. 1107/2009 concerning the placing of plant protection products on the market, or are contained in the database on biocidal active substances on the ECHA website (http://echa.europa.eu/web/guest/information-on-chemicals/biocidal-active-substances).

Exempted from registration under REACH are substances used in medicinal products for human or veterinary use (cf. Art. 2 para 5 of the REACH regulation). Thus, also for them no registration information is available. Accordingly, in the further analysis such substances are considered to be relevant, given that their use in medicinal products could be identified.

1.3.3 Relevant reprotoxins

The number of actual regulatory reprotoxins as listed in the C&L Inventory on the ECHA website with a harmonised classification as R 1A, H360 or as R 1B, H360, as updated on 30 October 2015, was about 220. That number is reduced in two ways, described in more detail in Section 1.4, below:

(i) substances also classified as either carcinogens (C 1A, H350 or C 1B, H350) or mutagens (M 1B, H340) are omitted;
(ii) reprotoxic lead and boron compounds are combined to form single entries.

As a result, the remaining number of actual regulatory reprotoxins is reduced to less than 100. For potential regulatory reprotoxins, due to their much smaller number, no such reduction was deemed necessary.

The relevance of each substance in the resulting sample of reduced actual regulatory reprotoxins and all potential regulatory reprotoxins is assessed by a tiered approach consisting of the following four steps:

As a *first* step, for each substance presumably placed on the market it was examined whether it has been registered under REACH and, if so, either with a full registration, or with a registration for use as an intermediate only, or as a NONS substance.

As a *second* step, for reprotoxins presumably placed on the market but without a registration under REACH, it was checked whether they are listed either as an active substance approved for use in plant protection products or as a biocidal active substance.

As a *third* step, for all remaining reprotoxins presumably placed on the market – those without a registration under REACH, without a listing either as an active substance for plant protection or as a biocidal active substance – it was checked whether they are used in medicinal products.

As a *fourth* and final step, it was checked whether any of the remaining reprotoxins presumably placed on the market (no registration under REACH, listed neither as an active substance for plant protection nor as a biocidal active substance, not used in medicinal products) are currently, or were in the past, subjected to certain regulatory processes at European level in the context of the REACH regulation, the CLP regulation or the CAD, or at national level in Germany or the Netherlands. Such processes are:
(i) in the context of the REACH regulation and the CLP regulation the inclusion in the Candidate List of Substances of Very High Concern for Authorisation in accordance with Art. 59 (10) of the REACH Regulation (electronically accessible at: http://echa.europa.eu/candidate-list-table); or the intention, initiation or completion of a harmonised classification as R 1A, H360 or as R 1B, H360;
(ii) in the context of the CAD the development of a recommendation by SCOEL;
(iii) at national level the derivation of an OEL in Germany or the Netherlands.

1.4 Method – specific selection criteria

In this section, the second step of the selection and differentiation process is addressed. By presenting detailed selection criteria, first, the reduction of the

number of actual regulatory reprotoxins is explained, and second, the grading of relevance is outlined.

1.4.1 Selection of actual regulatory reprotoxins

As indicated in the previous sub-section, two mechanisms were used for reducing the number of actual regulatory reprotoxins by more than 50 per cent in preparation for the subsequent examination of their registration status under REACH. Both are explained in detail below.

Omission of substances classified as either carcinogens (C 1A, H350 or C 1B, H350) or mutagens (M 1B, H340)

Reprotoxins that are also classified as either carcinogens or mutagens are within the scope of the Carcinogens and Mutagens Directive (Dir. 2004/37/EC, hereafter: CMD). As a legal consequence, OELs for those substances can be derived only under the CMD and, thus, have to fulfil the criteria of a binding OEL (in short: BOEL) as specified in Art. 16 paragraph 1 of the CMD. In other words, legally an OEL under the CAD cannot be derived for carcinogens or mutagens. Subsequently, such carcinogens or mutagens are omitted from the further analysis.

In contrast, reprotoxins that are at the same time *potential* regulatory carcinogens are not omitted from the further analysis as the duration for their re-classification as carcinogens (C 1A, H350 or C 1B, H350) is not predictable. Until then, they are within the scope of the CAD and an OEL might be warranted.

In the context of this report, a substance not classified as a carcinogen (C 1A, H350 or C 1B, H350) is considered to be a 'potential regulatory carcinogen' if at least one of certain conditions, analogous to the ones employed for the definition of a 'potential regulatory reprotoxin' (cf. Section 1.3, sub-section 'Reprotoxins', above), is met: the existence of a notified intention, initiation or finalisation of a process of harmonised classification either as C 1A, H350 or as C 1B, H350; the existence of a classification by the International Agency for Research on Cancer (IARC) either as 'carcinogenic to humans' (group 1) or as 'probably carcinogenic to humans' (group 2A); or the existence of a notification to the ECHA by one or more manufacturers or importers either as C 1A, H350 or as C 1B, H350, in conjunction with other supporting evidence, such as the inclusion in the risk management option analysis (RMOA), the inclusion in the Community Rolling Action Plan (CoRAP) or the derivation, or attempted derivation, of an exposure-risk-relationship at national level.

Combination of reprotoxic compounds of certain elements to single entries

For most metals for which an OEL has been derived, the scope of the OEL usually covers both the metal itself and its compounds or, as the case may be, its inorganic compounds. In the case of reprotoxic substances, this

pattern holds for lead and its inorganic compounds, and seems to be applicable for two groups of boron compounds also, borates and perborates.

Table 1 provides an overview of the two groups of compounds classified as reprotoxins (inorganic lead compounds, boron compounds) combined into a single entry each, covering 39 entries in total in the C&L Inventory on the ECHA website.

Table 1 **Reprotoxic compounds of certain elements combined into a single entry each**

Reprotoxic compounds	Number of individual entries in C&L Inventory on ECHA website
Inorganic lead compounds	16
Boron compounds: borates and perborates	23

1.4.2 Assessment of relevance of selected regulatory reprotoxins

The relevance of reprotoxins presumably placed on the market is graded according to either their registration status under REACH or their identification as a substance used in medicinal products or approved for use in plant protection products or biocidal products.

Relevance based on registration information

Less than 100 entries in the C&L Inventory on the ECHA website classified as R 1A, H360 or as R 1B, H360 remained after the selection process described above. For each of them it was checked whether an entry existed in the database on registered substances on the ECHA website. Similarly, for each of the three combined entries for inorganic lead compounds, borates and perborates it was checked whether an entry existed in the registration database for at least one related compound.

In the same way, for all potential regulatory reprotoxins (identified by searching the respective lists on the ECHA website addressed in Section 1.3, subsection 'Reprotoxins', above) their registration status under REACH was checked.

According to the type of registration, four different levels of relevance are defined for the purpose of this project:
– 'relevance' for registration type 'full';
– 'limited relevance' for registration type 'intermediate';
– 'unclear relevance' for reprotoxins either registered as 'NONS' or without registration which are, or have been, subjected to certain regulatory processes (as described in Section 1.3, sub-section 'Relevant reprotoxins');

– 'no relevance' for reprotoxins without registration unless they meet the criterion described under 'unclear relevance', above.

This grading of the level of relevance of a reprotoxin registered under REACH is based on the underlying definitions and obligations stipulated in the REACH regulation for substances placed on the market. A precondition for placing reprotoxins on the market with a tonnage greater than one tonne per year is registration in accordance with Art. 6 of REACH. If the full spectrum of uses is to be covered, a complete registration is necessary in accordance with Art. 10 of REACH; if the reprotoxin is to be manufactured and used as an on-site isolated intermediate under strictly controlled conditions only, in accordance with Art. 17 of REACH a less detailed registration suffices. For reprotoxins manufactured and placed on the market below one tonne per year, registration is not requested.

The term 'strictly controlled conditions' entails that the substance be 'rigorously contained by technical means during the whole lifecycle'; workers should thus not be exposed to such substances during manufacture and use. Exposure might be possible, however, during control tasks and through repair and maintenance work. Due to these remaining possibilities for workers' exposure, reprotoxins with registration as on-site isolated intermediates are still considered to be of limited relevance.

Due to the rather limited information publicly available for reprotoxins listed as NONS, their relevance status cannot be decided as, depending on their actual use, they could have qualified either for a full registration or for a registration as on-site isolated intermediates had they been registered according to the REACH criteria for phase-in substances. Thus, they are considered to be of unclear relevance.

In contrast, reprotoxins placed on the market without any registration are generally considered to be of no relevance, although it is impossible to differentiate whether they are manufactured and placed on the market not at all or below a tonnage of one tonne per year.

A subset of reprotoxins without any registration that are, or have been, subjected to one of the regulatory processes described in Section 1.3, sub-section 'Relevant reprotoxins', is considered to be of unclear relevance because the mere existence of such processes is indicative of a certain level of relevance. However, without additional information on the reasons for the respective process, that level cannot be specified for the particular reprotoxin.

Relevance based on use category

Reprotoxins without any entry in the database on registered substances on the ECHA website, but listed either as an active substance approved for use in plant protection products or as a biocidal active substance are considered to be of limited relevance in the context of this report. This is due to two considerations:

(i) in both regulations (on plant protection products and on biocidal products) the approval of reprotoxins as active substances is supposed to be prohibited or restricted to stringent conditions;
(ii) in both regulations, an Acceptable Operator Exposure Level (AOEL) might be established as part of the approval process for an active substance; thus, the derivation of an OEL under the CAD would result in legal interference and should not be considered to be a viable option, accordingly.

In contrast, reprotoxins without any entry in the database on registered substances on the ECHA website, but used in medicinal products are considered to be of unclear relevance. This is due to the following aspects:
– unavailability of any information on their actual use;
– unavailability of any information on use conditions;
– unavailability of any exposure information.

In addition, for this use category it remains to be discussed whether an OEL would be an appropriate regulatory tool or whether sector-specific control measures, analogous to those for laboratories, would be a better approach.

1.4.3 Refinement of level of relevance of reprotoxins placed on the market

The information publicly available on substances with full registration allows further differentiation of the qualifier 'relevance'. This could be based in particular on two parameters: (i) the tonnage band for the production volume; and (ii) the identified uses, expressed as process categories primarily for manufacture, formulation, uses at industrial sites and uses by professional workers. Both pieces of information are available in the registration database on the ECHA website (http://echa.europa.eu/information-on-chemicals/registered-substances).

Due to the comparatively small number of substances identified as 'relevant reprotoxins' (cf. Section 2.1), a further differentiation based on the tonnage band is considered to be of low added value and thus has not been done for the time being. Instead, for each reprotoxin with full registration the information on the tonnage band is listed in Tables 1–3 of the Annex.

In addition, we have tried to utilise the information on process categories (PROCs) as it facilitates deeper insight into potential exposure situations of workers. The following two process categories are considered to result in no exposure of workers, corresponding to the exposure situation of tasks involving intermediates:
(i) PROC 1: Use in closed process, no likelihood of exposure;
(ii) PROC 3: Use in closed batch process (synthesis or formulation).

However, no substance was identified for which solely PROC 1 or PROC 3 (or both) has been registered. Neither could any substance be identified for which, in addition to PROC 1 or PROC 3, one or more of the following three

PROCs have been registered:
(a) PROC 15: Use as a laboratory agent;
(b) PROC 0: Other: monomer in imported polymer;
(c) PROC 0: Other: production of pharmaceuticals / vaccines.

As a result, the level of relevance was not reduced for any of the reprotoxins with full registration.

2. Results

2.1 Substances toxic to reproduction selected with different levels of relevance

Altogether 141 reprotoxins or groups of reprotoxins have been selected and are allocated to three different relevance categories. These substances are listed in Tables 1–3 of the Annex.

2.1.1 Substances toxic to reproduction considered to be relevant

Based on the selection criteria described in Section 1.4 above, 66 reprotoxins are considered to be relevant and the derivation of an OEL is deemed appropriate for them; they are listed in Table 1 (Annex); 39 of them are *actual regulatory reprotoxins*, 27 are *potential* ones.

2.1.2 Substances toxic to reproduction considered to be potentially relevant

Based on the selection criteria described in Section 1.4 above, 28 reprotoxins are considered to be potentially relevant and are listed in Table 2 (Annex); 14 of them are actual regulatory reprotoxins, 14 are potential ones.

Nine of them are registered as intermediates only; the remaining 19 have no registration, but are included either in the database on biocidal active substances or in the list of active substances authorised for use in plant protection products.

2.1.3 Substances toxic to reproduction with unclear relevance

Based on the selection criteria described in Section 1.4 above, 47 reprotoxins are considered to be of 'unclear relevance' which are listed in Table 3 (Annex):

– 18 of them are actual regulatory reprotoxins and four are potential ones without registration under REACH and subject to one of the regulatory processes described in Section 1.3, sub-section 'Relevant reprotoxins';
– four of them are actual regulatory reprotoxins registered as NONS;

– two of them are actual regulatory reprotoxins and 19 are potential ones without registration under REACH used in medicinal products and thus are exempted from the registration obligation under REACH.

2.2 Additional information in Tables 1–3 of the Annex

Additional information is provided in Tables 1–3 (Annex) in two different ways, by subdividing each table in separate sections for specific classes of reprotoxins, and by entering notes in different columns on individual substances. This information might be useful for further refinement of the level of relevance and for future decisions on the necessity of deriving an OEL for the respective reprotoxin.

2.2.1 Special classes of substances toxic to reproduction

In chapter 1, a number of special classes of substances are addressed. To enable easier identification of reprotoxins belonging to one of these classes, in Tables 1–3 (Annex) they are displayed as separate sub-sections:
– substances notified as new substances (NONS) under Dir. 67/548/EEC;
– biocidal active substances or active substances authorised for use in plant protection products PPP);
– substances used in medicinal products.

2.2.2 Notes on classification, registration and regulatory processes

Tables 1–3 (Annex) comprise five columns each:
(i) name of substance or group of substances;
(ii) CAS number, if available, otherwise EC number;
(iii) classification with regard to reproductive toxicity;
(iv) registration status under REACH and tonnage band, if available;
(v) additional comments.

Standard information in *column (iii)* is the harmonised classification with regard to reproductive toxicity as available from Annex VI of the CLP regulation. For reprotoxins for which the intention of a process of harmonised classification was notified, or for which such a process was initiated, the intended or proposed harmonised classification is specified. For reprotoxins without such information, the notified self-classification of the manufacturer or importer is specified. For potential regulatory carcinogens (that is, substances without a harmonised classification as a carcinogen (C 1A / 1B)) which are classified by IARC as Group 1 or Group 2A carcinogens, also the IARC classification together with its year of publication is specified.

Standard information in *column (iv)* for reprotoxins with a full registration is the tonnage band; for other reprotoxins it is specified whether they are

registered as intermediates only, as NONS or not at all. Reprotoxins with both a full registration and one for use as intermediates are denoted by the additional note (a). Reprotoxins approved as active substances in plant protection products are denoted by the entry 'PPP'; and reprotoxins approved as biocidal active substances by the entry 'biocidal active substance'. For reprotoxins used in medicinal products their use as anti-cancer drug is denoted by the additional note (b).

For *column (v)* a variety of notes are foreseen, which are detailed in the Annex below Table 3 in sub-section 'Explanation of notes in Tables 1–3'. Reprotoxins that are also potential regulatory carcinogens (cf. Section 1.4) are denoted by the additional note (c).

The numerical notes are ordered in four groups, referring to REACH and CLP processes; OSH processes and instruments at EU level; and OSH processes and instruments at Member State level. Information on OELs at Member State level is based on the GESTIS database on international limit values for chemical agents, available at: http://www.dguv.de/ifa/GESTIS/GESTIS-Internationale-Grenzwerte-f%C3%BCr-chemische-Substanzen-limit-values-for-chemical-agents/index.jsp or directly at: http://limitvalue.ifa.dguv.de/.

In particular, the numerical notes in column (v) are intended to facilitate access to additional publicly available information. For example, for the majority of REACH and CLP processes, substance-specific information – including information on use – is available at the ECHA website for the respective process.

3. Discussion

Combining classification information from the CLP regulation, on one hand, with registration information under REACH, information for plant protection products, for biocidal products and for medicinal products, on the other, 141 reprotoxins or groups of reprotoxins have been identified as relevant and allocated to three categories of different level of relevance. Seventy seven of them are actual regulatory reprotoxins, 64 are potential ones. The category for the highest level of relevance comprises 66 reprotoxins (cf. Annex, Table 1) for which an OEL under the CAD might be suggested.

Of the remaining 75 reprotoxins, 19 are active substances authorised for use in biocidal or plant protection products. The specific legislation applicable to them should take precedence to OSH legislation so that for regulatory reasons the derivation of an OEL under the CAD does not seem to be a priority issue. Another 10 carcinogens are registered as intermediates only. Also for them the derivation of an OEL does not seem to be a priority issue.

Whether the derivation of an OEL under the CAD for any of the reprotoxins from the group of four NONS will become a priority issue will depend on the future availability of additional information, in particular on production or import volume, and on use patterns.

For the remaining 42 reprotoxins, 20 of which are used in medicinal products, the currently available information, in particular on volume, use patterns and extent of exposure, is assessed as insufficient for suggesting the derivation of an OEL under the CAD. Should additional information become available, however, or the application of assessment criteria different from the actual information be recommended, the derivation of an OEL for additional reprotoxins from this group might also be suggested.

Twenty of the 141 reprotoxins identified as relevant are also potential regulatory carcinogens (cf. Section 1.4), which means that they remain within the scope of the CAD until they are re-classified as carcinogens (C 1A, H350 or C 1B, H350) and then would fall within the scope of the CMD. Nineteen of them are medicinal products and only one is a reprotoxin for which the derivation of an OEL is suggested.

For 12 of the 66 reprotoxins or groups of reprotoxins, for which the derivation of an OEL is suggested, an IOELV under the CAD is either already in existence

or is under preparation. For another 18 a health-based OEL in at least one EU Member State (MS) has been derived and might be used as a starting point for the derivation of an OEL under the CAD. Twenty-five of the 30 reprotoxins with an OEL of either kind are actual regulatory reprotoxins, whereas just five are potential ones.

For 59 of the 66 reprotoxins or groups of reprotoxins for which the derivation of an OEL is suggested, tonnage information is available from their registration. In particular for 29 of the 36 reprotoxins without an IOELV or an OEL at MS level, that information might be used for further prioritisation of the derivation of an OEL under the CAD. For this purpose, the 14 substances in the three higher volume bands (1,000–1,000,000 t/a) might be given precedence over the 15 substances in the three lower volume bands (0–1,000 t/a).

For 15 of the 30 reprotoxins with either an IOELV under the CAD or an OEL at Member State level, information is available on whether the OEL is protective not only for adverse fertility effects but also for developmental effects. For seven substances the OEL is supposed to be protective for both kinds of adverse effects, whereas for another eight, developmental effects cannot be excluded even when the respective OEL is achieved.

Annex

Table 1 **List of substances/groups of substances toxic to reproduction considered to be relevant**

No.	Substance/group of substances	CAS no.	Harmonised (or notified) classification	Registered tonnage band [t/a]	Comments
1	Benzyl butyl phthalate	85-68-7	R 1B, H360Df	1,000–10,000	3), 4: 2/2015;, 31)
2	1,2-Bis(2-methoxyethoxy) ethane	112-49-2	R 1B, H360Df	10–100	3)
3	Bis(2-(2-methoxyethoxy)ethyl) ether	143-24-8	proposed: R 1B, H360F	100+	2: 12/2015
4	Bis(2-methoxyethyl) ether	111-96-6	R 1B, H360FD	100–1,000	H), 3), 4: 8/2017; 31), 35)
5	Boric acid and borates, boric oxide (diboron trioxide)	10043-35-3 1330-43-4 1332-77-0 1303-86-2	R 1B, H360FD	100,000–1,000,000, 1,000–10,000	3), 5), 9), 31), 34)
6	1-Bromopropane	106-94-5	R 1B, H360FD	1,000–10,000 a)	H), 3), 5), 31)
7	4-tert-Butylbenzoic acid	98-73-7	R 1B, H360F	100–1,000 a)	H), 7), 8), 31)
8	2-(4-tert-Butylbenzyl)propionaldehyde	80-54-6	notified: R 1B, H360	1,000–10,000	9), 10), 12)
9	n-Butyltin trichloride	1118-46-3	notified: R 1B, H360	1,000+	9)
10	Carbon monoxide	630-08-0	R 1A, H360D	1,000–10,000	23), 31), 35)
11	N-Carboxymethyl)iminobis (ethylenenitrilo)tetra(acetic acid) (DTPA acid)	67-43-6	to be proposed: R 1B, H360D	1,000 – 10,000 a)	8)
12	Dibutylbis(pentane-2,4-dionato-O,O')tin	22673-19-4	intended: R 1B, H360FD	100–1,000	1: 9/2015
13	Dibutyl phthalate	84-74-2	R 1B, H360Df	1,000–10,000 a)	3), 4: 2/2015; 7), 26), 31), 34)
14	Dibutyltin dichloride	683-18-1	R 1B, H360FD	1,000–10,000	3), 36), 38)
15	Dibutyltin dilaurate	77-58-7	R 1B, H360FD	100–1,000	agreed at RAC-33
16	Dicyclohexyl phthalate	84-61-7	R 1B, H360D	100–1,000	to be included via 9. ATP 7), 8), 31)
17	Di-(2-ethylhexyl) phthalate (DEHP)	117-81-7	R 1B, H360FD	100,000–1,000,000 a)	H), 3), 4: 2/2015; 31), 34)
18	Dihexyl phthalate	84-75-3	R 1B, H360FD	not registered, but contaminant of ↓	3), 6)
19	1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters	68515-51-5		100–1,000	3), 7), 8)
20	Diisobutyl phthalate	84-69-5	R 1B, H360Df	0–10 a)	3), 4: 2/2015; 31)
21	Di-'isononyl' phthalate	28553-12-0	proposed: R 1B, H360Df	100,000–1,000,000 related to ↓	2: 11/2015, 31)
22	1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich	68515-48-0	proposed: R 1B, H360Df	100,000–1,000,000	2: 11/2015
23	Diisopentyl phthalate	605-50-5	R 1B, 360FD	10–100	3), 5)
24	1,2-Dimethoxyethane	110-71-4	R 1B, 360FD	100–1,000	3), 31)

Table 1 **List of substances/groups of substances toxic to reproduction considered to be relevant**

No.	Substance/group of substances	CAS no.	Harmonised (or notified) classification	Registered tonnage band [t/a]	Comments
25	N,N-Dimethylacetamide	127-19-5	R 1B, 360D	10,000–100,000	H), 3), 23), 31), 34)
26	N,N-Dimethylformamide	68-12-2	R 1B, 360D	10,000–100,000 a)	H), 3), 7), 8), 23), 31), 35)
27	Dinoseb (ISO) (2-tert-Butyl-4,6-dinitrophenol)	88-85-7	R 1B, 360Df	100–1,000	3)
28	Dioctyltin dilaurate	3648-18-8	intended: R 1B, H360D	100–1,000	1: 9/2015
29	2,3-Epoxypropyl methacrylate (glycidyl methacrylate)	106-91-2	proposed: R 1B, H360F	1,000–10,000	c) 2: 9/2014
30	Ethanol, 2,2′-iminobis-, N-(C13-15-odd numbered, branched and linear alkyl) derivs.	97925-95-6	intended: R 1B, H360FD	1,000–10,000	1: 6/2015
31	2-Ethoxyethanol	110-80-5	R 1B, H360FD	100–1,000	H), 3), 23), 31), 35)
32	Ethylene thiourea	96-45-7	R 1B, H360D	100–1,000	3), 31)
33	2-Ethylhexanoic acid	149-57-5	R2, H361	100,000–1,000,000	9), 10), 31)
34	2-Ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate (Dioctyltin bis(2-ethylhexyl mercaptoacetate) (DOTE))	15571-58-1	intended: R 1B, H360FD	1,000–10,000	1: 2/2016 3), 7), 8), 36), 38)
35	3-Ethyl-2-methyl-2-(3-methylbutyl)-1,3-oxazolidine	143860-04-2	R 1B, H360F	NONS, confidential	3) mono constituent substance
36	N-Ethyl-2-pyrrolidone	2687-91-4	R 1B, H360D	1,000 +	H), 36), 37)
37	Formamide	75-12-7	R 1B, H360D	10–100 a)	H), 3), 31)
38	Imidazole	288-32-4	R 1B, H360D	100–1,000 a)	7. ATP 9), 10)
39	4,4-Isobutylethylidenediphenol	6807-17-6	R 1B, H360F	NONS, confidential	7) polymer
40	4,4′-Isopropylidenediphenol (Bisphenol A)	80-05-7	R 1B, H360F	1,000,000–10,000,000	agreed at RAC-28 7), 9), 10), 23), 31), 34)
41	Lead (metallic)	7439-92-1	R 1A, H360DF	1,000,000–10,000,000	agreed at RAC-27 24), 26), 31)
42	Lead compounds, inorganic; e.g. tetralead trioxide sulphate lead monoxide trilead dioxide phosphonate orange lead pentalead tetraoxide sulphate lead dioxide	 12202-17-4 1317-36-8 12141-20-7 1314-41-6 12065-90-6 1309-60-0	R 1A, H 360Df **IARC**: 2A (2006)	1,000,000–10,000,000	b) 3), 4: 5/2015; 6), 7), 8), 24), 26), 31)
	Lead alkyl compounds		R 1A, H360Df		H)
43	Tetraethyl lead	78-00-2	notified: R 1A, H360	1,000–10,000	H), 3), 31), 35)
44	Mercury	7439-97-6	R 1B, H360D	100–1,000	H), 7), 8), 23), 31)
45	2-Methoxyethanol	109-86-4	R 1B, H360FD	1,000–10,000	H), 3), 23), 31), 35)
46	2-Methoxyethyl acrylate	3121-61-7	notified: R 1B, H360	100– 1,000	1: 12/2015, 11)
47	N-Methylacetamide	79-16-3	R 1B, H360D	confidential	3)
48	2-Methylimidazole	693-98-1	proposed: R 1B, H360D	confidential a)	2: 2/2016

Table 1 **List of substances/groups of substances toxic to reproduction considered to be relevant**

No.	Substance/group of substances	CAS no.	Harmonised (or notified) classification	Registered tonnage band [t/a]	Comments
49	2-Methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	71868-10-5	R 1B, H360FD	1,000–10,000	agreed at RAC-33
50	N-Methyl-2-pyrrolidone	872-50-4	R 1B, H360D	10,000–100,000	H), 3), 23), 31), 34)
51	Mixture of two components: N-(1,3-dimettylbutyl)-N'-phenyl-p-phenylenediamine N1-(1,3-dimethylbutyl)-N4-(4-(1-methyl-1-phenylethyl)-phenyl)benzene-1,4-diamine	EC number: 448-020-2	notified: R 1B, H360	100–1,000	9)
52	Nitrobenzene	98-95-3	R 1B, H360F	100,000–1,000,000 a)	H), 3), 7), 8), 23), 31)
53	Pentasodium (carboxylato-methyl)iminobis(ethylenenitrilo) tetraacetate Na5DTPA	140-01-2	to be proposed: R 1B, H360	10,000–100,000 a)	7), 8)
54	Perboric acid, sodium salt	11138-47-9 7632-04-4	R 1B, H360Df	10,000–100,000	3), 6)
55	Phenol, dodecyl-, sulfurized, calcium salts	68855-45-8	notified: R 1B, H360	1,000–10,000	9), 12)
56	Potassium permanganate	7722-64-7	proposed: R 1B, H360Df	1,000–10,000	2: 2/2015
57	Retinol	68-26-8	notified: R 1B, H360	0–10	7), 8), 11)
58	Retinyl propionate	7069-42-3	notified: R 1B, H360	0–10	7), 8), 11)
59	Tetrahydrofurfuryl alcohol	97-99-4	R 1B, H360Df	1,000–10,000	
60	Tetrahydrothiopyran-3-carbox-aldehyde	61571-06-0	R 1B, H360D	confidential	
61	Tetrapropenylphenol (TPP), (Phenol, dodecyl-, branched)	121158-58-5	R 1B, H360F	10,000–100,000 a)	agreed at RAC-27
62	Theophylline	58-55-9	intended: R 1B, H360D	0–10 a)	1: 9/2015; 31)
63	Tris(2-chloroethyl)phosphate	115-96-8	R 1B, H360F	10–100	3), 4: 8/2015
64	Tris(2-methoxyethoxy)vinyl-silane	1067-53-4	notified: R 1B, H360Df	1,000–10,000	7), 12)
65	Trixylyl phosphate	25155-23-1	R 1B, H360F	100–1,000	3), 6), 7)
66	1-Vinylimidazole	1072-63-5	proposed: R 1B, H360D	confidential	2: 6/2015

Table 2 **List of additional substances/groups of substances toxic to reproduction considered to be potentially relevant**

Substance/group of substances	CAS no.	Harmonised classification	Registered tonnage band [t/a]	Comments
2-(2-Aminoethylamino) ethanol	111-41-1	R 1B, H360Df	intermediate only	31)
2-Bromopropane	75-26-3	R 1A, H360F	intermediate only	31)
2-Butyryl-3-hydroxy-5-thiocyclohexan-3-yl-cyclohex-2-en-1-one	94723-86-1	R 1B, H360D	intermediate only	
Chloromethylene dimethyl-ammonium chloride	3724-43-4	R 1B, H360D	intermediate only	
Cyclic 3-(1,2-Ethanediylacetale)-estra-5(10),9(11)-diene-3,17-dione	5571-36-8	R 1B, H360F	intermediate only	
Methoxyacetic acid	625-45-6	R 1B, H360FD	intermediate only	H), 3); 31), 35)
N-Methylformamide	123-39-7	R 1B, H360D	intermediate only	
Quinolin-8-ol (8-hydroxyquinoline)	148-24-3	R 1B, H360D	intermediate only	agreed at RAC-33
Tributyltin compounds (Bis(tributyltin) oxide; Tributyltin chloride)	(56-35-9 1461-22-9)	R 1B, H360FD	intermediate only	agreed at RAC-27 3), 25), 31), 34)
Biocidal active substances or active substances authorised for use in plant protection products (PPP)				
Brodifacoum (ISO)	56073-10-0	R 1A, H360D	biocidal active substance	agreed at RAC-28
Bromadiolone (ISO)	28772-56-7	R 1B, H360D	biocidal active substance; PPP	agreed at RAC-28
Carbetamide (ISO)	16118-49-3	R 1B, H360D	PPP	agreed at RAC-32
Chlorophacinone (ISO)	3691-35-8	R 1B, H360D	biocidal active substance	agreed at RAC-28
Coumatetralyl (ISO)	5836-29-3	R 1B, H360D	biocidal active substance	agreed at RAC-28
Cyproconazole (ISO)	94361-06-5	R 1B, H360D	biocidal active substance	agreed at RAC-34
Difenacoum (ISO)	56073-07-5	R 1B, H360D	biocidal active substance; PPP	agreed at RAC-28
Difethialone (ISO)	104653-34-1	R 1B, H360D	biocidal active substance	agreed at RAC-28
Epoxiconazole (ISO)	135319-73-2 133855-98-8 106325-08-0	R 1B, H360Df	PPP	
Flocoumafen (ISO)	90035-08-8	R 1B, H360D	biocidal active substance	agreed at RAC-28
Flumioxazin (ISO)	103361-09-7	R 1B, H360D	PPP	2: 6/2015: R 2, H361d
Flusilazole (ISO)	85509-19-9	R 1B, H360D	PPP	
Glufosinate (ISO)	77182-82-2	R 1B, H360Fd	PPP	
Linuron (ISO)	330-55-2	R 1B, H360Df	PPP	
Quizalofop-P-tefuryl	119738-06-6 200509-41-7	R 1B, H360Df	PPP	2: 9/2014: R 2, H361fd
Thiacloprid (ISO)	111988-49-9	R 1B, H360FD	biocidal active substance; PPP	agreed at RAC-32
Triadimenol (ISO)	55219-65-3	R 1B, H360	PPP	agreed at RAC-34

Table 2 **List of additional substances/groups of substances toxic to reproduction considered to be potentially relevant (cont.)**

Substance/group of substances	CAS no.	Harmonised classification	Registered tonnage band [t/a]	Comments
Triflumizole (ISO)	68694-11-1 99387-89-0	R 1B, H360D	PPP	agreed at RAC-31
Warfarin (ISO)	81-81-2	R 1A, H360D	biocidal active substance; PPP a)	H), 31), 35)

Table 3 **List of additional substances/groups of substances toxic to reproduction considered to be of unclear relevance**

Substance/group of substances	CAS no.	Harmonised classification	Registered tonnage band [t/a]	Comments
Ammonium pentadecafluoro-octanoate (APFO)	3825-26-1	R 1B, H360D	not registered	3), 31)
1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich	71888-89-6	R 1B, H360D	not registered	3), 5)
1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters	68515-42-4	R 1B, H360Df	not registered	3), 5)
1,2-Benzenedicarboxylic acid, dipentyl ester, branched and linear	84777-06-0	R 1B, H360FD	not registered	3), 5)
Bis(2-methoxyethyl) phthalate	117-82-8	R 1B, H360Df	not registered	3), 5)
1,2-Diethoxyethane	629-14-1	R 1A, H360Df	not registered	3)
Dihexyl phthalate	84-75-3	R 1B, H360FD	not registered	cf. no. 18 in table 1
Diisohexyl phthalate	71850-09-4	proposed: R 1B, H360FD	not registered	2: 12/2015
Diisohexyl phthalate (DIHP) (1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear)	68515-50-4	R 1B, H360FD	not registered	7. ATP 3), 6)
Diisooctyl phthalate	27554-26-3	intended: R 1B	not registered	1: 2/2016
Di-n-pentyl phthalate	131-18-0	R 1B, H360FD	not registered	3), 5)
Diphenylether; octabromo derivate	32536-52-0	R 1B, H360Df	not registered	25)
2-Ethoxyethyl acetate	111-15-9	R 1B, H360FD	not registered	H), 3), 23), 31), 35)
2-Methoxyethyl acetate	110-49-6	R 1B, H360FD	not registered	H), 23), 31), 35)
2-Methoxypropanol	1589-47-5	R 1B, H360D	not registered	H), 31), 35)
2-Methoxypropyl acetate	70657-70-4	R 1B, H360D	not registered	H), 31), 35)
Nickel tetracarbonyl	13463-39-3	R 1A, H360D	not registered	31)
Nonadecafluorodecanoic acid; ammonium nonadecafluoro-decanoate; sodium nona-decafluorodecanoate	335-76-2 3108-42-7 3830-45-3	R 1B, H360Df	not registered	agreed at RAC-35 7)
N-Pentyl-isopentylphthalate	776297-69-9	R 1B, H360FD	not registered	3), 5)

Table 3 **List of additional substances/groups of substances toxic to reproduction considered to be of unclear relevance (cont.)**

Substance/group of substances	CAS no.	Harmonised classification	Registered tonnage band [t/a]	Comments
Perfluorononan-1-oic acid and its sodium and ammonium salts	375-95-1 21049-39-8 4149-60-4	R 1B, H360Df	not registered	agreed at RAC-30 3), 7), 8)
Perfluorooctanoic acid (PFOA) and its salts	335-67-1 3825-26-1	R 1B, H360D	not registered	H), 3), 36), 38)
Perfluorooctane sulfonic acid and its salts	1763-23-1 2795-39-3 29081-56-9 29457-72-5 70225-14-8	R 1B, H360D	not registered	H), 31), 35)
Tetramethyl lead	75-74-1	notified: R 1A, H360	not registered	H), 31), 35)
Substances notified as new substances (NONS) under Dir. 67/548/EEC				
(E)-3-[1-[4-[2-(Dimethylamino) ethoxy] phenyl]-2-phenylbut-1-enyl] phenol	82413-20-5	R 1B, H360F	NONS, confidential	polymer
N,N-(Dimethylamino) thioacetamide hydrochloride	27366-72-9	R 1B, H360D	NONS, confidential	polymer
(4-Ethoxyphenyl)(3-(4-fluoro-3-phenoxyphenyl)propyl) dimethylsilane	105024-66-6	R 1B, H360F	NONS, confidential	polymer
2-[2-Hydroxy-3-(2-chlorophenyl) carbamoyl-1-naphthylazo]-7-[2-hydroxy-3-(3-methylphenyl) carbamoyl-1-naphthylazo] fluoren-9-one	151798-26-4	R 1B, H360D	NONS, confidential	polymer
Substances used in medicinal products				
5-Azacytidine	320-67-2	notified: R 1B, H360 **IARC**: 2A (1990)	not registered b)	c) 12)
Azathioprine	446-86-6	notified: R 1A / 1B, H360 **IARC**: 1 (2012)	not registered	c) 11), 41)
1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU) (Carmustine)	154-93-8	notified: R 1B, H360 **IARC**: 2A (1987)	not registered b)	c)
Busulfan (1,4-Butanediol-bis(methanesulfonate))	55-98-1	notified: R 1A, H360 **IARC**: 1 (2012)	not registered b)	c) 12)
Bleomycin (sulphate)	9041-93-4	notified: R 1B, H360 **IARC**: 2B (1987)	not registered b)	c) 12), 42)
Chlorambucil	305-03-3	notified: R 1A / 1B, H360 **IARC**: 1 (2012)	not registered b)	c) 12)
Chloramphenicol	56-75-7	notified: R 1B, H360 **IARC**: 2A (1990)	not registered	c) 12), 31)
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) (Lomustine)	13010-47-4	notified: R 1B, H360 **IARC**: 2A (1987)	not registered b)	c) 12)

Table 3 **List of additional substances/groups of substances toxic to reproduction considered to be of unclear relevance (cont.)**

Substance/group of substances	CAS no.	Harmonised classification	Registered tonnage band [t/a]	Comments
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU) (Semustine)	13909-09-6	notified: R 1B, H360 **IARC**: 1 (2012)	not registered b)	c)
Cisplatin	15663-27-1	notified: R 1B, H360 **IARC**: 2A (1987)	not registered b)	c) 12), 41)
Cycloheximide	66-81-9	R 1B, H360D	not registered	
Cyclophosphamide	50-18-0 6055-19-2	notified: R 1A / 1B, H360 **IARC**: 1 (2012)	not registered b)	c) 11)
Cyclosporin	59865-13-3 79217-60-0	notified: R 1A / 1B, H360 **IARC**: 1 (2012)	not registered	c) 11)
Etoposide	33419-42-0	notified: R 1A / 1B, H360 **IARC**: 1 (2012)	not registered b)	c) 12)
Ketoconazole	65277-42-1	R 1B, H360F	not registered	
Melphalan	148-82-3	notified: R 1A, H360 **IARC**: 1 (2012)	not registered b)	c) 12)
Mitomycin C	50-07-7	notified: R 1A / 1B, H360 **IARC**: 2B (1987)	not registered b)	c) 12), 42)
Procarbazine hydrochloride	366-70-1	notified: R 1A / 1B, H360 **IARC**: 2A (1987)	not registered b)	c) 41)
Tamoxifen	10540-29-1	notified: R 1A / 1B, H360 **IARC**: 1 (2012)	registered as intermediate only b)	c) 7)
Teniposide	29767-20-2	notified: R 1B, H360 **IARC**: 2A (2000)	not registered b)	c) 12)
Thiotepa (Tris(1-aziridinyl)phosphine sulfide)	52-24-4	notified: R 1B, H360 **IARC**: 1 (2012)	not registered b)	c) 12), 42)

Explanation of notes in Tables 1–3

Column 'Harmonised classification':
IARC: IARC classification; year of publication.

Column 'Registered tonnage band':
a) additional registration(s) for 'intermediate use only'.
b) use as anti-cancer drug.

Column 'Comments':
c) substance is also a potential regulatory carcinogen.

re. REACH and CLP processes
1) Intention of CLH process notified; date of notification.
2) CLH process initiated; date of initiation.
3) Substance (or compounds of it) included in REACH candidate list (according to Art. 59 (10)).
4) Substance (or compounds of it) included in REACH authorisation list; sunset date.
5) Inclusion of substance (or compounds of it) in REACH authorisation list recommended by ECHA.
6) Inclusion of substance (or compounds of it) in REACH authorisation list considered by ECHA (consultation phase).
7) Substance (or compounds of it) included in risk management option analysis (RMOA).
8) RMOA result available.
9) Substance (or compounds of it) included in Community Rolling Action Plan (CoRAP).
10) Substance evaluation report (or other substance evaluation documents) available.
11) Notified classification submitted by majority of notifiers.
12) Notified classification submitted by some notifiers only.

re. OSH processes and instruments (at EU level)
23) IOELV under the CAD in existence or in preparation.
24) BOEL under the CAD in existence.
25) SCOEL recommendation published.
26) SCOEL recommendation under development.

re. OSH processes and instruments (at MS level)
31) Health-based OEL derived in at least one EU Member State.
34) Additional notation in Germany: the health-based OEL is protective also for developmental effects.
35) Additional notation in Germany: developmental effects cannot be excluded even when the health-based OEL is achieved.
36) Health-based MAC value derived by German MAC Commission.
37) The health-based MAC value is, in addition, protective for developmental effects.

38) Developmental effects cannot be excluded even when the health-based MAC value is achieved.
41) Exposure–risk relationship (ERR) derived (in the Netherlands).
42) ERR not derivable (in the Netherlands).