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**Report 136**

etui.

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**european trade union institute**

Henning Wriedt is a researcher at the Beratungsstelle Arbeit & Gesundheit (Occupational Health & Safety Advice Centre), Hamburg, Germany.
Contact: wriedt@arbeitundgesundheit.de.

Brussels, 2016

Print: ETUI Printshop, Brussels

D/2016/10.574/08
ISBN: 978-2-87452-402-8 (print version)
ISBN: 978-2-87452-403-5 (electronic version)

The ETUI is financially supported by the European Union. The European Union is not responsible for any use made of the information contained in this publication.

# Contents

## Executive summary

The objective of this project is the identification of at least 50 carcinogens that are relevant for workers' exposure via inhalation at a considerable number of workplaces in Europe and thus, for which a Binding Occupational Exposure Limits (BOEL) under the Carcinogens and Mutagens Directive (CMD) might be suggested.

As a starting point, the terms 'carcinogen' and 'relevance' are defined for their use in the context of the project. In addition, the conditions under which an Occupational Exposure Limit Value (OEL) would be appropriate as a regulatory tool are reflected on. Then the methods applied to select carcinogens and assess their relevance are detailed. In addition to carcinogens already included in Annex VI of the CLP regulation, further substances are considered to be future (or 'potential') carcinogens 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, and the IARC classification of carcinogens.

The analysis results in the selection of 187 carcinogens or groups of carcinogens divided into three categories of different levels of relevance. For 71 of them a BOEL under the CMD might be suggested.

In an Annex, all selected carcinogens, 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 issues, for the establishing of 50 binding limit values for carcinogenic substances in use at workplaces in the European Union. By this request, the ETUC is strongly supporting a proposal made by several EU Member States earlier in the year.

The proposal was made as part of a letter signed by the ministers of labour and social affairs of Austria, Belgium, Germany and the Netherlands. It was sent to the then Commissioner in charge of the Directorate General on Employment, Social Affairs and Inclusion in March 2014 in response to the decision of the Commission, announced in October 2013, to halt the revision of the Carcinogens and Mutagens Directive (Dir. 2004/37/EC – CMD for short) during its mandate as part of the so-called REFIT programme.

The need for an urgent update of the CMD was underlined in the ministers' letter by stressing that some 50,000 to 100,000 workers in the EU die each year as a result of exposure to carcinogenic substances and that more than 30 million workers are exposed to these substances beyond levels considered acceptable. In contrast, only three binding limit values have been established under the CMD at EU level, whereas some EU Member States have identified limit values for carcinogens at national level. There are thus large differences in levels of protection in the EU. To ameliorate this situation, in their letter the four ministers point out that a future selection of only 50 substances could account for more than 80 or 90 per cent of all exposure situations to carcinogens. They therefore recommend that such a basic set of 50 high-quality Binding Occupational Exposure Limits (BOELs) should be established by 2020.

To identify relevant carcinogens that should be included in such a basic set of 50 substances, recent or still ongoing work at both Member State and EU level was utilised. In the Netherlands, since the mid-1990s risk-based Occupational Exposure Limit Values (OELs) have been derived for about 25 carcinogens. In Germany, since 2007 either risk- or health-based OELs have been derived or are still in the process of being derived for more than forty carcinogens. Last but not least, at EU level the derivation of BOELs for an additional 23 carcinogens was initiated in 2008. These substances could be used to constitute the core of the basic set addressed by the ministers.

## 1.2 Objectives and limitations

The objective of this project is the identification of at least 50 carcinogens that can be considered to be relevant in the sense that a considerable number of workers in Europe are affected by exposure via inhalation to them.

To this end, two terms need to be defined in the context of this project, 'carcinogen' and 'relevance'. In addition, the exposure routes of the relevant carcinogens identified have to be assessed, and carcinogens that are relevant with regard to dermal exposure only are to be excluded. Finally, it has to be considered whether – and if so, under what conditions – an OEL would be an appropriate regulatory instrument for mixtures of carcinogens.

### Definition of 'carcinogen'

It has to be observed, however, that different definitions of the term 'carcinogen' exist, depending on the respective context, be it regulatory or scientific. In the context of this project, precedence is given to the regulatory definition as established in Article 2 a) of the CMD. Based on that definition, all substances or mixtures included in Annex VI of the Classification, Labelling and Packaging Regulation (Regulation (EC) No 1272/2008, CLP for short) classified as C 1A, H350 or C 1B, H350 are considered to be carcinogens. In addition, all substances, mixtures or processes referred to in Annex I of the CMD, and all substances or mixtures released by a process referred to in Annex I of the CMD are also considered to be carcinogens.

Beside the regulatory definition, there are also scientific definitions of the term 'carcinogen'. Different scientific bodies and committees, such as the International Agency for Research on Cancer (IARC), the Scientific Committee on Occupational Exposure Limits of the EU (SCOEL), or the German MAC Commission, have derived slightly differing definitions and categories for carcinogens. For this project, the IARC definitions and classifications are utilised as the relevant scientific definition. Details can be found at: http://monographs.iarc.fr/ENG/Classification/index.php.

### 'Relevance' of a carcinogen

From an occupational health and safety perspective, the relevance of a carcinogen is based on several factors:

- the number of workers exposed to it;
- the extent of the exposure (level, duration and frequency of exposure);
- the potency of the carcinogen, which can be indicated by its exposure–risk relationship

Given that quantitative data for these factors were available, both the statistical individual risk for any worker exposed to a specific carcinogen and the

statistical collective risk of all workers exposed to that carcinogen could be calculated.

Assessments of the relevance of individual carcinogens could then be based on either the quantified collective risk, or the frequency distribution of the quantified individual risk, or a combination of both.

Because, however, the necessary data for the two former factors – that is, the number of workers exposed and the extent of their exposure – are not available, and information on the latter factor is limited (because exposure–risk relationships have been determined for a limited number of carcinogens as yet), the relevance of a carcinogen cannot be determined by this method. Instead, other criteria have to be employed.

## 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.

For mixtures of carcinogens, the appropriateness of an OEL, as a regulatory instrument, or of several OELs, as the case may be, depends on several aspects:

– Have the carcinogenic constituents of the mixture been identified? In that case, for each of them the derivation of an OEL seems appropriate.
– Alternatively, has the mixture as a whole been identified as carcinogenic? In that case, the derivation of an OEL seems appropriate only if there are measurement methods available for determining the concentration of either the mixture as a whole or a characteristic component of it in the workplace air. For the latter case, however, the composition of the mixture needs to be stable but not variable.

However, due to the variable composition of the constituents of certain complex carcinogenic mixtures, an OEL for the mixture as a whole does not seem to be an appropriate regulatory tool for such mixtures. Examples of such mixtures relevant at workplaces are listed in Table 1.

Table 1 **List of complex carcinogenic mixtures with variable composition of constituents**

| Complex mixture | Classification/Inclusion in Annex I of CMD | Substance(s) listed in Annex, Table 1 | Comments |
|---|---|---|---|
| Mineral oils, used | | Benzo(a)pyrene | Process-generated |
| N-Nitrosamines | | N-Nitroso diethanolamine, N-Nitroso diethylamine, N-Nitroso dimethylamine, N-Nitroso di-n-propylamine | Process-generated |
| Petroleum and coal stream substances and mixtures | | Benzene, Benzo(a)pyrene, 1,3-Butadiene | Placed on the market |
| Polychlorinated biphenyls | IARC: 1 | Polychlorinated biphenyls | Legacy substances |
| Polychlorinated dibenzo-para-dioxins | IARC: 3 | 2,3,7,8-Tetrachloro-dibenzo-para-dioxin | Process-generated |
| Polychlorinated dibenzofurans | IARC: 3 | 2,3,4,7,8-Pentachloro-dibenzofuran | Process-generated |
| Polycyclic aromatic hydrocarbons (PAHs) | CMD, Annex I | Benzo(a)pyrene | Process-generated |
| Rubber dusts and fumes | IARC: 1 | 1,3-Butadiene, N-Nitroso diethanolamine, N-Nitroso diethylamine, N-Nitroso dimethylamine, N-Nitroso di-n-propylamine | Process-generated |

## 1.3 Method – general definitions

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

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

### Carcinogens

Given the purpose of this report – to provide a list of carcinogens for which BOELVs under the CMD should be established – substances selected should come within the scope of the CMD as defined in Art. 2 para. a) of the Directive (cf. sub-section 'Definition of 'carcinogen', above). For the purpose of simplification, these carcinogens will be denoted '**actual** regulatory carcinogens'.

Actual regulatory carcinogens 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). The additional process-generated regulatory carcinogens are referred to in Annex I of the CMD.

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

(i) a process of harmonised classification either as C 1A, H350 or as C 1B, H350 was initiated and resulted in an 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 C 1A, H350 or as C 1B, H350 was initiated, but not finalised by November 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);
(iii) a substance is classified by IARC (cf. Section 1.2, above) either as 'carcinogenic to humans' (group 1) or as 'probably carcinogenic to humans' (group 2A); information on the IARC classification is available on the IARC website (http://monographs.iarc.fr/ENG/Classification/vol1_112.php); or
(iv) a substance without a harmonised classification with regard to carcinogenicity has been notified to ECHA by one or more manufacturers or importers either as C 1A, H350 or as C 1B, H350; 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) to (iii) have been checked systematically for all entries in the respective list, no such systematic check has been undertaken for condition (iv). Not only is the number of substances with such notifications – with about 1,350 entries – rather large, but also the criteria for 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 C 1A, H350

or as C 1B, H350, whereas other notifiers of the same substance indicated either no notification for carcinogenicity or a notification for suspected carcinogenicity (C 2, H351) only. In conclusion, substances with a notification either as C 1A, H350 or as C 1B, H350 are included as 'potential regulatory carcinogens' only if other supporting evidence has been found, such as 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), 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, or attempted derivation, of an exposure–risk relationship at national level.

It should also be noted that condition (iii) can also apply for process-generated carcinogens.

The reason for considering 'potential regulatory carcinogens' is the expectation that in the foreseeable future many of them will become 'actual regulatory carcinogens' by inclusion in Annex VI of the CLP regulation classified as C 1A, H350 or C 1B, H350 or, in the case of process-generated carcinogens, by inclusion in Annex I of the CMD.

## Relevance

In the absence of comprehensive knowledge on both the extent of exposure to the majority of carcinogens at workplaces in the EU and the potency of many carcinogens, surrogate signifiers have to be employed to assess the relevance of individual carcinogens.

For substances placed on the market, an initial approach for approximating exposure information is the use of 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 carcinogens above a production or import volume above 1 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, however, such registration information is not available. 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 abovementioned 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.

Process-generated substances are outside the scope of REACH as they are not placed on the market and, thus, for them no registration information exists. As direct or indirect exposure information is not easily available for them either, in the further analysis process-generated carcinogens are generally considered to be relevant. Due to their comparatively small number and the issue of the appropriateness of an OEL as a regulatory instrument for those of them that are mixtures of different substances (for details cf. Section 1.2, above), a case-by-case assessment could be performed for them at a later stage, if deemed necessary.

## Relevant carcinogens

Because the number of actual regulatory carcinogens as defined above is rather large (the list of substances on the ECHA website with a harmonised classification as C 1A, H350 or as C 1B, H350 – as updated on 30 October 2015 – comprised about 1,000 entries), that number is reduced in two ways, which are described in more detail in Section 1.4, below:

- carcinogenic metals and their compounds are combined to single entries ('metal' and their compounds);
- petroleum and coal stream substances and mixtures are omitted

As a result, the number of remaining actual regulatory carcinogens is reduced to about 200 entries. For potential regulatory carcinogens, 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 carcinogens and all potential regulatory carcinogens is assessed by a tiered approach, consisting of the following five steps:

As a first step, for each substance it was checked whether it is process-generated, whether it should be considered to be a 'legacy substance' or whether it is presumably placed on the market. By the term 'legacy substance' in this report a substance is denoted which, although neither process-generated nor registered under REACH, can be present at a considerable number of work-

places due to past uses. Legacy substances can be part of all sorts of objects and products, from industrial sites to buildings to machinery, vehicles and appliances. A number of tasks involving those objects and products – in particular maintenance and repair work, demolition or recycling – will result in exposure to legacy substances, such as asbestos, carcinogenic glass fibres, PAHs or polychlorinated biphenyls (PCBs) for the foreseeable future.

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

As a third step, for carcinogens 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 fourth step, for all remaining carcinogens 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 fifth and final step, it was checked whether any of the remaining carcinogens 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:

– in the context of the REACH regulation and the CLP regulation, 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 C 1A, H350 or as C 1B, H350;
– in the context of the CAD, the development of a recommendation by SCOEL;
– at national level, the derivation of an exposure–risk relationship (ERR), or an attempt to do so, in Germany or the Netherlands, or inclusion in the list of particularly hazardous carcinogens in the German Hazardous Substance Ordinance.

## 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 carcinogens is explained, and second, the grading of relevance is outlined.

## Selection of actual regulatory carcinogens

As indicated in the previous sub-section, two mechanisms were used to reduce the number of actual regulatory carcinogens by 80 per cent in preparation for the subsequent examination of their registration status under REACH. Both are explained in detail below.

### Combination of carcinogenic metals and their compounds 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. Therefore, it is assumed that if a BOEL were to be derived for a carcinogenic metal, that BOEL would cover all, or nearly all, of its compounds also classified as carcinogens.

Table 2 provides an overview of the six carcinogenic metals and their compounds classified as carcinogens combined to a single entry each, covering 174 entries in total in the C&L Inventory on the ECHA website.

Table 2 **Carcinogenic metals and their compounds combined to a single entry each**

| Carcinogenic metal/metal compounds | Number of individual entries in C&L Inventory on ECHA website |
|---|---|
| Arsenic compounds | 5 |
| Beryllium and its compounds | 3 |
| Cadmium and its compounds | 7 |
| Chromium(VI) compounds | 16 |
| Cobalt and its compounds | 5 |
| Nickel and its compounds | 138 |

### Petroleum and coal stream substances and mixtures

Most carcinogenic petroleum and coal stream substances and mixtures are complex mixtures; in addition, their composition can vary depending on the natural source from which the raw material originated. Therefore, deriving OELs for individual carcinogens from this class of substances would be futile, when specific measurands characterising the individual carcinogen cannot be determined. As a consequence, this whole group of substances – which comprises about 660 entries in the C&L Inventory on the ECHA website – are omitted from the further analysis unless they are subjected to one of the regulatory processes described in Section 1.3, sub-section 'Relevant carcinogens'.

This decision to omit nearly all carcinogens in that group should not be misconstrued to mean that all of them are to be considered to be 'not relevant' at

workplaces. It implies only that deriving an OEL would not be an appropriate approach for regulating this group of substances. Instead, a different approach seems to be warranted for dealing with them.

Some of the petroleum and coal stream substances and mixtures are classified as carcinogens due to their content of specific carcinogens, such as benzene, benzo(a)pyrene, or 1,3-butadiene, all of which are kept for the further analysis. In other words, OELs for the latter three carcinogens could be used for regulating the respective petroleum and coal stream substances.

The validity of this approach can be tested once first results emerge from the working group to address petroleum and coal stream substances set up by ECHA in September 2015. As a first step, a set of 65 of such substances with uses by consumers and in professional settings has been prioritised by the group. Once this list becomes publicly available, it can be checked whether for any of the substances the derivation of an OEL seems appropriate. In that case, the above argument on the futility of OELs for individual carcinogens from this class of substances would be invalidated as being too general.

## Assessment of relevance of selected regulatory carcinogens

All carcinogens identified as process-generated or as legacy substances are considered to be 'relevant', irrespective of any specific exposure information available, as for both categories the general assumption of widespread exposure in open processes can be made.

The relevance of carcinogens presumably placed on the market is graded either according to their registration status under REACH or to 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

About 200 entries in the C&L Inventory on the ECHA website classified as C 1A, H350 or as C 1B, H350 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 six combined entries for the carcinogenic metals it was checked whether an entry existed in the registration database for the metal itself or for at least one related compound.

In the same way, for all potential regulatory carcinogens (identified by searching the lists on the ECHA website addressed in Section 1.3, subsection 'Carcinogens', 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 carcinogens 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 carcinogens');
- 'no relevance' for carcinogens without registration unless they meet the criterion described under 'unclear relevance', above.

This grading of the level of relevance of a carcinogen 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 carcinogens on the market with a tonnage greater than 1 tonne per year is a registration according to 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 carcinogen 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 carcinogens manufactured and placed on the market below 1 tonne per year, registration is not requested.

As the term 'strictly controlled conditions' is specified as meaning that the substance 'is rigorously contained by technical means during the whole lifecycle', workers should 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, carcinogens with a registration as on-site isolated intermediates are still considered as of limited relevance.

Due to the rather limited information publicly available for carcinogens listed as NONS, their relevance status cannot be decided because, 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, carcinogens 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 1 tonne per year.

A subset of carcinogens without any registration, which are, or have been, subjected to one of the regulatory processes described in Section 1.3, subsection 'Relevant carcinogens', 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 carcinogen.

Additionally, two other groups are also considered to be of unclear relevance. Members of these groups have a full registration and are either:

– notified carcinogens belonging to the chemical group of fluorinated hydrocarbons, but not subject to one of the regulatory processes described in Section 1.3, as their carcinogenicity might be closely related to the effects posed by two carcinogens classified by IARC in group 2A (tetrafluoroethylene and vinyl fluoride); or
– substances that are not regulatory carcinogens (according to the definitions given above), but whose carcinogenicity status is currently under discussion and, thus, which are subjected to ongoing regulatory processes.

#### Relevance based on use category

Carcinogens 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 carcinogens 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 a BOEL under the CMD would result in legal interference and should not be considered to be a viable option, accordingly.

In contrast, carcinogens 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 considerations:

– 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.

## Refinement of level of relevance of carcinogens placed on the market

The information publicly available for substances with a full registration would allow a further differentiation of the qualifier ‘relevance’. This could be based in particular on two parameters: the tonnage band for the production volume; and 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 accessible 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 carcinogens' (cf. Section 2.1), a further differentiation based on the tonnage band is considered to be of low added value and, thus, not done for the time being. Instead, for each carcinogen with a full registration, the information on the tonnage band is listed in Tables 1–3 of the Annex.

In contrast, the information on process categories (PROCs) has been utilised 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).

For substances, for which solely PROC 1 or PROC 3 (or both) have been registered, the level of relevance is reduced to 'limited relevance'. The same is done for substances, for which, in addition to PROC 1 or PROC 3, one or more of the following three PROCs have been registered:
(i) PROC 15: use as a laboratory agent;
(ii) PROC 0: other: monomer in imported polymer;
(iii) PROC 0: other: production of pharmaceuticals/vaccines.

# 2. Results

## 2.1 Carcinogens selected with different levels of relevance

Altogether 187 carcinogens or groups of carcinogens have been selected and allocated to three different relevance categories. These substances are listed in Tables 1–3 of the Annex.

### 2.1.1 Carcinogens considered to be relevant

This category for the highest level of relevance has been subdivided into two groups: (i) carcinogens for which an OEL is deemed appropriate, and (ii) carcinogens for which this is not the case.

#### Carcinogens for which an OEL would be appropriate

Based on the selection criteria described in Section 1.4, above, 47 **actual regulatory carcinogens** are selected as relevant, which are listed in Table 1 (Annex), including six substances that are not registered under REACH, but are **process-generated** or **legacy** carcinogens.

Based on the selection criteria described in Section 1.4, above, 24 **potential regulatory carcinogens** are selected as relevant that are also listed in Table 1 (Annex), including seven substances that are not registered under REACH, but are **process-generated** or **legacy** carcinogens. Two of the process-generated potential regulatory carcinogens have been recommended for inclusion in Annex I of the CMD.

#### Carcinogens for which an OEL might not be appropriate

Thirteen regulatory carcinogens (seven actual and six potential) from the group of PAHs and their nitro compounds have been included in a separate section in Table 1 (Annex). For them the derivation of an OEL is not deemed appropriate as they usually are part of mixtures of PAHs of variable composition (cf. Section 1.2, sub-section 'Appropriateness of an OEL as a regulatory instrument', above). An exemption is made for benzo(a)pyrene which is listed in the main section of Table 1 (Annex), because it serves two functions

simultaneously: as a carcinogen in its own right and as a proxy for all other carcinogenic PAHs.

In addition, four regulatory carcinogens (two actual and two potential) from the group of petroleum and coal stream substances and mixtures have been included in another separate section in Table 1 (Annex). For them the derivation of an OEL is not deemed appropriate, as explained in Section 1.4, above.

### 2.1.2 Carcinogens considered to be potentially relevant

Based on the selection criteria described in Section 1.4, above, 35 carcinogens are considered to be potentially relevant which are listed in Table 2 (Annex); 28 of them are actual regulatory carcinogens, seven are potential.

Twenty-six of them are registered as intermediates only; four have full registration but the process categories (PROCs) registered for them indicate exposure levels of workers that correspond to those of tasks involving intermediates; the remaining five 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 Carcinogens with unclear relevance

Based on the selection criteria described in Section 1.4, above, 64 carcinogens are considered to be of 'unclear relevance' which are listed in Table 3 (Annex):

- 18 of them are actual regulatory carcinogens without a registration under REACH subject to one of the regulatory processes described in Section 1.3, sub-section 'Relevant carcinogens';
- 13 of them are actual regulatory carcinogens registered as NONS;
- 28 of them are potential regulatory carcinogens without a registration under REACH; 27 of these are used in medicinal products and, thus, are exempted from the registration obligation under REACH, the majority of them being drugs used in cancer treatment; the remaining one is subject to one of the regulatory processes described in Section 1.3, sub-section 'Relevant carcinogens';
- 3 of them are potential regulatory carcinogens due to notifications with a full registration but without 'supporting evidence', as described in Section 1.3, sub-section 'Carcinogens'; instead, their identification is justified by their belonging to the same chemical class of fluorinated hydrocarbons as Tetrafluoroethylene and Vinyl fluoride, both of which are classified by IARC as 'probably carcinogenic to humans' (group 2A) and are, thus, selected as relevant carcinogens and listed in Table 1 (Annex), accordingly; and
- 2 of them are not classified as carcinogens, but have a full registration under REACH and are subjected to one of the regulatory processes described in Section 1.3, sub-section 'Relevant carcinogens'.

## 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 into separate sections for specific classes of carcinogens, 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 a BOEL for the respective carcinogen.

### 2.2.1 Special classes of carcinogens

In chapter 1, a number of special classes of substances are addressed. To enable easier identification of carcinogens belonging to one of these classes, in Tables 1–3 (Annex) they are displayed as separate sub-sections:

- fluorinated hydrocarbons;
- polycyclic aromatic hydrocarbons (PAHs) and their nitro compounds;
- petroleum and coal stream substances and mixtures;
- 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:[1]

(i) name of substance or group of substances;
(ii) CAS number, if available, otherwise EC number;
(iii) classification with regard to carcinogenicity or indication of inclusion in Annex I of the CMD;
(iv) registration status under REACH and tonnage band, if available, or indication of status as process-generated or legacy substance;
(v) additional comments.

Standard information in **column 3** is the harmonised classification with regard to carcinogenicity as available from Annex VI of the CLP regulation. For carcinogens for which the intention of a process of harmonised classification is announced in a substance evaluation report or was formally notified, or for which such a process was initiated, the intended or proposed harmonised classification is specified. For carcinogens without such information, the notified self-classification of the manufacturer or importer is specified. For substances without a harmonised classification as a carcinogen (C 1A/1B) which are classified by IARC as group 1 or group 2A

1. In addition to these five columns, Table 1 enumerates the most relevant substances in a separate column.

carcinogens, also the IARC classification together with its year of publication is specified.

Standard information in **column 4** for carcinogens with a full registration is the tonnage band; for other carcinogens it is specified whether they are registered as intermediates only, as NONS, or not at all. Carcinogens with both a full registration and one for use as intermediates are denoted by the additional note a). Carcinogens approved as active substances in plant protection products are denoted by the entry 'PPP'; and carcinogens approved as biocidal active substances by the entry 'biocidal active substance'. Carcinogens that are process-generated or legacy substances are denoted by the entry 'process-generated' or 'legacy substance', respectively. For carcinogens used in medicinal products their use as an anti-cancer drug is denoted by the additional note b). For carcinogens with a full registration for which their level of relevance is changed from 'relevant' to 'potentially relevant' due to their process categories (PROCs) registered (cf. Section 1.4, sub-section 'Refinement of level of relevance of carcinogens placed on the market'), the registered PROCs are also specified.

For **column 5** 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'. These notes are ordered in four groups, referring to REACH and CLP processes; OSH processes and instruments at EU level; OSH processes and instruments at Member State level (Germany); and OSH processes and instruments at Member State level (Netherlands).

For carcinogens registered as NONS, the type of substance is listed if specified in the database. For six of them, 'polymer' is specified.

In particular, the notes in column 5 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 on the ECHA website for the respective process.

# 3. Discussion

Combining classificatory information from the CLP regulation and from IARC, on one hand, with registration information under REACH, information for plant protection products, for biocidal products, for medicinal products, and information from Annex I of the CMD on the other, 187 carcinogens or groups of carcinogens have been identified as relevant and allocated to three categories of different levels of relevance. A total of 115 of them are actual regulatory carcinogens, 72 are potential ones. The category for the highest level of relevance comprises 88 carcinogens (cf. Annex, Table 1), for 71 of which a BOEL under the CMD might be suggested.

Of the remaining 116 carcinogens, 13 are PAHs and 9 are petroleum and coal stream substances and mixtures, for which regulatory tools other than OELs seem more appropriate. Four carcinogens 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 a BOEL under the CMD does not seem to be a priority issue. Another 26 carcinogens are either registered as intermediates only or their process categories (PROCs) registered indicate their exclusive use in a closed system. Also for them the derivation of an OEL does not seem to be a priority issue.

Whether the derivation of a BOEL under the CMD for any of the carcinogens from the group of 13 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 a group of five potential regulatory carcinogens (including three fluorinated hydrocarbons; listed in Annex, Table 3) with high or very high production volume (between 1,000 and 10,000,000 t/a each) there is currently no indication of an imminent CLH process that might result in their promotion to become an actual regulatory carcinogen. For this reason, the derivation of a BOEL under the CMD is not suggested for them. Due to their high volume, however, the derivation of an OEL under the CAD might be considered instead.

For the remaining 46 carcinogens, 28 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 a BOEL under the CMD. Should, however, additional informa-

tion become available, or the application of different assessment criteria to the actual information be recommended, the derivation of a BOEL for additional carcinogens from this group might also be suggested.

For 57 of the 71 carcinogens or groups of carcinogens for which the derivation of a BOEL is suggested, tonnage information is available from their registration that might be used for prioritising the derivation of a BOEL. The annual volume produced or imported ranges from the lowest band (0–10 t) to the highest one (1,000,000–10,000,000 t) with a fairly smooth distribution across the whole range of seven bands.

For 29 of the 71 carcinogens or groups of carcinogens for which the derivation of a BOEL is suggested, neither a BOEL under the CMD is in existence or has been recommended by the Advisory Committee on Safety and Health (ACSH) as part of the revision of the CMD, nor is an IOELV under the CAD in existence or under preparation, nor have risk-based or health-based OELs in Germany or the Netherlands been derived or are under preparation. For 23 of these 29 carcinogens tonnage information is available, the distribution of which shows a clear maximum in the lowest two bands (the annual volume of 12 substances is in the range below 100 t), which could be interpreted to mean that these substances have been considered less relevant by regulatory bodies in the past. The eight carcinogens in the four highest-volume bands of this subgroup (1,000–10,000,000 t/a) are potential regulatory carcinogens. Probably due to this fact of being potential, but not actual regulatory carcinogens they have not been included in past and current programmes for the derivation of OELs for carcinogens at EU or Member State level. For these eight substances the derivation of a BOEL under the CMD or an OEL under the CAD should be considered to be urgent due to their high tonnage.

This observation of the relevance of certain potential regulatory carcinogens emphasises the necessity of permanently scrutinising the ongoing CLH processes for identifying additional substances to be classified as carcinogens (C 1A/1B) at an early stage, in order to decide on the timely derivation of a BOEL under the CMD for them. Because the number of CLH processes covering carcinogenicity has been limited in past years, the future number of additional carcinogens identified in this way for which a BOEL is deemed necessary should be manageable.

# Annex

Table 1 **List of relevant carcinogens/groups of carcinogens**

| No. | Substance/group of substances | CAS no. | Classification harmonised (or notified)/Inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|---|
| 1 | Acetaldehyde (ethanal) | 75-07-0 | proposed:<br>C 1B, H350 | 10–100<br>a) | 2: 2/2015, 33) |
| 2 | Acrylamide | 79-06-1 | C 1B, H350 | 100,000–1,000,000<br>a) | 3), 22), 25), 32), 40), 41) |
| 3 | Acrylonitrile | 107-13-1 | C 1B, H350 | 1,000,000–10,000,000 | 6), 7), 25), 31), 40) |
| 4 | Aluminium silicate fibres (refractory ceramic fibres) | (142844-00-6) | C 1B, H350i | 10,000–100,000 | 3), 22), 25), 31), 40) |
| 5 | Anthraquinone | 84-65-1 | C 1B, H350 | 1,000–10,000 | agreed at RAC-35 |
| 6 | Arsenic trioxide and other arsenic compounds classified as C1A/C1B | 1327-53-3<br>7778-39-4 | C 1A, H350<br>notified:<br>C 1A, H350 | 100–1,000<br>100–1,000 | 3), 4), 26), 31), 40), 41) |
| 7 | Asbestos (Chrysotile) | 1332-21-4<br>12001-29-5<br>12172-73-5<br>77536-66-4<br>77536-67-5<br>77536-68-6<br>132207-32-0 | C 1A, H350 | not registered/ legacy substance | 26), 31), 40) |
| 8 | Benzene | 71-43-2 | C 1A, H350 | 1,000,000–10,000,000<br>a) | 21), 25), 31), 40), 43) |
| 9 | Benzo(a)pyrene | 50-32-8 | C 1B, H350 | Not registered/ process-generated/ legacy substance | 22), 31), 40), 41) |
| 10 | Benzoyl chloride | 98-88-4 | Acute Tox. 4<br>**IARC**: 2A (1999) | 10,000–100,000 | |
| 11 | Beryllium and beryllium compounds | 7440-41-7 | C 1B, H350i | 10–100 | 6), 8), 9), 26), 33), 40) |
| 12 | 4,4'-Bis(dimethylamino)-4''-(methylamino)trityl alcohol | 561-41-1 | C 1B, H350 | 10–100 | 3) |
| 13 | 1,3-Butadiene | 106-99-0 | C 1A, H350 | 1,000,000–10,000,000 | 8), 22), 25), 31), 40), 41) |
| 14 | Butanone oxime | 96-29-7 | to be proposed:<br>C 1B, H350 | 1,000– 10,000 | 8), 9), 33) |
| 15 | tert-Butyl-4-methoxyphenol | 25013-16-5 | notified: C 1B, H350 | 100–1,000 | 6), 12), 33) |
| 16 | Cadmium and cadmium compounds | 7440-43-9 | C 1B, H350 | 100–1,000 | 3), 6), 25), 32), 40) |
| 17 | 2-Chloro-1,3-butadiene (Chloroprene) | 126-99-8 | C 1B, H350 | 10,000–100,000 | 38), 40) |
| 18 | 1-Chloro-2,3-epoxypropane (Epichlorohydrine) | 106-89-8 | C 1B, H350 | 100,000–1,000,000<br>a) | 6), 22), 25), 32), 40), 41) |
| 19 | α-Chlorotoluene | 100-44-7 | C 1B, H350 | 10–100 | 6), 40) |
| 20 | Chromium (VI) trioxide and other chromium (VI) compounds | 1333-82-0 | C 1A, H350<br>C 1B, H350 | 10,000–100,000 | 3), 4), 22), 25), 31), 40) |

Table 1 **List of relevant carcinogens/groups of carcinogens (cont.)**

| No. | Substance/group of substances | CAS no. | Classification harmonised (or notified)/Inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|---|
| 21 | C.I. Basic Violet 3 | 548-62-9 | C 1B, H350 | 0–10 | 3) |
| 22 | C.I. Solvent Blue 4 | 6786-83-0 | C 1B, H350 | 10–100 | 3) |
| 23 | Cobalt compounds classified as C 1B | 7646-79-9<br>10124-43-3 … | C 1B, H350 | 1,000–10,000 | 3), 26), 31), 40) |
| 24 | 4,4'-Diaminodiphenylmethane (4,4'-methylene dianiline, MDA) | 101-77-9 | C 1B, H350 | 10,000–100,000 | 3), 4), 22), 25), 31), 40), 41) |
| 25 | Poly[(aminophenyl)methyl]-aniline (technical MDA) | 25214-70-4 | C 1B, H350 | 100–1,000<br>a) | 3), 4) |
| 26 | 1,2-Dibromoethane | 106-93-4 | C 1B, H350 | 1,000–10,000 | 6), 22), 25), 40), 41) |
| 27 | 1,2-Dichloroethane | 107-06-2 | C 1B, H350 | 100,000–1,000,000 | 3), 4), 22); 32), 40) |
| 28 | Dichloromethane | 75-09-2 | C 2, H351<br>**IARC**: 2A (in prep.) | 100,000–1,000,000 | 8), 23), 33) |
| 29 | 2,2'-Dichloro-4,4'-methylene-dianiline (4.4'-Methylenebis(2-chloroaniline), MOCA) | 101-14-4 | C 1B, H350 | 1,000–10,000 | 3), 4), 22), 25), 40), 41) |
| 30 | 1,2-Dichloropropane | 78-87-5 | C 1B, H350<br>**IARC**: 1 (in prep.) | 1,000–10,000<br>a) | Revised classification agreed at RAC-29 |
| 31 | Diesel engine exhaust emissions | | Annex I (recomm.)<br>**IARC**: 1 (2013) | Process-generated | 22), 36), 40) |
| 32 | N,N-Dimethylhydrazine | 57-14-7 | C 1B, H350 | 0–10 | |
| 33 | 1,4-Dioxane | 123-91-1 | Intended:<br>C 1B, H350 | 100+ | 1: 8/2014, 23), 33) |
| 34 | 2,3-Epoxypropyl methacrylate (glycidyl methacrylate) | 106-91-2 | C 1B, H350 | 1,000–10,000 | agreed at RAC-35 |
| 35 | Ethylene oxide | 75-21-8 | C 1B, H350 | 1,000,000+<br>a) | 8), 9), 22), 25), 31), 40), 41) |
| 36 | Formaldehyde | 50-00-0 | C 1B, H350 | 1,000,000+<br>a) | 6), 7), 25), 33), 43) |
| 37 | Gallium arsenide | 1303-00-0 | C 1B, H350 | 10–100 | |
| 38 | Glycidol (2,3-Epoxypropan-1-ol) | 556-52-5 | C 1B, H350 | 10–100 | 40) |
| 39 | Hydrazine | 302-01-2 | C 1B, H350 | 10,000–100,000 | 3), 22), 25), 31), 40) |
| 40 | Isoprene (2-Methyl-1,3-butadiene) | 78-79-5 | C 1B, H350 | 100,000–1,000,000 | 33) |
| 41 | Lead compounds, inorganic; e.g. tetralead trioxide sulphate, lead monoxide, trilead dioxide phosphonate, orange lead, pentalead tetraoxide sulphate, lead dioxide | 12202-17-4<br>1317-36-8<br>12141-20-7<br>1314-41-6<br>12065-90-6<br>1309-60-0 | R 1A, H 360Df<br>STOT RE2, H373<br>**IARC**: 2A (2006) | 1,000,000–10,000,000 | 24) |
| 42 | Leather dust | | **IARC**: 1 (2012) | Process-generated | |
| 43 | Methylhydrazine | 60-34-4 | C 1B, H350 | 10–100<br>a) | Agreed at RAC-34 |
| 44 | Nickel monoxide and other nickel compounds classified as C 1A/C 1B | 1313-99-1 | C 1A, H350 | 10,000–100,000 | 6), 25), 31), 40) |

Table 1 **List of relevant carcinogens/groups of carcinogens (cont.)**

| No. | Substance/group of substances | CAS no. | Classification harmonised (or notified)/Inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|---|
| 45 | 2-Nitropropane | 79-46-9 | C 1B, H350 | 1,000–10,000 | 22), 31), 40), 41) |
| 46 | N-Nitroso diethanolamine (2,2'-(Nitrosoimino)bisethanol) | 1116-54-7 | C 1B, H350 | Not registered/ process-generated | 31) |
| 47 | N-Nitroso diethylamine (Diethylnitrosoamine) | 55-18-5 | Notified: C 1B, H350 **IARC** 2A (1987) | Not registered/ process-generated | 31) |
| 48 | N-Nitroso dimethylamine | 62-75-9 | C 1B, H350 | Not registered/ process-generated | 31), 40), 41) |
| 49 | N-Nitroso di-n-propylamine (Nitrosodipropylamine) | 621-64-7 | C 1B, H350 | Not registered/ process-generated | |
| 50 | 2-Nitrotoluene | 88-72-2 | C 1B, H350 | 10–100 a) | 40) |
| 51 | 2,3,4,7,8-Pentachloro-dibenzofuran | 57117-31-4 | **IARC**: 1 (2012) | Not registered/ process-generated | |
| 52 | Phenolphtalein | 77-09-8 | C 1B, H350 | 10–100 | 3) |
| 53 | Polychlorinated biphenyls (PCB) | 1336-36-3 | STOT RE2, H373 **IARC**: 1 (in prep.) | Not registered/ legacy substance | |
| 54 | Potassium bromate | 7758-01-2 | C 1B, H350 | 0–10 | |
| 55 | 1,3-Propanesultone | 1120-71-4 | C 1B, H350 | 0–10 a) | 3), 6), 7), 25), 39) |
| 56 | Propylene oxide (1,2-Epoxypropane) | 75-56-9 | C 1B, H350 | 1,000,000+ | 3), 22), 25), 33), 40) |
| 57 | Quartz (crystalline silica) | 14808-60-7 14464-46-1 15468-32-3 | Annex I (recomm.) **IARC**: 1 (2012) | Process-generated | 22), 25), 36), 40) |
| 58 | Quinoline | 91-22-5 | C 1B, H350 | 100–1,000 a) | 6), 7) |
| 59 | Silicone carbide fibres | 409-21-2 | Proposed: C 1B, H350 **IARC**: 2A (in prep.) | 100,000+ | 2: 2/2015 |
| 60 | Styrene oxide ((Epoxyethyl)benzene) | 96-09-3 | C 1B, H350 | 100–1,000 a) | |
| 61 | 2,3,7,8-Tetrachlorodibenzo-para-dioxin | 1746-01-6 | **IARC**: 1 (2012) | Not registered/ process-generated | 35), 40) |
| 62 | Tetrachloroethylene | 127-18-4 | C 2, H351 **IARC**: 2A (2014) | 100,000–1,000,000 | 23), 33), 43) |
| 63 | Tetrafluoroethylene | 116-14-3 | Notified: C 1B, H350 **IARC**: 2A (in prep.) | 10,000–100,000 | 11) |
| 64 | Titanium dioxide | 13463-67-7 | Proposed: C 1B, H350i | 1,000,000–10,000,000 | 2: 11/2015, 8) |
| 65 | o-Toluidine | 95-53-4 | C 1B, H350 | 10,000–100,000 a) | 3), 22), 34), 39), 40) |
| 66 | Tributyl O-acetylcitrate | 77-90-7 | Notified: C 1B, H350 | 10,000–100,000 | 6), 12) |
| 67 | Trichloroethylene | 79-01-6 | C 1B, H350 | 10,000–100,000 | 3), 4), 22), 25), 31), 40) |
| 68 | 1,2,3-Trichloropropane | 96-18-4 | C 1B, H350 | 1,000–10,000 | 3), 25), 39), 41) |

Table 1 **List of relevant carcinogens/groups of carcinogens (cont.)**

| No. | Substance/group of substances | CAS no. | Classification harmonised (or notified)/Inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|---|
| 69 | Vinyl chloride | 75-01-4 | C 1A, H350 | 1,000,000–10,000,000 | 21), 22), 25), 38), 40) |
| 70 | Vinyl fluoride | 75-02-5 | Notified: C 1B, H350 **IARC**: 2A (2008) | Confidential | 12) |
| 71 | Wood dust | | Annex I | Process-generated | 21), 22), 25), 34), 40), 41) |
| | Polycyclic aromatic hydrocarbons (PAHs) and their nitro compounds | | | | |
| | Benz[e]acephenanthrylene | 205-99-2 | C 1B, H350 | Not registered/ process-generated/ legacy substance | |
| | Benz[a]anthracene | 56-55-3 | C 1B, H350 | Not registered/ process-generated/ legacy substance | |
| | Benzo[j]fluoranthene | 205-82-3 | C 1B, H350 | Not registered/ process-generated/ legacy substance | |
| | Benzo[k]fluoranthene | 207-08-9 | C 1B, H350 | Not registered/ process-generated/ legacy substance | |
| | Benzo[e]pyrene | 192-97-2 | C 1B, H350 | Not registered/ process-generated/ legacy substance | |
| | Chrysene | 218-01-9 | C 1B, H350 | Not registered/ process-generated/ legacy substance | |
| | Cyclopenta[cd]pyrene | 27208-37-3 | **IARC**: 2A | Not registered/ process-generated/ legacy substance | |
| | Dibenz[a,j]acridine | 224-42-0 | Notified: C 2, H351 **IARC**: 2A | Not registered/ process-generated/ legacy substance | |
| | Dibenz[a,h]anthracene | 53-70-3 | C 1B, H350 | Not registered/ process-generated/ legacy substance | |
| | Dibenzo[a,h]pyrene (Dibenzo[b,def]chrysene) | 189-64-0 | Proposed: C 1B, H350 | Not registered/ process-generated/ legacy substance | 2: 6/2015 |
| | Dibenzo[a,l]pyrene (Dibenzo[def,p]chrysene) | 191-30-0 | Notified: C 1B, H350 **IARC**: 2A | Not registered/ process-generated/ legacy substance | |
| | 6-Nitrochrysene | 7496-02-8 | Notified: C 1B, H350 **IARC**: 2A | Not registered/ process-generated/ legacy substance | |
| | 1-Nitropyrene | 5522-43-0 | Notified: C 2, H351 **IARC**: 2A | Not registered/ process-generated/ legacy substance | |

Table 1 **List of relevant carcinogens/groups of carcinogens (cont.)**

| No. | Substance/group of substances | CAS no. | Classification harmonised (or notified)/Inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|---|
| | Petroleum and coal stream substances and mixtures | | | | |
| | Anthracene oil | 90640-80-5 | C 1B, H350 | 10,000–100,000 | 3), 5) |
| | Pitch, coal tar, high temperature | 65996-93-2 | C 1A, H350 | 1,000,000–10,000,000 | 3), 5) |
| | Shale oils | 68308-34-9 | Notified:<br>C 1B, H350<br>**IARC**: 1 (2012) | 100,000–1,000,000 | 11) |
| | Shale oil bitumen | EC number:<br>447-780-2 | Notified:<br>STOT RE 2, H373 | Confidential | 8) |

Table 2 **List of potentially relevant carcinogens/groups of carcinogens**

| Substance/group of substances | CAS no. | Classification harmonised (or notified)/Inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|
| 4-Aminoazobenzene | 60-09-3 | C 1B, H350 | Registered as intermediate only | 3) |
| 4-Chloroaniline | 106-47-8 | C 1B, H350 | Registered as intermediate only | 38), 40) |
| 1,2-Dibromo-3-chloropropane | 96-12-8 | C 1B, H350 | Registered as intermediate only | |
| 1,3-Dichloro-2-propanol | 96-23-1 | C 1B, H350 | Registered as intermediate only | |
| α,α-Dichlorotoluene | 98-87-3 | C 2, H351<br>**IARC**: 2A (1999) | Registered as intermediate only | |
| Diethyl sulfate | 64-67-5 | C 1B, H350 | Registered as intermediate only | 3), 25), 34), 39), 40), 42) |
| Dimethylcarbamoyl chloride | 79-44-7 | C 1B, H350 | Registered as intermediate only | 39) |
| Dimethylsulfamoyl chloride | 13360-57-1 | C 1B, H350 | Registered as intermediate only | |
| Dimethyl sulfate | 77-78-1 | C 1B, H350 | Registered as intermediate only | 3), 25), 34), 39), 40), 42) |
| Dinitrotoluene | 25321-14-6 | C 1B, H350 | Registered as intermediate only | |
| 2,3-Epoxypropyltrimethyl-ammonium chloride (glycidyl trimethylammonium chloride) | 3033-77-0 | C 1B, H350 | 0–10<br>a), PROC: 1 | |
| Ethylene imine | 151-56-4 | C 1B, H350 | 100+<br>a), PROC: 1, 3 | 34), 40), 41) |
| 2-Methoxyaniline (o-Anisidine) | 90-04-0 | C 1B, H350 | Registered as intermediate only | 3), 25), 40) |
| 6-Methoxy-m-toluidine (p-Cresidine) | 120-71-8 | C 1B, H350 | Registered as intermediate only | 3), 40) |
| 4,4′-Methylenedi-o-toluidine (3,3`-Dimethyl-4.4′-aminodiphenylmethane) | 838-88-0 | C 1B, H350 | Registered as intermediate only | 3), 40) |
| 4-Methyl-m-phenylendiamine (Toluene-2,4-diamine) | 95-80-7 | C 1B, H350 | Registered as intermediate only | 3), 40) |
| 4,4′-Oxydianiline and its salts | 101-80-4 | C 1B, H350 | 10–100<br>PROC: 1, 8 | 3) |
| Phenyl glycidyl ether (2,3-epoxypropyl phenyl ether) | 122-60-1 | C 1B, H350 | Registered as intermediate only | |
| Phenylhydrazine | 100-63-0 | C 1B, H350 | Registered as intermediate only | 38) |
| 1,3-Propiolactone (3-propanolide) | 57-57-8 | C 1B, H350 | 0–10<br>PROC: 3; 15, 8 | |
| Propyleneimine | 75-55-8 | C 1B, H350 | Registered as intermediate only | 41) |
| α,α,α 2-Tetrachlorotoluene | 2136-89-2 | notified:<br>C 1B, H350 | Registered as intermediate only | 6), 12) |
| α,α,α 4-Tetrachlorotoluene | 5216-25-1 | C 1B, H350 | Registered as intermediate only | 6) |

Table 2 **List of potentially relevant carcinogens/groups of carcinogens**

| Substance/group of substances | CAS no. | Classification harmonised (or notified)/Inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|
| Thioacetamide | 62-55-5 | C 1B, H350 | Registered as intermediate only | 38) |
| α,α,α–Trichlorotoluene | 98-07-7 | C 1B, H350 | Registered as intermediate only | 38), 40) |
| Vinyl bromide (bromoethylene) | 593-60-2 | C 1B, H350 | Registered as intermediate only | 22), 25), 41) |
| **Petroleum and coal stream substances and mixtures** | | | | |
| Anthracene oil, anthracene-low | 90640-82-7 | C 1B, H350 | Registered as intermediate only | 3) |
| Anthracene oil, anthracene paste | 90640-81-6 | C 1B, H350 | Registered as intermediate only | 3) |
| Anthracene oil, anthracene paste, distn. lights | 91995-17-4 | C 1B, H350 | Registered as intermediate only | 3) |
| Creosote | 8001-58-9 | C 1B, H350<br>**IARC**: 2A (2010) | Biocidal active substance | |
| **Biocidal active substances or active substances authorised for use in plant protection products (PPP)** | | | | |
| Glyphosate (ISO) | 1071-83-6 | Eye Dam. 1, H318<br>**IARC**: 2A (in prep.) | PPP | 1: 7/2015:<br>STOT RE 2; H373 |
| Malathion (ISO) | 121-75-5 | Acute Tox 4, H302<br>**IARC**: 2A (in prep.) | PPP | |
| 4,4′-Methylenedimorpholine | 5625-90-1 | C 1B, H350 | Biocidal active substance | Agreed at RAC-35 |
| Spirodiclofen (ISO) | 148477-71-8 | Proposed:<br>C 1B, H350 | PPP | 2: 1/2015; CLH consultation 10/2015 |
| **Substances used in medicinal products** | | | | |
| Tamoxifen | 10540-29-1 | Notified:<br>C 1A, H350<br>C 1B, H350<br>**IARC**: 1 (2012) | Registered as intermediate only<br>b) | 6) |

Table 3 **List of carcinogens/groups of carcinogens with unclear relevance**

| Substance/group of substances | CAS no. | Harmonised classification/ inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|
| o-Aminoazotoluene | 97-56-3 | C 1B, H350 | Not registered | 3) |
| Antimony trioxide | 1309-64-4 | C 2, H351 | 10,000+ | 8), 26), 37), 40) |
| Biphenyl-4-ylamine (4-Aminobiphenyl) | 92-67-1 | C 1A, H350 | Not registered | 3) |
| Bis(chlorormethyl) ether | 542-88-1 | C 1A, H350 | Not registered | 25), 39) |
| 4,4'-Bis(dimethylamino) benzophenone (Michler's ketone) | 90-94-8 | C 1B, H350 | Not registered | 3) |
| Bitumen | 8052-42-4 | **IARC**: 2A/2B (2013) | 1,000,000–10,000,000 | 26), 38), 40) |
| Carbadox (INN) | 6804-07-5 | C 1B, H350 | Not registered | 41) |
| Chlorodimethyl ether | 107-30-2 | C 1A, H350 | Not registered | 39) |
| C.I. Basic Blue 26 | 2580-56-5 | C 1B, H350 | Not registered | 3) |
| C.I. Direct Black 38 | 1937-37-7 | C 1B, H350 | Not registered | 3) |
| C.I. Direct Red 28 | 573-58-0 | C 1B, H350 | Not registered | 3) |
| 2,4-Dinitrotoluene | 121-14-2 | C 1B, H350 | Not registered | 3), 4), 26) |
| E-glass microfibres (Calcium-aluminium-silicate fibres) | | C 1B, H350i | Not registered | Agreed at RAC-31 |
| Furan | 110-00-9 | C 1B, H350 | Not registered | 3) |
| Hexamethylphosphoric triamide | 680-31-9 | C 1B, H350 | Not registered | 25), 39) |
| Indium phosphide | 22398-80-7 | C 1B, H350 **IARC**: 2A (2006) | Not registered | |
| 5-Nitroacenaphthene | 602-87-9 | C 1B, H350 | Not registered | 41) |
| 2-Nitronaphthalene | 581-89-5 | C 1B, H350 | Not registered | 42) |
| N,N,N',N'-Tetramethyl-4,4'-methylenedianiline (Michler's base) | 101-61-1 | C 1B, H350 | Not registered | 3), 40) |
| Urethan (Ethylcarbamat) | 51-79-6 | C 1B, H350 | Not registered | 25), 41) |
| **Fluorinated hydrocarbons** | | | | |
| 1,1-Difluoroethane | 75-37-6 | Notified: C 1A, H350 | 1,000–10,000 | 12) |
| 1,1-Difluoroethylene | 75-38-7 | Notified: C 1A, H350 | 10,000–100,000 | 12) |
| Difluoromethane | 75-10-5 | Notified: C 1A, H350 | 10,000–100,000 | 12) |
| **Petroleum and coal stream substances and mixtures** | | | | |
| Anthracene oil, anthracene paste, anthracene fraction | 91995-15-2 | C 1B, H350 | Not registered | 3) |
| **Substances notified as new substances (NONS) under Dir. 67/548/EEC** | | | | |
| 4-Amino-3-fluorophenol | 399-95-1 | C 1B, H350 | NONS, confidential a) | |
| R-1-Chloro-2,3-epoxypropane | 51594-55-9 | C 1B, H350 | NONS, confidential | Polymer |
| (2-Chloroethyl)(3-epoxypropyl) ammonium chloride | 40722-80-3 | C 1B, H350 | NONS, confidential | Polymer |

Table 3 **List of carcinogens/groups of carcinogens with unclear relevance (cont.)**

| Substance/group of substances | CAS no. | Harmonised classification/ inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|
| N-[6,9-Dihydro-9-[[2-hydroxy-1-(hydroxymethyl) ethoxy]methyl]-6-oxo-1H-purin-2-yl]acetamide | 84245-12-5 | C 1B, H350 | NONS, confidential | Polymer |
| R-2,3-Epoxy-1-propanol | 57044-25-4 | C 1B, H350 | NONS, confidential | |
| O-Hexyl-N-ethoxy carbonyl-thiocarbamate | EC number: 432-750-3 | C 1B, H350 | NONS, confidential | Polymer |
| Hydrazine-trinitromethane | EC number: 414-850-9 | C 1B, H350 | NONS, confidential | |
| 6-Hydroxy-1-(3-isopropoxy-propyl)-4-methyl-2-oxo-5-[4-(phenylazo)phenylazo] -1,2-dihydro-3-pyridine-carbonitrile | 85136-74-9 | C 1B, H350 | NONS, confidential | |
| (6-(4-Hydroxy-3-(2-methoxyphenylazo)-2-sulfonato-7-naphthylamino-1,3,5-triazin-2,4-diyl) bis[(amino-1-methylethyl) ammonium] formate | 108225-03-2 | C 1B, H350 | NONS, confidential | |
| O-Isobutyl-N-ethoxy carbonylthiocarbamate | 103122-66-3 | C 1B, H350 | NONS, confidential | Polymer |
| (Methylenebis(4,1-phenylen-azo (1-(3-(dimethylamino) propyl)-1,2-dihydro-6-hydroxy-4-methyl-2-oxopyridine-5,3-diyl)))-1,1′-dipyridinium dichloride dihydrochloride | 118658-99-4 | C 1B, H350 | NONS, confidential | |
| Oxiranemethanol, 4-methyl-benzene-sulfonate, (S)- | 70987-78-9 | C 1B, H350 | NONS, confidential | Polymer |
| Trisodium [4′-(8-acetyl-amino-3,6-disulfonato-2-naphthylazo)-4″-(6-benzoylamino-3-sulfonato-2-naphthylazo)-biphenyl-1,3′,3″,1‴-tetraolato-O,O′,O″,O‴]copper(II) | 164058-22-4 | C 1B, H350 | NONS, confidential | |
| **Substances used in medicinal products** | | | | |
| Adriamycin (Doxorubicin) | 23214-92-8 | Notified: C 1B, H350 **IARC**: 2A (1987) | Not registered b) | 42) |
| 5-Azacytidine | 320-67-2 | Notified: C 1B, H350 **IARC**: 2A (1990) | Not registered b) | 11) |
| Azathioprine | 446-86-6 | Notified: C 1A/1B, H350 **IARC**: 1 (2012) | Not registered | 41) |
| 1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU) (Carmustine) | 154-93-8 | Notified: C 1B, H350 **IARC**: 2A (1987) | Not registered b) | |
| Bleomycin (sulphate) | 9041-93-4 | Notified: C 1B, H350 **IARC**: 2B (1987) | Not registered b) | 12), 42) |

Table 3 **List of carcinogens/groups of carcinogens with unclear relevance (cont.)**

| Substance/group of substances | CAS no. | Harmonised classification/ inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|
| Busulfan (1,4-Butanediol-bis(methanesulfonate)) | 55-98-1 | Notified:<br>C 1A/1B, H350<br>**IARC**: 1 (2012) | Not registered<br>b) | |
| Chlorambucil | 305-03-3 | Notified:<br>C 1A/1B, H350<br>**IARC**: 1 (2012) | Not registered<br>b) | 11) |
| Chloramphenicol | 56-75-7 | Notified:<br>C 1A/1B, H350<br>**IARC**: 2A (1990) | Not registered | 11) |
| 1-(2-Chloroethyl)-3-cyclo-hexyl-1-nitrosourea (CCNU) (Lomustine) | 13010-47-4 | Notified:<br>C 1B, H350<br>**IARC**: 2A (1987) | Not registered<br>b) | |
| 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitroso-urea (Methyl-CCNU) (Semustine) | 13909-09-6 | Notified:<br>C 1B, H350<br>**IARC**: 1 (2012) | Not registered<br>b) | |
| Chlorozotocin | 54749-90-5 | Not notified<br>**IARC**: 2A (1990) | Not registered<br>b) | |
| Cisplatin | 15663-27-1 | Notified:<br>C 1B, H350<br>**IARC**: 2A (1987) | Not registered<br>b) | 41) |
| Cyclophosphamide | 50-18-0<br>6055-19-2 | Notified:<br>C 1A/1B, H350<br>**IARC**: 1 (2012) | Not registered<br>b) | |
| Cyclosporin | 59865-13-3<br>79217-60-0 | Notified:<br>C 1B, H350<br>**IARC**: 1 (2012) | Not registered | 11) |
| Dacarbazine | 4342-03-4 | Notified:<br>C 1B, H350<br>**IARC**: 2B (1987) | Not registered<br>b) | 41) |
| Etoposide | 33419-42-0 | Notified:<br>C 1A/1B, H350<br>**IARC**: 1 (2012) | Not registered<br>b) | |
| Melphalan | 148-82-3 | Notified:<br>C 1A/1B, H350<br>**IARC**: 1 (2012) | Not registered<br>b) | |
| 5-Methoxypsoralen | 484-20-8 | Notified:<br>C 1B, H350<br>**IARC**: 2A (1987) | Not registered | 12) |
| Methyl methanesulfonate | 66-27-3 | Notified:<br>C 1B, H350<br>**IARC**: 2A (1999) | Not registered<br>b) | |
| Metronidazole | 443-48-1 | Notified:<br>C 1B, H350<br>C2, H351 | Not registered | 41) |
| Mitomycin C | 50-07-7 | Notified:<br>C 1B, H350<br>**IARC**: 2B (1987) | Not registered<br>b) | 12), 42) |
| Phenacetin (N-(4-ethoxy-phenyl)acetamide) | 62-44-2 | Notified:<br>C 1B, H350<br>**IARC**: 1 (2012) | Not registered | 11) |

Table 3 **List of carcinogens/groups of carcinogens with unclear relevance (cont.)**

| Substance/group of substances | CAS no. | Harmonised classification/ inclusion in annex I of CMD | Registered tonnage band [t/a]/process-generated substance | Comments |
|---|---|---|---|---|
| Pioglitazone | 111025-46-8 | Notified:<br>Acute Tox. 4<br>**IARC**: 2A (in prep) | Not registered | |
| Procarbazine hydrochloride | 366-70-1 | Notified:<br>C 1B, H350<br>**IARC**: 2A (1987) | Not registered<br>b) | 41) |
| Teniposide | 29767-20-2 | Notified:<br>C 1B, H350<br>**IARC**: 2A (2000) | Not registered<br>b) | |
| Thiotepa (Tris(1-aziridinyl) phosphine sulfide) | 52-24-4 | Notified:<br>C 1B, H350<br>**IARC**: 1 (2012) | Not registered<br>b) | 42) |
| Treosulfan | 299-75-2 | Not notified<br>**IARC**: 1 (2012) | Not registered<br>b) | |

## Explanation of notes in Tables 1–3

**Column 'Harmonised classification/inclusion in annex I of CMD':**
IARC: IARC classification; year of publication

**Column 'Registered tonnage band/process-generated substance':**
a) additional registration(s) for 'intermediate use only'
b) use as anti-cancer drug
PROC: process category (PROC) registered under REACH (cf. Section 1.4)

**Column 'Comments':**
*– 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* (acc. to art. 59 (10))
4) substance (or compounds of it) included in REACH *authorisation list*
5) inclusion of substance (or compounds of it) in REACH *authorisation list recommended* by ECHA
6) substance (or compounds of it) included in risk management option analysis (*RMOA*)
7) RMOA result available
8) substance (or compounds of it) included in Community Rolling Action Plan (*CoRAP*)
9) 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)*

21) BOEL under the CMD in existence
22) BOEL under the CMD recommended by ACSH
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 Member-State level: Germany)*

31) exposure–risk relationship (ERR) derived
32) ERR derived, additional health-based threshold for non-carcinogenic effects determined
33) health-based OEL derived
34) ERR not derivable
35) ERR not derived (considered to be not relevant)
36) ERR/health-based OEL currently under derivation
37) derivation of ERR/health-based OEL temporarily put on hold
38) derivation of ERR /health-based OEL intended
39) use of substance permitted in closed system only
40) technical-based OEL existed in the past

*– re. OSH processes and instruments (at Member-State level: Netherlands)*

41) ERR derived
42) ERR not derivable
43) health-based OEL derived