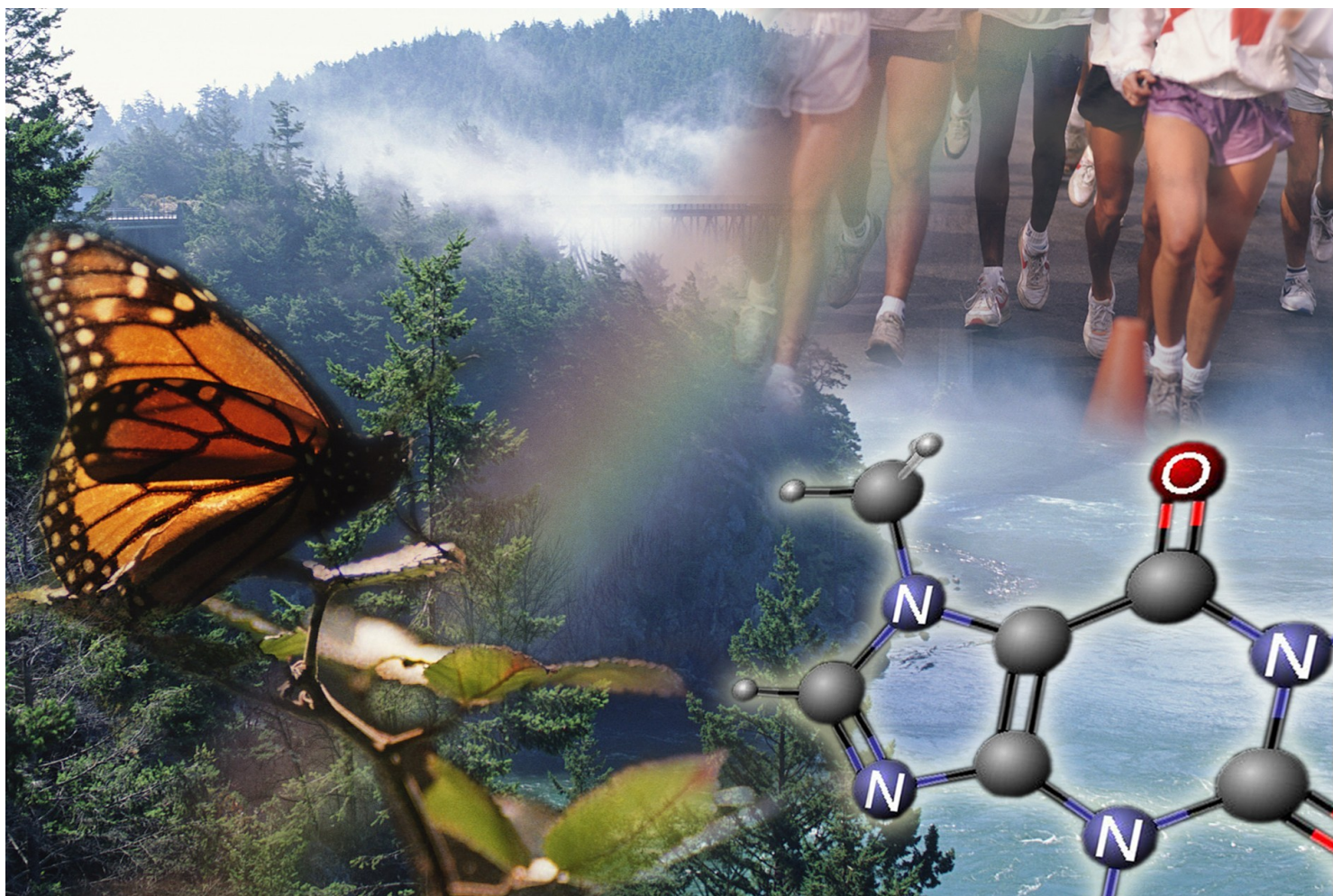


# Guidance for the preparation of an Annex XV Dossier on Harmonised Classification and Labelling



**June 2007**

## **LEGAL NOTICE**

This document contains guidance on REACH explaining the REACH obligations and how to fulfil them. However, users are reminded that the text of the REACH regulation is the only authentic legal reference and that the information in this document does not constitute legal advice. The European Chemicals Agency does not accept any liability with regard to the contents of this document.

## PREFACE

This document describes how Member States Competent Authorities can prepare an Annex XV dossier for a Harmonised Classification and Labelling proposal under REACH. It is part of a series of guidance documents that are aimed to help all stakeholders with their preparation for fulfilling their obligations under the REACH regulation. These documents cover detailed guidance for a range of essential REACH processes as well as for some specific scientific and/or technical methods that industry or authorities need to make use of under REACH.

The guidance documents were drafted and discussed within the REACH Implementation Projects (RIPs) lead by the European Commission services, involving all stakeholders: Member States, industry and non-governmental organisations. These guidance documents can be obtained via the website of the European Chemicals Agency ([http://echa.europa.eu/reach\\_en.html](http://echa.europa.eu/reach_en.html)). Further guidance documents will be published on this website when they are finalised or updated.

The legal reference for the document is the REACH Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006<sup>1</sup>.

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<sup>1</sup> Corrigendum to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006)



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# 1 INTRODUCTION

## 1.1 About this guidance

This document provides technical guidance to the Member States in preparing an Annex XV dossier for proposing and justifying Harmonised Classification and Labelling under Regulation (EC) No 1907/2006 of the European Parliament and of the Council, of 18 December 2006, concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

The classification and labelling requirements under Directive 67/548/EEC will be amended by a Regulation to implement the Globally Harmonised System of Classification and Labelling of Chemicals (GHS - UNECE, 2005). This guidance document is written on the basis of the current requirements of the REACH Regulation in relation to Annex I of Directive 67/548/EEC.

### 1.1.1 Structure of the guidance

This introductory section contains background information. It also describes some aspects which are common to all types of Annex XV dossier. This includes the information basis which will be available in REACH at different stages, and an overview of the general process for the preparation of an Annex XV dossier. There is information on the relation between this guidance and that for other parts of REACH, and the possible contribution of other activities under REACH to the dossier. There are also general remarks on consultation and how to proceed when the conclusion based on the preparatory work is that an Annex XV dossier is not appropriate.

The formats for the Annex XV reports and examples of Annex XV reports are included as Appendices. It is emphasised that although these examples are based on actual substances, the data and the conclusions have been adapted so that they demonstrate the issue being discussed. Hence the conclusions in the examples do not necessarily reflect the decisions actually made.

### 1.1.2 What is Annex XV

Annex XV of the REACH Regulation lays down general principles for preparing dossiers to propose and justify:

- harmonised classification and labelling of substances as carcinogenic, mutagenic, toxic to reproduction (CMR) respiratory sensitiser and other effects;
- the identification of a substance as a CMR Cat 1 and Cat 2, PBT, vPvB or a substance of equivalent concern (in this guidance the term “substances of very high concern (SVHC)” is used) according to Article 59 ;
- restrictions on the manufacture, placing on the market or use of substances within the Community.

Agreement (Commission comitology decision) on a dossier for harmonised classification and labelling will lead to the addition of the classification to Annex I of Directive 67/548/EEC (Article 115). In addition, an Member State competent authority (MS CA) may prepare an Annex XV dossier to propose a substance that has been included in Annex I as CMR category 1 or 2 to be included in the candidate list (in accordance with Article 59) for eventual inclusion in Annex XIV (list of substances subject to authorisation).

### **1.1.3 Who is the guidance for?**

This guidance is intended for use by those within the Member State competent authorities responsible for the preparation of Annex XV dossiers. In general, it assumes that the user has suitable experience for the part of the guidance they are using. However, the full range of Annex XV dossiers covers a wide range of subject areas and so some areas include more basic guidance.

The guidance will also be useful for registrants, being the ‘parties concerned’ in Article 115(2), and others involved with a substance for following the process and understanding the basis of the Annex XV dossiers and the justification for any proposal.

## **1.2 Overview of the preparation of Annex XV dossiers**

### **1.3 What is an Annex XV dossier?**

The Annex XV dossier consists of two parts, in parallel to the registration dossiers for substances manufactured or imported in quantities of ten tonnes or more per year which consist of a technical dossier and a Chemical Safety Report (CSR). The two parts of the Annex XV dossier are:

1. The Annex XV report. For consistency between all the documentation produced under REACH, the format of the parts of the Annex XV report relating to the hazard and risk assessment of the substance follows closely that for (evaluation and of) the CSR. The basic format has been adapted to the specific requirements of the individual Annex XV dossiers in some cases. The formats for the three types of Annex XV report are included as Appendices to the guidance. The report will be produced and attached to the technical dossier in IUCLID.
2. A technical dossier supporting the Annex XV report and stored in IUCLID. This can include robust study summaries imported from registration dossiers available in IUCLID. These reference study records may be annotated by the Agency or a MS CA. Robust study summaries or study summaries can also be created by the MS CA in the case of additional data being available (see appropriate guidance from the [Guidance on registration](#)).

The term Annex XV dossier is used to refer to the package of the Annex XV report and the technical dossier. The guidance on reporting the results relates to the preparation of the Annex XV report.

### **1.4 Information sources**

The main source of information on substances under REACH is the registration dossier. A registration dossier will be produced by each manufacturer or importer registering the substance. These will be stored within IUCLID in the REACH-IT system. The registration dossier consists of a technical dossier and, in some cases a CSR.

A technical dossier is submitted for all substances manufactured or imported in quantities of one tonne or more per year. The technical dossier contains study summaries and robust study summaries. In the case of multiple registrants for one substance, most parts of the technical dossier will be submitted in a joint dossier, including these summaries unless companies demonstrate that they have reasons to submit parts individually. The information required to be included in this technical dossier is all of the relevant physicochemical, toxicological and ecotoxicological information available to the registrant; the minimum required depends on the quantity manufactured or imported, with thresholds of 1, 10, 100 and 1,000 tonnes per year leading to increased data

requirements. The requirements are also modified by the expected classification and the use pattern. The time by which the registration is required to be submitted also depends on the quantity and the classification of the substance. Details of the information requirements are set out in Annexes VII to XI and are included in the Chemical Safety Assessment (CSA) guidance (XXX).

For substances manufactured or imported in quantities of ten tonnes or more per year, a CSA is required to accompany the technical dossier. This includes a hazard assessment (human health and environment) and a PBT/vPvB assessment for the substance. If this hazard assessment shows that the substance meets the criteria for classification according to Directive 67/548/EEC, or the substance is assessed as a PBT or vPvB, then an exposure assessment and risk characterisation must also be carried out. The results of the CSA are documented in the CSR.

A further source of information under REACH is through dossier or substance evaluation. Under compliance check (part of the dossier evaluation) registrants may be required to submit any information needed to bring the registration(s) in compliance with the REACH requirements. Following examination of testing proposals (another part of dossier evaluation) more information will have to be generated and submitted. Substance evaluation is the procedure by which further information (such as testing or exposure and use information) may be requested to clarify risks from substances. After the generation of any requested information, conclusions will be drawn and documented by the Agency.

The amount of information available to a MS CA when beginning the preparation of an Annex XV dossier will, therefore, depend on the status of the substance in REACH, and this may have an influence on the development of the dossier. Possible scenarios of data availability through REACH are:

- Substance is not registered because:
  - it is exempt from registration
  - the timeline for registration has not yet been reached.
- Substance has been registered but no CSR exists (i.e. the substance is produced at quantities starting at 1 but below 10 tonnes/year).
- Substance has been registered and a CSR exists.
- Substance has been registered and has undergone dossier or substance evaluation.

There could also be situations where more than one of these applies, in particular where some manufacturers or importers dealing with higher tonnages have registered the substance, but the timetable for other registrations at lower tonnages is still to be completed, or where an existing substance is imported or manufactured by a new manufacturer/importer, resulting in a new registration.

For the second and third cases listed above], the primary information source will be the registration dossier. The technical dossiers will contain study summaries and robust study summaries in some cases, and will also contain a proposal for the classification and labelling. For the third and fourth cases listed, the CSR will document how the registrant reached the reported conclusions on the classification and labelling and will include an assessment of whether the substance meets the PBT or vPvB criteria based on the information in the technical dossier. With respect to the fourth case it shall be noted that the substance can be registered but the technical dossier does not yet contain all relevant information as the registration included testing proposals. These testing proposals need to be examined before the registrant can conduct the test.

If in exceptional cases an Annex XV dossier is being prepared where a substance has not been registered or is exempted from registration, then there will be no information within the REACH-IT system at the time, apart from the classification and labelling inventory entries, and so other sources of information will then need to be considered. Reviews may have been produced by other fora such as the OECD, IPCS, IARC, national reviews by Member States etc., and if so it will be useful to use these to identify the information that is available. There may also be new studies published in the literature or new research reports. A more detailed search of the literature could potentially help to identify relevant information where there are significant gaps in any available reviews, or where there are no reviews.

Given the possible importance of the outcome, it is recommended that the primary sources of data, for example the full study reports, where available to the MS CA, should be reviewed for the Annex XV dossier, particularly for the key studies. Information from secondary sources should not generally be used as the basis for the proposal unless there is a high confidence in the robustness of the approach used to review the data for the secondary source (for example where it is documented that the secondary source had recently reviewed the original full study report against known and acceptable criteria).

## **1.5 Confidential data**

A registrant may identify certain information in their registration as commercially sensitive. If the justification with regard to information listed in Article 119 (2) is accepted as valid by the Agency, then this information will be marked as commercially sensitive in REACH-IT. Such information can be used in the preparation of an Annex XV dossier for discussion with the Agency and Member States, as such discussions can be confidential. However, such information must not be included in any documents to be used for public consultation. The MS CA therefore has to consider this when preparing an Annex XV dossier.

Authorities need to pay attention also to information listed in Article 118 (2). Information to which access cannot be granted under Article 118 must not be published on the internet because the Agency would already have to deny access to such information on request in a single case on the basis of Regulation 1049/2001.

The general provisions on access to information are twofold:

- Some pieces of information will be made available over the internet in accordance with Article 119 (1).
- Access to other pieces of information will be granted by the Agency on request on a case by case basis in accordance with Regulation 1049/2001, as per Article 118 (1). Regulation 1049/2001 defines cases in which access to information has to be denied e.g. for reasons related to the protection of commercial interests which are further explained in Article 118 (2). It also requires the Agency to check with companies that have submitted information to it whether the company claims that the information asked for is confidential. The Agency then has to take a decision.

## **1.6 Links to other REACH guidance and processes**

This guidance is not intended to be used as stand alone guidance. Much of the guidance needed for carrying out hazard assessment and risk assessment is covered in the [Guidance on the Chemical Safety Report](#). The same approaches should be used in most cases and so these are not repeated

here. Instead, this guidance indicates when to refer to the [Guidance on the Chemical Safety Report](#), and identifies areas where the approaches in that guidance need to be adapted for the purpose of the Annex XV dossier.

Substance evaluation is likely to be a part of the process of producing an Annex XV dossier, as described in the next section. As such there is a clear link between the two activities. Some of the guidance for Annex XV dossiers may be useful for carrying out parts of the substance evaluation, in terms of justifying a request for further information based on review of the available data and on risk assessment.

The [Guidance on evaluation](#)) may also provide further information where this should have been provided in the registration(s).

The [Guidance on Classification, Labelling and Packaging](#) will develop guidance on the implementation of the new GHS criteria within the EU which are based on the UN Globally Harmonised System for the Classification and Labelling of chemicals (GHS).

## **1.7 General process**

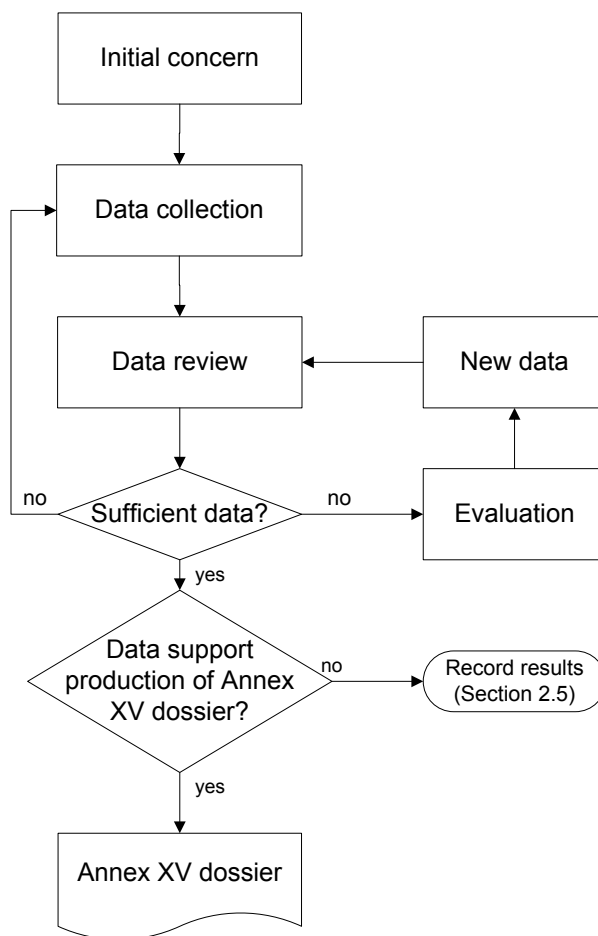
The Annex XV process could be seen simply as the preparation of the Annex XV dossier, and the subsequent review, discussion, and agreement or rejection as described in the REACH Regulation. This guidance is intended to reflect a broader description. It also includes some steps of substance evaluation, or which might need to be performed to justify a request for further information in the evaluation. A distinction has to be made between the work that is done and the final result that is documented in an Annex XV dossier.

The use of substance evaluation as a way to increase the data available for the C&L dossier is considered here as a part of the process, as sufficient information has to be obtained before the formal submission of the Annex XV dossier proposing harmonised classification and labelling. It should be noted that development of parts of such dossier (or at least material for parts of the dossier) may take place both before, during and after substance evaluation. The specific requirements for substance evaluation, in terms of identifying the required information and providing justification, are not included here, but can be found in the [Guidance on evaluation](#).

The normal procedure during the initial development of the Annex XV dossier would be that the readily available sources such as registration dossiers and results from previous evaluation(s) are obtained and reviewed. Following the review of these sources it may be that there are gaps in the information available. If such information should have been in the registration dossier according to the information requirements, this information can be required by the Agency through dossier evaluation. Information could also be requested through substance evaluation performed by a Member State. Other possibilities could include more specific searching for information, or consideration of other substances for read-across. It is likely that an iterative process between information gathering and review may be useful in some cases. The aim is to ensure that, once the substance evaluation process is complete, there are sufficient data available with which to prepare the Annex XV dossier.

The basic process for Annex XV dossiers is set out in Figure 1.

**Figure 1** Basic process for Annex XV dossier production



Notes: Sufficient data – are there sufficient data to make a decision on whether the substance meets the criteria.

### 1.8 What to do when an Annex XV dossier is not appropriate

This guidance on the compilation of the Annex XV report considers the situation where the substance meets the criteria for harmonised classification and labelling. There may be cases where the MS CA carries out work towards an Annex XV dossier but concludes at some point that there is in fact no need for a dossier because it is concluded that the substance does not meet the criteria for CMR, respiratory sensitisation or other endpoints. In this case it can document the conclusions in the form of an Annex XV dossier which can be included in the classification and labelling inventory. It is important that the work that has already been undertaken is not lost but is made available for future work.

The examples mentioned above involve the preparation of an Annex XV dossier even though the MS CA has decided not to proceed further. These may be seen as ideal cases and this level of work may not be required in all cases; for some situations a simple statement of the reasons why it was decided not to proceed may be more appropriate. It is up to the MS CA to decide how much of the work they have done needs to be documented, and this will be on a case-by-case basis. The key outcome must be that the work undertaken by one MS CA should be known and available to the Agency and other Authorities so that the process works efficiently and without undue duplication of effort.

## **1.9 Importance of consultation with stakeholders**

Although Annex XV includes no specific requirement for Authorities to engage in consultation, stakeholder involvement in the process is important. Industry and other stakeholders have no legal obligation to provide information for the development of an Annex XV dossier, so consultation may be an important way for the MS CA to obtain additional information. It should be noted that the term consultation is used throughout this document to refer to contacts with stakeholders aiming at voluntary submission of information and should not be confused with the formal invitation for commenting and providing information which will follow the submission of a finalised dossier to the Agency (such as under Articles 59(3) and 69(6) of the REACH Regulation).

The MS CA preparing the dossier should decide upon the need for consultation and the resources and time to be allocated to consultation activities. However, Authorities are encouraged to engage interested parties in the development of the dossier as early in the process as possible. This will facilitate the timely collection of the necessary information and will contribute to the transparency and representativeness of the dossier. At the very least, the MS CA should consider informing the identified interested parties that work related to a possible proposal for a harmonized classification and labelling Annex XV dossier has been initiated.

## 2 DOSSIER FOR HARMONISED CLASSIFICATION AND LABELLING

**Aim:** The objective is to develop an Annex XV dossier for harmonized classification and labelling for CMRs, respiratory sensitizers or other effects (on a case-by-case basis where a justification demonstrating the need for action at Community level is provided).

**Scope:** The basic steps required are:

- Identification of information;
- Evaluation of hazard information and classification;
- Compiling a justification for Community level action for endpoint other than CMR and respiratory sensitizers;
- Completion of report sections.

The amount of work required for these steps will depend to some extent on the stage in the REACH process at which the substance is being considered, but the same general principles apply.

### 2.1 Legal basis

The legal basis for harmonisation of classification and labelling is given in Directive 67/548/EEC and in Article 115 of the REACH Regulation. The latter states:

1. *Harmonised classification and labelling at Community level shall, from 1 June 2007, normally be added to Annex I of Directive 67/548/EEC for classification of a substance as carcinogenic, mutagenic or toxic for reproduction category 1, 2 or 3, or as a respiratory sensitiser. Harmonised classification and labelling for other effects may also be added to Annex I of Directive 67/548/EEC on a case-by-case basis if justification is provided demonstrating the need for action at Community level. To this end, Member State competent authorities may submit proposals to the Agency for harmonised classification and labelling in accordance with Annex XV.*
2. *The Committee for Risk Assessment shall adopt an opinion on the proposal, giving parties concerned the opportunity to comment. The Agency shall forward this opinion and any comments to the Commission, which shall take a decision in accordance with Article 4(3) of Directive 67/548/EEC.*

The classification and labelling requirements under Directive 67/548/EEC will be replaced by a Regulation to implement the Globally Harmonised System of Classification and Labelling of Chemicals (UNECE, 2005). This guidance document is written on the basis of the current requirements of the REACH Regulation in relation to Annex I of Directive 67/548/EEC. Some of the terminology may change in the future once the GHS is implemented (for example the GHS specifies categories 1A, 1B and 2 for the hazard classes carcinogenic, mutagenic and toxic to reproduction (CMR) instead of categories 1, 2 and 3).

The primary responsibility for classification and labelling lies with the manufacturer or importer of the substance (Enterprises). Enterprises are required to submit to the Agency classifications for all substances subject to registration, and to notify the Agency of the classification and labelling of other substances that are placed on the market (independent of the quantity in which the substance

is placed on the market) and that meet the criteria for classification as dangerous. The Agency will collate all this information on classification and labelling into a publicly accessible classification and labelling inventory. This inventory will indicate the relevant registration number(s) – if available - and for each entry whether the classification has been harmonised by an entry in the Annex I of Directive 67/548/EEC or whether the entry is agreed by two or more manufacturers or importers (Article 114). In the first case, suppliers will have to apply the classification included in this Annex. In the latter case, where there is no entry in Annex I of Directive 67/548 but an entry in the inventory that has been agreed between two or more registrants, the general rule applies that each supplier is self-responsible for his classification. This means that each supplier can use and shall take account of other entries in the inventory, but each supplier has to decide and be able to justify himself the classification of the substances he supplies. Thus, if entries in the inventory differ, there is no obligation to apply the classification that has been notified by the majority of suppliers. No supplier can force another supplier to follow his classifications. Suppliers of substances shall however make every effort to come to an agreed entry. Any agreements will then have to be communicated to the Agency, and the Agency will update the inventory accordingly.

According to the REACH Regulation, new entries into Annex I of Directive 67/548/EEC will primarily be substances classified as CMR categories 1, 2 and 3 and as respiratory sensitisers. However, the proposal also allows for harmonised classification and labelling for other effects to be added to Annex I of Directive 67/548/EEC on a case-by-case basis if justification is provided demonstrating the need for action at Community level (for further guidance see Section 2.6.2).

It is the responsibility of Authorities to prepare an Annex XV dossier to propose a harmonised classification. This proposal will be discussed by the Committee for Risk Assessment and its opinion on the inclusion of the substance in Annex I of Directive 67/548/EEC will be forwarded by the Agency to the Commission. Parties concerned, which include (potential) registrants, will be given the opportunity to comment on the proposal before it is forwarded to the Commission. The Commission will take a decision on whether to include the substance into Annex I to Directive 67/548/EEC in the regulatory comitology procedure.

The main purpose for proposing harmonised classification and labelling for certain effects is to ensure that the criteria for classification are applied correctly in those cases, so that information for risk management on the basis of the classification is harmonised throughout the EU. Furthermore it facilitates the application of legislation which depends on the classification in a consistent way throughout the EU. The REACH Regulation focuses on harmonised classification and labelling for CMR and respiratory sensitisers to ensure that the authorities' resources can be concentrated on those properties which are of particular concern. The requirements under the other provisions of REACH should provide the appropriate framework for dealing with properties of other concern, but for those cases where harmonised classification is also considered necessary on a case-by case basis, the REACH Regulation allows such harmonisation. In addition, for CMR categories 1 and 2, agreement of the classification will facilitate the inclusion of the substance on the candidate list of substances from which the substances may be prioritised for inclusion in Annex XIV and through this to be subject to authorisation.

This guidance relates only to the preparation of Annex XV proposals for harmonised classification and labelling produced by MS CAs. Guidance for data evaluation for the purposes of classification and labelling is given in the [Guidance on information requirements](#) and in the [Guidance on the Chemical Safety Report](#). It should be noted that according to Article 115, Annex XV proposals for harmonised classification and labelling are for substances and not for preparations.

Enterprises have a requirement, under current legislation as well as in the future when the GHS will be implemented in Community law, to carry out a self-classification for all substances they place on the market. If an entry is included in Annex I to Directive 67/548/EEC, enterprises have to apply

the classification for the endpoint(s) included in the Annex if they supply the substance. For substances for which entries are included in the REACH classification and labelling inventory only, but not in Annex I to Directive 67/54/EEC, each enterprise still has to take its own decision on the classification of its substance(s).

A MS CA may prepare an Annex XV dossier to propose a harmonised classification and labelling, using the registrants' self-classification(s) as a basis to initiate a process to include this classification and labelling in Annex I of Directive 67/548/EEC. For a proposal for a harmonised classification for effect(s) other than CMR or respiratory sensitisation, it will have to include in the Annex XV dossier a justification of the need for harmonised classification at the Community level (see Section 2.5).

## 2.2 Process

The basic process for preparing an Annex XV dossier is described in Section 2.5. The overall process leading to the Annex XV dossier will start when a MS CA considers that a substance meets the criteria for classification as a CMR or a respiratory sensitiser, or when harmonised classification and labelling for another effect is considered justified. The next steps will be to obtain the relevant available information and review it. If the available data are considered by the MS CA to be sufficient for making the classification and labelling proposal then the Annex XV dossier can be prepared. In cases where the data are not sufficient for making the classification and labelling proposal, but where there are still concerns that the substance may meet the criteria for classification and action on a Community-wide basis is needed, a substance evaluation could be initiated to generate the required information to clarify the concerns (see the [Guidance on evaluation](#)). The following sections in the guidance present the information collection, information review and preparation of the report as consecutive steps, but in some cases an iterative approach will be needed (as described in Section 2.5).

There may be different reasons why a MS CA wishes to initiate the process leading to the production of an Annex XV dossier for proposing a harmonised classification and labelling. First, registration dossiers have already identified that the substance should be classified for the relevant endpoint. In this case, adequate risk management measures (RMMs) should be in place already throughout the supply chain and so the actual need for a proposal for harmonized classification and labelling should be considered. It could be that different registrants did not manage to agree on the classification for the same substance and that different RMMs are applied as a result. In this case, if some of the RMMs are not adequate, a harmonised classification and labelling might be considered as an option.

In other cases the MS CA may not agree with the registrants' classification(s), or with the interpretation of some of the data given in the registration dossier; or new data not considered in the registration dossier<sup>1</sup> may have become available, for example the results of a new study published in the open, publicly available, literature.

When a MS CA considers the need for developing an Annex XV dossier for an harmonised classification and labelling, the first step is to check via REACH-IT the 'registry of intentions' whether another Member State is already preparing such an Annex XV dossier on the same

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<sup>1</sup> In such cases where new information has become available since the submission of a registration, the registrant should also consider this, revise the CSR if appropriate and submit a revised classification to the inventory.

substance. The Agency's registry of intentions includes also information on the intentions of Authorities to prepare an Annex XV dossier for restriction and for identification of SVHCs. It is recommended that the MS CA checks also the stage of any such work on the same substance. If the MS CA decides to proceed with the preparation of an Annex XV dossier for harmonised C&L although other Annex XV dossier for a restriction proposal or for the identification of SVHC is under preparation, it is recommended that he contacts the other Authorities working on the substance to ensure that work is not duplicated. The registry is accessible for the Agency, the Commission the Member States and interested parties.

### 2.3 Information collection

**Aim:** to identify sources of the information required to assess whether the substance meets the classification criteria.

**Output:** identified data sources (to be reviewed in the next step).

As described in Section 2.2, registration dossier(s) will be the primary source of information. The information needed for the dossier depends on whether the Annex XV dossier is being developed for a carcinogenic substance, a mutagenic substance, a substance toxic to reproduction, a respiratory sensitiser or a substance with other hazardous endpoints. The Annex XV dossier can consider one of these endpoints, or any combination of these endpoints. However, in order to ensure that the appropriate RMMs and Operational Conditions (OCs) are applied as a result of the classification, a MS CA may wish to consider several relevant endpoints in the same Annex XV dossier.

The technical dossiers in the registration dossiers will contain study summaries, and robust study summaries in some cases, and will also contain the classification and labelling by the registrant. The CSR will document how the registrant reached the reported conclusions on the classification and labelling based on the information in the technical dossier.

The potentially relevant parts of the technical dossiers and CSRs are shown in Table 1.

**Table 1** Technical dossier and CSR sections relevant for a classification and labelling Annex XV dossier

Topic	Sections in technical dossiers	Sections in CSR (all in Part B)
Identification of the substance and physical and chemical properties	Section 1, Section 3	Section 1
Classification and labelling	Section 1.5	Section 3
Human health hazard assessment	Section 6	Section 5
Environmental hazard assessment	Section 5	Section 7

In the case where the substance has been the subject of a substance evaluation, there will also be an evaluation report. Depending on which types of substance(s) and the reasons for considering that the substance presents a risk and leading to the substance evaluation, this evaluation report may have considered the relevant endpoints already.

Where the substance has not (yet) been registered or is exempted from registration, there may be an entry in the Classification and Labelling Inventory, but there will be no supporting information available at the Agency. The MS CA will need to consider other sources of information, as indicated in Section 2.2. Whether such a substance should be a priority for resources depends on the

reasons for considering the need for harmonised classification and labelling and whether the substance is pre-registered; in the latter case it is likely that enterprises will generate the information for their registration dossiers.

In addition, for some substances there may be documentation available from previous classification and labelling work which may be a useful source of information for the Annex XV dossier.

## 2.4 Information review

**Aim:** to review the information sources identified in the previous stage and select the data to support the proposed harmonised classification.

**Output:** information to be included in the Annex XV dossier.

The specific types of information needed for the classification and labelling for a given endpoint are outlined in Directive 67/548/EEC. The criteria and guidance for classifying substances as CMRs, respiratory sensitisers or having other effects in Directive 67/548/EEC will be subject to future adaptations to technical progress, and in particular will be replaced by legislation to implement the GHS. Guidance on the evaluation of the various studies is being developed in the [Guidance on information requirements](#) and this should be used in the review of the studies. This guidance therefore does not discuss technical issues. This section provides guidance on the kinds of information which may be useful in the development of the Annex XV report, and on some situations which may arise in using the REACH-related data sources.

Where a dossier or substance evaluation has already been completed then the results of the(se) evaluation(s) should be considered first. In such cases there may be little or no need for further data review at this point and the Annex XV dossier can be prepared directly. The following notes relate to other situations, or where only part of the required information has been reviewed under any evaluation carried out so far.

Where several registration dossiers for one substance have been submitted which contain different results on the classification or different interpretation of data for the endpoints being considered, the justifications provided in all those registration dossiers will need to be examined to draw conclusions on a harmonised classification.

If the review leads to the conclusion that registration dossier(s) are not in compliance with the registration requirements, the Member State should point this out to the Agency for it to consider when setting priorities for compliance checking. If the review leads to the conclusion that further information is needed to draw appropriate conclusions on the classification, substance evaluation could be initiated (see the [Guidance on evaluation](#)).

The studies which are considered to be the key ones for each endpoint should have been identified within the registration dossiers. Comments on the studies included in the technical dossiers from registrations can be added as annotations. All (robust) study summaries chosen by the MS CA as necessary to support the Annex XV dossier should be copied from registration dossiers into a new “Annex XV technical dossier” to be prepared. It is important to highlight in the dossier where studies have been interpreted in a different way, and to explain which interpretation is followed and why. (Robust) study summaries of any new data to be included in the Annex XV dossier should be recorded in the technical dossier for the Annex XV dossier.

Information on other related substances and other supporting information should be reviewed in a similar way using the relevant sections of the [Guidance on information requirements](#) and in the [Guidance on the Chemical Safety Report](#). When making use of information on related substances,

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the MS CA will need to explain how these relate to the substance being assessed, and how this justifies the use of the information. The amount of information needed for related substances used to support the proposal is likely to vary case-by-case, depending for example on whether or not there was an agreed classification for the similar substance or not. Guidance on the use of a category approach is developed in the [Guidance on information requirements](#). This may be of relevance here.

It may also be the case that the substance is undergoing testing, for example as a consequence of a testing proposal for Annex IX or X requirements included in the registration. Any such testing should be considered in case it might be of relevance to the proposal. If the testing is relevant, then it should be considered very carefully whether to proceed or to await the result of the testing.

The MS CA may also wish to consult external experts or carry out consultation among stakeholders in some cases. This may be of greater usefulness and importance where the available information is less consistent.

An Annex XV dossier can be prepared:

- for a given substance, or
- for several substances for which a harmonised classification and labelling is proposed because they contain a given constituent meeting classification criteria.

When the MS CA prepares an Annex XV dossier proposing a harmonised classification and labelling for several substances because they contain a constituent or impurity meeting classification criteria, it has to list those substances in the dossier. In such cases, if a substance evaluation is felt necessary in order to clarify the concern, the Agency may consider to include all substances containing such a constituent on the Community Rolling Action Plan (CRAP, see the [Guidance on evaluation](#)).

#### Examples of possible situations

This section considers a number of possible situations which may be encountered after the collection of the information or following an initial brief review.

- The substance is registered and the registration contains a relevant classification (either there is only one registration dossier or all those available are in line with respect to the relevant classification). In this case, the information and discussion in the registration dossier(s) will support the proposal, and only a brief review may be needed to identify what to include in the dossier. However, it should be carefully considered whether a substance for which there is already one relevant classification as a result of registrants' self-classification(s) is a priority for a proposal for harmonised classification and labelling.
- The substance is registered, with registration dossiers which contain different classifications for the relevant hazards. In this case, an examination of the data sets used in the different registration dossiers and the arguments presented for different classifications or for not classifying should be carried out. These arguments will need to be refuted, or demonstrated to be not appropriate. The degree of work required may depend on the degree of difference in interpretation - borderline cases may be easier to reconcile than large differences.
- The substance is registered and all available registration dossiers conclude that it should not be classified for that property. As the MS CA will already have substantive information that the substance should be classified, for example as the result of the initial data collection, the focus of the review should be on the reasons why the interpretation of studies in the CSRs differs from that the Member State considers correct. This may require detailed examination of the relevant

studies. It may also be that it is other information not included in the CSRs which leads the MS CA to consider the classification justified. In such cases the review should consider how the new information overturns that in the CSRs.

- The substance is not registered. In this case the Authority will need to identify and review the information gathered against the criteria using the [Guidance on the Chemical Safety Report](#).

## **2.5 Justification demonstrating the need for action at Community level for hazards other than CMRs and respiratory sensitisers**

For proposals for harmonised classification and labelling for effects other than CMR and respiratory sensitisation, a justification demonstrating the need for action at Community level needs to be included in the Annex XV dossier. This could include consideration of a number of issues.

The primary reason for proposing a harmonised classification and labelling is that such harmonisation is necessary to ensure adequate risk management throughout the Community. Harmonised classification and labelling could be justified when, e.g:

- there are differences in the self-classifications in the inventory which have not been resolved, and which would lead to significant differences in the required level of risk management;
- the classification has implications for the management of risks under downstream legislation. Appendix IV of this guidance document gives a non-exhaustive overview of Community legislation referring to the classification of substances under Directive 67/548/EEC;
- Substances in biocides and in plant protection products notified under Directive 98/8/EC and 91/414/EEC, respectively, need harmonised classifications for product authorisation.

The other component to be considered is the type and magnitude of the possible risks that are to be managed:

- the type and magnitude of hazardous effects;
- the substance is used by large numbers of workers or consumers;
- the level of exposure.

## **2.6 Preparing the report**

**Aim:** to include the selected information in the relevant sections of the Annex XV report.

**Output:** the completed Annex XV report with proposal for harmonised classification.

As noted in Section 2.1, the Annex XV dossier consists of two parts. This section of the guidance considers the preparation of the Annex XV report. Preparation of the technical dossier is not addressed here, the appropriate guidance from the [Guidance on registration](#) should be followed along with the [Guidance on IUCLID](#).

The Annex XV report consists of three parts: a proposal, a justification and other information. The approach to completing the report is similar for all endpoints. This guidance focuses on the four endpoints specifically identified (carcinogenicity, mutagenicity, reprotoxicity and respiratory sensitisation), but the same principles can be applied to other endpoints. For the latter, in addition, a case by case justification demonstrating the need for action at Community level has to be included in the report. The format for the Annex XV report is given in Appendix 1.

Examples of completed harmonised classification and labelling Annex XV reports for CMR endpoints are given in Appendix 2 (carcinogenicity and mutagenicity) and Appendix 3 **Error! Reference source not found.** (toxicity for reproduction).

For clarity, references to sections within the report are written in italic thus: *Section 1.1*, to differentiate them from the sections in this guidance.

### 2.6.1 Proposal

The first part of the Annex XV report outlines the proposed classification. This contains details of the identity of the substance (substance name, CAS/EC number(s), registration number(s) (if available), molecular formula, structural formula, purity and impurities). The proposed classification and labelling, any proposed specific concentration limits, and a clear statement as to which of the endpoints have been considered and analysed in the dossier should also be given. The classification and labelling based on GHS should also be indicated. In particular, it is important to distinguish between endpoints which have been considered but for which no classification is proposed<sup>2</sup> and those that have not been considered. It is also important to indicate in this part of the Annex XV report if the classification is based on an impurity present in the substance rather than based on the properties of the substance itself. In such cases the identity of the impurity and composition of the impurity in the substance leading to the classification should be identified. The applicability of the classification to the same substance but with different levels of the impurity should also be considered.

### 2.6.2 Justification

The second part of the Annex XV report contains the detailed technical and scientific justification for the harmonised classification and labelling proposal. The format for this section of the Annex XV report follows the format of the CSR. The objective of having compatible formats for different types of reports within REACH (for registration, for evaluation, for Annex XV) is to facilitate the use of already available data within the system. Details of the reviewed relevant information should be entered into the relevant sections of the format. The headings outlined in the format should be used in all cases, but it is recognised that some of the headings will not be relevant in all cases. Therefore information need only be entered under relevant headings, and wording along the lines of 'not relevant for this dossier' should be entered under the headings not used. This is shown in broad terms in the report format in Appendix 1, and more specific examples are shown in the example Annex XV reports in Appendices 2 and 3.

The information required for the Annex XV report should in most cases be extracted from the relevant technical dossiers, either those from the registration dossiers or that created by the MS CA for the Annex XV dossier. The technical dossiers will contain endpoint summaries and study summaries, with appropriate tables and text content. The MS CA will be able to add comments to

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<sup>2</sup> Note: In the course of producing an Annex XV dossier the Authority may have considered some or all of the possible endpoints and decided that the substance does not meet the criteria for some of these. Although it is up to the Authority to decide whether other endpoints are considered, it is useful to document what other endpoints have been considered, and on the basis of what information, in order to prevent a later superfluous re-evaluation of the same data. In such cases it would be useful to include a short summary of what was evaluated and the reasons why no classification was proposed.

these as necessary. The use of material extracted from the technical dossiers is not illustrated in the examples.

The format for the justification of the Annex XV report is broken down into a number of sections. The guidance below focuses on the sections in which information should be included for a dossier for harmonised classification and labelling. In addition to the information indicated, the MS CA should outline in *Sections 4, 5 and 7* any differences in interpretation of the key data compared to the source of the information (for example the registration dossier submitted by registrant(s)).

- *Section 1*. This outlines the identity of the substance and includes a summary table of the physico-chemical properties. *Section 1.1* should be used to outline the purity of the substance and any impurities and additives present in the substance. This is particularly important in relation to substances being classified on the basis of the presence of an impurity. Where possible the impurities and additives should be identified by chemical name and CAS Number, and the level of such impurities/additives present in the substance should be given. The [Guidance on substance identification](#) provides further guidance in relation to defining the substance identity in terms of composition and purity. For the physico-chemical properties, it is not necessary to complete the table for all properties. The most useful properties in relation to classification and labelling considerations are likely to be the physical state of the substance, melting point, boiling point, vapour pressure, water solubility, n-octanol/water partition coefficient, granulometry (if relevant), dissociation constant (if relevant) and viscosity (if relevant), and it is recommended that at least these fields are completed.
- *Section 2*. This section is not relevant for a classification and labelling report.
- *Section 3*. This outlines different classification(s) included in the classification and labelling inventory (including also the current classification listed in Annex I of Directive 67/548/EEC). The classification being proposed by the MS CA should not be included here, but should be given in the *Proposal* part of the report.
- *Section 4*. This outlines the environmental fate properties of the substance. This section is not likely to be relevant for a CMR or respiratory sensitisation report; however information on degradation and bioaccumulation may be relevant if endpoints other than CMR or respiratory sensitisation are being considered on a case-by-case basis, for example in relation to a harmonised classification for effects on the environment.
- *Section 5*. This outlines the mammalian toxicity data for the human health hazard assessment. The data directly relevant to the named effect(s) under consideration should be added to the appropriate section (*Section 5.5* for respiratory sensitisation, *Section 5.7* for mutagenicity, *Section 5.8* for carcinogenicity, *Section 5.9* for toxicity to reproduction). Data relevant to other effects should be included in the appropriate sections.

For CMR endpoints, each section can be sub-divided to allow different types of data to be reported together (for example *in vitro* and *in vivo* mutagenicity data or exposures via oral, inhalation or dermal routes for carcinogenicity or toxicity to reproduction). A separate heading is given for human data where the information important to the classification proposal, for example epidemiological data, should be summarised. Other toxicity data or toxicokinetic data for the substance itself that are to be used as supportive information should be summarised in the appropriate section (i.e. *Section 5.1* for toxicokinetic data, *Section 5.6* for repeated dose toxicity etc). Other relevant information used to support the proposal, for example information from structurally related substances (read-across) should be summarised under the 'Summary and discussion' heading for the endpoint under consideration.

An overall summary and discussion of the findings and how they relate to the classification of the substance should be given at the end of the section under ‘Summary and discussion’. Specific sub-sections have been included in the format for respiratory sensitisers (*Section 5.5.3*), mutagens (*Section 5.7.5*), carcinogens (*Section 5.8.6*) and substances toxic to reproduction (*Section 5.9.5*). Given the importance of human data for classification of these endpoints, it is recommended that the available human data are considered first in this summary.

It will be helpful to future readers of the report if the MS CA can indicate endpoints in the format where the data have not been reviewed, by including ‘data not reviewed for this report’ under the appropriate heading.

The example Annex XV reports in Appendices 2 and 3 illustrate how the data should be presented.

- *Section 6*. This section relates to the human health hazard assessment of physico-chemical properties. This section is not relevant for a CMR or respiratory sensitisation report; however it may be relevant if endpoints other than CMR or respiratory sensitisation are being considered on a case-by-case basis.
- *Section 7*. This section considers the available ecotoxicity data for the substance. Information on toxicity to environmental organisms may be relevant if endpoints other than CMR or respiratory sensitisation are being considered on a case-by-case basis. The conclusions on harmonised classification for effects on the environment shall be reported in *Section 7.6* based on the individual data in previous sections. If toxicity data from non-mammalian species are being used to support a CMR classification proposal then this should be added to the appropriate section (for example *Section 7.2.1.4* for avian toxicity data).
- *Section 8*. This concerns the PBT and vPvB and equivalent concern assessment and is not relevant for this type of report.
- *Section 9*: This part of the Annex XV report should contain a justification for action on a Community-wide basis. In the case of classification and labelling for CMR and respiratory sensitisation, the identification of the substance as falling within one of these categories is sufficient justification. Therefore there is no need for a detailed justification in this *Section* of the Annex XV report for these endpoints. For proposals for harmonised classification and labelling for effects other than CMR and respiratory sensitisers, a justification demonstrating the need for action at Community level needs to be included in the report.

### 2.6.3 Other information

The final section of the Annex XV report can be used to present any other information that is considered to be relevant to the dossier. An example of information that could be included here would be details of any consultation which took place during the development of the dossier. This could indicate who was consulted and by what means, what comments (if any) were received and how these were dealt with. Other similar types of information could also be included here.

The sources of the information used in the report could also be indicated in this section (see the examples in Appendices 2 and 3). However, this section should not contain any new technical information. All technical information should be reported in the *Justification* part of the Annex XV report.



**APPENDIX 1   FORMAT FOR CLASSIFICATION AND LABELLING ANNEX XV  
REPORT**

**Annex XV dossier**

**PROPOSAL FOR HARMONISED CLASSIFICATION AND  
LABELLING**

**Substance Name:**

**EC Number:**

**CAS Number:**

**Submitted by:**

**Version**

## PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

**Substance Name:**

**EC Number:**

CAS number:

Registration number (s):

Purity:

Impurities:

**Proposed classification based on Directive 67/548/EEC criteria:**

**Proposed classification based on GHS criteria:**

**Proposed labelling:**

**Proposed specific concentration limits (if any):**

**Proposed notes (if any):**

*[Note: In case where the proposed classification is based on the presence of an impurity, this should clearly be stated, along with the identity of the impurity and the composition of impurity in the substance leading to the classification].*

## JUSTIFICATION

### 1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

[click here to insert text]

#### 1.1 Name and other identifiers of the substance

Chemical Name:

EC Name:

CAS Number:

IUPAC Name:

#### 1.2 Composition of the substance

*For each constituent/ impurity/ additive, fill in the following table (which should be repeated in case of more than one constituent). The information is particularly important for the main constituent(s) and for the constituents (or impurity) which influence the outcome of the dossier.*

Chemical Name:

EC Number:

CAS Number:

IUPAC Name:

Molecular Formula:

Structural Formula:

Molecular Weight:

Typical concentration (% w/w):

Concentration range (% w/w):

### 1.3 Physico-chemical properties

**Table 2** Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1		
VII, 7.2	Melting/freezing point	3.2		
VII, 7.3	Boiling point	3.3		
VII, 7.4	Relative density	3.4 density		
VII, 7.5	Vapour pressure	3.6		
VII, 7.6	Surface tension	3.10		
VII, 7.7	Water solubility	3.8		
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient		
VII, 7.9	Flash point	3.11		
VII, 7.10	Flammability	3.13		
VII, 7.11	Explosive properties	3.14		
VII, 7.12	Self-ignition temperature			
VII, 7.13	Oxidising properties	3.15		
VII, 7.14	Granulometry	3.5		
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17		
XI, 7.16	Dissociation constant	3.21		
XI, 7.17,	Viscosity	3.22		
	Auto flammability	3.12		
	Reactivity towards container material	3.18		
	Thermal stability	3.19		
	[enter other property or delete row]			

## **2 MANUFACTURE AND USES**

### **2.1 Manufacture**

### **2.2 Identified uses**

### **2.3 Uses advised against**

## **3 CLASSIFICATION AND LABELLING**

### **3.1 Classification in Annex I of Directive 67/548/EEC**

*This should include the classification (including specific concentration limits) listed in Annex I of Directive 67/548/EEC (including the Index Number)*

### **3.2 Self classification(s)**

*This should include the classification, the labelling and the specific concentrations limits. The reason and justification for no classification should be reported here.*

*It should be stated whether the classification is made according to Directive 67/548/EEC criteria or according to GHS criteria.*

## **4 ENVIRONMENTAL FATE PROPERTIES**

### **4.1 Degradation**

#### **4.1.1 Stability**

*Corresponds to IUCLID 4.1*

#### **4.1.2 Biodegradation**

##### **4.1.2.1 Biodegradation estimation**

##### **4.1.2.2 Screening tests**

##### **4.1.2.3 Simulation tests**

#### **4.1.3 Summary and discussion of persistence**

### **4.2 Environmental distribution**

#### **4.2.1 Adsorption/desorption**

*Corresponds to IUCLID 4.4.1*

#### **4.2.2 Volatilisation**

*Corresponds to IUCLID 4.4.2*

#### **4.2.3 Distribution modelling**

### **4.3 Bioaccumulation**

#### **4.3.1 Aquatic bioaccumulation**

##### **4.3.1.1 Bioaccumulation estimation**

**4.3.1.2 Measured bioaccumulation data**

**4.3.2 Terrestrial bioaccumulation**

**4.3.3 Summary and discussion of bioaccumulation**

**4.4 Secondary poisoning**

*Assessment of the potential for secondary poisoning*

## **5 HUMAN HEALTH HAZARD ASSESSMENT**

*Where appropriate, the proposed classification(s) should be included in the summary and discussions sections which will include weight of evidence considerations.*

### **5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)**

### **5.2 Acute toxicity**

#### **5.2.1 Acute toxicity: oral**

#### **5.2.2 Acute toxicity: inhalation**

#### **5.2.3 Acute toxicity: dermal**

#### **5.2.4 Acute toxicity: other routes**

#### **5.2.5 Summary and discussion of acute toxicity**

*C&L including weight-of-evidence considerations.*

### **5.3 Irritation**

#### **5.3.1 Skin**

#### **5.3.2 Eye**

#### **5.3.3 Respiratory tract**

#### **5.3.4 Summary and discussion of irritation**

*C&L including weight-of-evidence considerations.*

### **5.4 Corrosivity**

### **5.5 Sensitisation**

**5.5.1 Skin**

**5.5.2 Respiratory system**

**5.5.3 Summary and discussion of sensitisation**

*C&L including weight-of-evidence considerations.*

**5.6 Repeated dose toxicity**

**5.6.1 Repeated dose toxicity: oral**

**5.6.2 Repeated dose toxicity: inhalation**

**5.6.3 Repeated dose toxicity: dermal**

**5.6.4 Other relevant information**

**5.6.5 Summary and discussion of repeated dose toxicity:**

*C&L, dose-response estimation including weight-of-evidence considerations.*

**5.7 Mutagenicity**

**5.7.1 *In vitro* data**

**5.7.2 *In vivo* data**

**5.7.3 Human data**

**5.7.4 Other relevant information**

**5.7.5 Summary and discussion of mutagenicity**

*C&L, dose-response estimation including weight-of-evidence considerations.*

**5.8 Carcinogenicity**

**5.8.1 Carcinogenicity: oral**

**5.8.2 Carcinogenicity: inhalation**

**5.8.3 Carcinogenicity: dermal**

**5.8.4 Carcinogenicity: human data**

**5.8.5 Other relevant information**

**5.8.6 Summary and discussion of carcinogenicity**

*C&L, dose-response estimation including weight-of-evidence considerations.*

**5.9 Toxicity for reproduction**

**5.9.1 Effects on fertility**

**5.9.2 Developmental toxicity**

**5.9.3 Human data**

**5.9.4 Other relevant information**

**5.9.5 Summary and discussion of reproductive toxicity**

*C&L, dose-response estimation including weight-of-evidence considerations.*

**5.10 Other effects**

**5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response**

*Not relevant for this type of dossier.*

**6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES**

**6.1 Explosivity**

*Including C&L*

**6.2 Flammability**

*Including C&L*

**6.3 Oxidising potential**

*Including C&L*

**7 ENVIRONMENTAL HAZARD ASSESSMENT**

**7.1 Aquatic compartment (including sediment)**

**7.1.1 Toxicity test results**

**7.1.1.1 Fish**

Short-term toxicity to fish

Long-term toxicity to fish

**7.1.1.2 Aquatic invertebrates**

Short-term toxicity to aquatic invertebrates

Long-term toxicity to aquatic invertebrates

**7.1.1.3 Algae and aquatic plants**

**7.1.1.4 Sediment organisms**

**7.1.1.5 Other aquatic organisms**

**7.1.2 Calculation of Predicted No Effect Concentration (PNEC)**

*Not relevant for this type of dossier.*

## **7.2 Terrestrial compartment**

### **7.2.1 Toxicity test results**

#### **7.2.1.1 Toxicity to soil macro organisms**

#### **7.2.1.2 Toxicity to terrestrial plants**

#### **7.2.1.3 Toxicity to soil micro-organisms**

#### **7.2.1.4 Toxicity to other terrestrial organisms**

Toxicity to birds

Toxicity to other above ground organisms

### **7.2.2 Calculation of Predicted No Effect Concentration (PNEC<sub>soil</sub>)**

*Not relevant for this type of dossier.*

## **7.3 Atmospheric compartment**

## **7.4 Microbiological activity in sewage treatment systems**

### **7.4.1 Toxicity to aquatic micro-organisms**

### **7.4.2 PNEC for sewage treatment plant**

*Not relevant for this type of dossier.*

## **7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC<sub>oral</sub>)**

*Not relevant for this type of dossier.*

## **7.6 Conclusion on the environmental classification and labelling**

## **JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS**

*Harmonised classification and labelling for CMR and respiratory sensitisation is a Community-wide action under Article 115. Proposals for harmonised classification for other endpoints should include here the reasons why there is a need for action at the Community level.*

## **OTHER INFORMATION**

*It is suggested to include here information on any consultation which took place during the development of the dossier. This could indicate who was consulted and by what means, what comments (if any) were received and how these were dealt with. The data sources (e.g registration dossiers, other published sources) used for the dossier could also be indicated here.*

**APPENDIX 2 EXAMPLE CLASSIFICATION ANNEX XV REPORT FOR A  
CARCINOGEN AND MUTAGEN**

**Annex XV**

**Proposal for Harmonised Classification and Labelling of a Chemical  
Substance**

**Example for Carcinogenicity and Mutagenicity**

## PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

**Substance name:** Example carcinogen

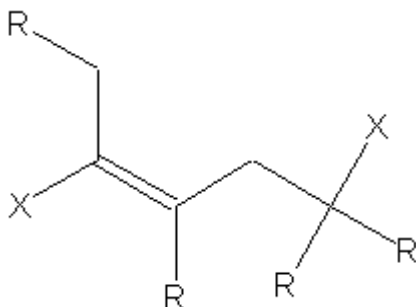
**EC number:** XXX-XXX-X

**CAS number:** YY-YY-Y

**Registration number(s):** ZZZZ1, ZZZZ2, ZZZZ3

**Molecular formula:** C<sub>a</sub>H<sub>b</sub>X<sub>c</sub>

**Structural formula:**



**Purity:** The substance is >98% pure.

**Impurities:** No information

**Proposed classification based on Directive 67/548/EEC :** Carc. Cat. 2, R45 and Muta. Cat. 3, R68

**Proposed classification based on GHS:** Carc. 1B with hazard statement H350 and Muta. 2 with hazard statement H341

**Proposed labelling:** T; R45-68

S53-45

**Proposed specific concentration limits (if any):** None.

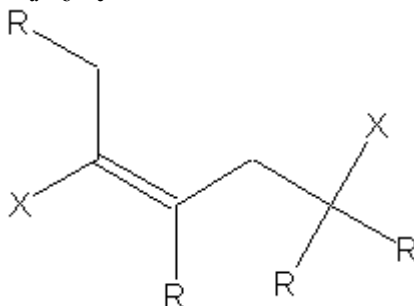
**Proposed notes (if any):** None.

This dossier reviewed the carcinogenicity and mutagenicity endpoints only. Classification for toxicity to reproduction or for respiratory sensitisation was not considered. The classification is based on the properties of the substance itself.

## JUSTIFICATION

### 1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

Name: Example carcinogen  
 EC Number: XXX-XXX-X  
 CAS Number: YY-YY-Y  
 IUPAC Name: Example carcinogen  
 Molecular Formula:  $C_aH_bX_c$   
 Structural Formula:



Molecular Weight: 135 g/mole  
 Synonyms: Example mutagen

#### 1.1 Purity/Impurities/Additives

The purity is 99% (Reference A) or >98% (Reference B and C). No additives are present in the commercially supplied product.

#### 1.2 Physico-Chemical properties

**Table 1** Summary of physico-chemical properties

REACH ref Annex, §	Property	Value	Reference
V, 5.1	Physical state at 20 C and 101.3 KPa	Colourless liquid.	Reference A, B, C
V, 5.2	Melting / freezing point	-40°C.	Reference A, B, C
V, 5.3	Boiling point	95°C	Reference A, B, C
V, 5.5	Vapour pressure	106 Pa at 25°C.	Reference A
V, 5.7	Water solubility	54 mg/l.	Reference A
V, 5.8	Partition coefficient n-octanol/water (log value)	2.78	Reference A

### 2 MANUFACTURE AND USES

Not relevant for this dossier.

### **3 CLASSIFICATION AND LABELLING**

The substance is not currently classified in Annex I of Directive 67/548/EEC. A classification of Carc. Cat. 2; R45: Muta. Cat. 3; R68 is listed in the publicly available classification and labelling database resulting from the self-classification by industry.

### **4 ENVIRONMENTAL FATE PROPERTIES**

Not relevant for this dossier.

### **5 HUMAN HEALTH HAZARD ASSESSMENT**

#### **5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)**

No data reviewed for this example dossier.

#### **5.2 Acute toxicity**

Not relevant for this example dossier.

#### **5.3 Irritation**

Not relevant for this example dossier.

#### **5.4 Corrosivity**

Not relevant for this type of dossier.

#### **5.5 Sensitisation**

Respiratory sensitisation has not been considered as part of this dossier.

*(Note: The unused subheadings have been deleted.)*

#### **5.6 Repeated dose toxicity**

Not relevant for example dossier.

#### **5.7 Mutagenicity**

*[Note: In this example, as the Member State agrees with the industry self-classification, only a short summary of the main findings from the relevant studies is given in the Annex XV report. Full details of the studies will be given in the technical dossier supporting the Annex XV report.]*

*The information is presented in this example in text form. It will be possible to extract information from the technical dossiers in IUCLID in table form to include in the Annex XV report.]*

### **5.7.1 In vitro data**

The results of three Ames tests are available. In the first test (Reference A) an increased mutation frequency was observed in the presence of rat liver S9 in *S. typhimurium* strain TA1535. No further details of this test are available.

The second test (Reference B) was carried out with two strains (TA98 and TA1537) using a concentration range of 1-1,000 µg/plate. The substance gave a negative response both in the presence and absence of S9.

The third test (Reference C) was carried out with strains TA98, TA100, TA1535 and TA1537 at concentrations up to 10,000 µg/plate. The substance gave positive results with strains TA1535 and TA100 both in the presence and absence of S9. A negative result was found with the other strains tested.

In addition to the Ames test, results from two other *in vitro* tests are available.

The substance showed a positive response in a mammalian cell gene mutation assay using L5178Y TK<sup>+/+</sup> mouse lymphoma cells (Reference A). The concentration range tested was 0.0005-100 µl/ml and a dose-related increase in the number of mutant colonies was observed in both the presence and absence of S9. Appropriate responses were seen for the positive control used in the test.

A positive response has also been observed in an assay investigating the induction of chromosome aberrations and SCEs in CHO cells. The concentration range tested was 0-5,000 µg/ml and the exposure time was 26 hours (SCEs) or 12-13 hours (chromosome aberrations) in the absence of S9 or 2 hours in the presence of S9. A dose-related increase in SCE was reported both in the presence and absence of S9. A statistically significant increase in the number of chromosome aberrations was evident both in the presence and absence of S9.

### **5.7.2 In vivo data**

A positive response has been seen in a micronucleus assay using B6C3F1 mice. The animals were exposed by inhalation to concentrations of 0, 0.04, 0.11, 0.32, 0.63 and 1.26 mg/l for 6 hours/day, 5 days/week for 13 weeks. Blood samples were taken from 10 animals per treatment group for analysis of micronucleated normochromatic erythrocytes. A statistically significant increase in the frequency of micronuclei was observed in males at 0.63 and 1.26 mg/l and in females at 0.32 and 1.26 mg/l.

### **5.7.3 Human data**

No data available for this dossier.

### **5.7.4 Other relevant information**

None for this example dossier.

### 5.7.5 Summary and discussion of mutagenicity

No data from humans are available on the mutagenicity of the substance.

*In vitro*, the substance gave positive results in the Ames test in strains TA 100 and TA1535 and in a mouse lymphoma assay, both in the presence and absence of S9. Positive results were also obtained for the induction of chromosomal aberrations and SCEs. Data are available from a single *in vitro* study in the mouse indicating the induction of micronuclei in peripheral blood following inhalation exposure for 13 weeks.

The substance is clearly mutagenic *in vitro*. The induction of micronuclei in peripheral blood has been demonstrated in mice *in vivo*, raising concerns that the substance could possess genotoxic potential *in vivo*. Therefore, classification with **Muta. Cat. 3; R68** is proposed based on these findings.

## 5.8 Carcinogenicity

### 5.8.1 Oral studies

No data available.

### 5.8.2 Dermal studies.

No data available.

### 5.8.3 Inhalation studies

*[Note: In this example, as the Member State agrees with the industry self-classification, only a short summary of the main findings from the relevant studies is given in the Annex XV report. Full details of the studies will be given in the technical dossier supporting the Annex XV report.]*

The results from two studies are available. The first study was a two year study using F344 rats (Reference A). Groups of 56 males and 56 females were exposed to concentrations of 0, 0.16, 0.32 or 0.63 mg/l for 6 hours/day, 5 days/week for 103 weeks. Ten animals per sex/group were evaluated at 15 months for alterations in haematology, histology and clinical chemistry parameters. No treatment-related clinical signs of toxicity were observed.

A dose-related increase in the incidence of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined) was evident in males, reaching statistical significance at the two highest dose levels. The incidence of alveolar/bronchiolar carcinoma was significantly greater than controls in males at 0.63 mg/l.

In females, the incidence of alveolar/bronchiolar adenoma was significantly greater than controls at 0.63 mg/l. The incidence of adenoma or carcinoma (combined) was increased at 0.16 and 0.63 mg/l and was statistically significant at the highest dose level compared with the control.

The non-neoplastic findings included an increased incidence of alveolar epithelial hyperplasia in males and females at 0.63 mg/l at the 15 month evaluation; statistically significant in males only. At the end of the 2-year study, a dose-related increase in the incidence of alveolar epithelial

hyperplasia in both males and females compared to controls was observed. This effect was statistically significant in males at the two highest dose levels and in females at all dose levels.

The second study was carried out with B6C3F1 mice (Reference B). Groups of 60 male and 60 female mice were exposed to concentrations of 0, 0.16, 0.32 or 0.63 mg/l for 6 hours/day, 5 days/week for 103 weeks. Ten animals per sex/group were evaluated at 15 months for clinical pathology and histopathology.

An increase in the incidence of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) compared to the control group was observed in males, reaching statistical significance at the two highest dose levels. An increase in the incidence of alveolar/bronchiolar carcinoma in males compared to the control group was also observed. Additionally, a marginal increase in thyroid gland follicular cell adenoma was evident in males at 0.63 mg/ml compared with the control group.

In females, an increase in the incidence of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined) compared to the control group was evident, and was statistically significant at the highest dose level.

Non-neoplastic findings included an increased incidence of alveolar epithelial hyperplasia in all exposure groups of males and females compared to the control groups, the incidences were statistically significant in both sexes at the two highest dose levels. A significant increase in the incidence of thyroid gland follicular cell hyperplasia was observed in males at 0.16 and 0.63 mg/l compared to controls. An increase in the incidence of minimal to mild haemosiderin pigment in the spleen was evident in males at 0.32 and 0.63 mg/l compared to controls. In females, an increase in the incidence of serous exudates and olfactory epithelium atrophy compared to the control group was evident.

#### **5.8.4 Human data**

No data available.

#### **5.8.5 Other relevant information**

No data available.

#### **5.8.6 Summary and discussion of carcinogenicity**

No data from humans are available on the carcinogenicity of the substance.

The carcinogenic potential of the substance has been investigated in well-conducted lifetime studies in both rats and mice. An increase in the incidence of lung tumours in male (adenoma and carcinoma) and female (adenoma only) rats was observed. Non-neoplastic findings included alveolar epithelial hyperplasia, evident in all treated groups. Lung tumours in rats are considered rare and in this study were shown to exceed the range of historical controls, therefore this increase in lung adenomas and carcinomas may represent clear evidence of carcinogenicity. Supporting evidence was obtained in female mice, since the increased incidence of alveolar/bronchiolar adenoma or carcinoma (combined) observed was shown to exceed the range of historical controls.

No information is available to inform on the mechanism of carcinogenicity. The tumours were noted to occur in the presence of alveolar epithelial hyperplasia, suggestive of a non-genotoxic

mechanism. However, the available genotoxicity data suggest that substance may possess genotoxic potential *in vivo* and therefore a possible genotoxic mechanism cannot be confidently ruled out.

Overall, the increased incidences of lung tumours in two species, rat and mouse, are of concern for humans and thus classification as a carcinogen is warranted. The positive *in vivo* genotoxicity data suggests that genotoxicity may be involved in the causation of these tumours and therefore a classification with **Carc. Cat. 2; R45** is proposed.

### **5.9 Toxicity for reproduction**

Toxicity for reproduction has not been considered as part of this dossier and the data have not been reviewed.

*(Note: The unused sub-headings have been deleted.)*

### **5.10 Other effects**

Not relevant for this example dossier.

## **6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICOCHEMICAL PROPERTIES**

Not relevant for this example dossier.

## **7 ENVIRONMENTAL HAZARD ASSESSMENT**

Not relevant for this example dossier.

## **8 PBT, vPvB AND EQUIVALENT CONCERN ASSESSMENT**

Not relevant for this type of dossier.

## **JUSTIFICATION FOR ACTION AT COMMUNITY LEVEL**

It is proposed that the substance is classified as Carc. Cat. 2, R45 and Muta. Cat. 3, R68. Harmonised classification and labelling for carcinogens and mutagens is considered a community-wide action under Article 115 and it is recommended that the classification proposal is considered for inclusion on Annex I of Directive 67/548/EEC

## **OTHER INFORMATION**

Close co-operation has been maintained with the producers of this substance during the development of this dossier.

The information used in this dossier was taken from the following sources.

Reference A Registration Dossier submitted by Company A.

Reference B Registration Dossier submitted by Company B.

Reference C Registration Dossier submitted by Company C.

**APPENDIX 3 EXAMPLE CLASSIFICATION ANNEX XV REPORT FOR A  
SUBSTANCE TOXIC FOR REPRODUCTION**

**Annex XV**

**Proposal for Harmonised Classification and Labelling of a Chemical  
Substance**

**Example for reproductive toxicity**

## PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

**Substance name:** Example reprotoxicant

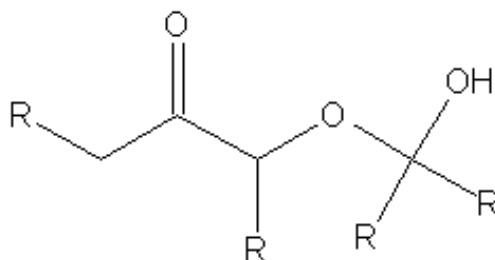
**EC number:** XXX-XXX-X

**CAS number:** YY-YY-Y

**Registration number(s):** ZZZZ

**Molecular formula:** C<sub>a</sub>H<sub>b</sub>O<sub>3</sub>

**Structural formula:**



**Purity:** >95%

**Impurities:** The main impurity is water (CAS Number 7732-18-5).

**Proposed classification under Directive 67/548/EEC:** Repr. Cat. 2; R61 and Repr. Cat.3; R62

**Proposed classification under GHS:** Repr. 1B with hazard statement H360D  
and Repr. 2 with hazard statement H361f

**Proposed labelling:** T; R61-62

S53-45

**Proposed specific concentration limits (if any):** None.

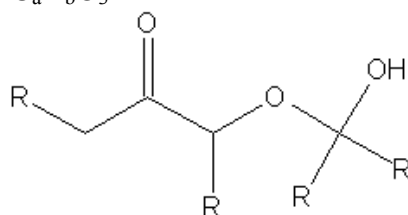
**Proposed notes (if any):** None.

This dossier reviewed the reprotoxicity endpoints only. Classification for carcinogenicity, mutagenicity or respiratory sensitisation was not considered. The classification is based on the properties of the substance itself.

## JUSTIFICATION

### 1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

Name: Example reprotoxicant  
 EC Number: XXX-XXX-X  
 CAS Number: YY-YY-Y  
 IUPAC Name: Example reprotoxicant  
 Molecular Formula: C<sub>a</sub>H<sub>b</sub>O<sub>3</sub>  
 Structural Formula:



Molecular Weight: 202 g/mole  
 Synonyms: Substance XX

#### 1.1 Purity/Impurities/Additives

The purity is >95% (reference 1). The main impurity is water (CAS Number 7732-18-5). No additives are present in the commercially supplied product.

#### 1.2 Physico-Chemical properties

**Table 1** Summary of physico-chemical properties

REACH ref Annex, §	Property	Value	Reference
V, 5.1	Physical state at 20 C and 101.3 KPa	Liquid.	Reference 1
V, 5.2	Melting / freezing point	-60°C.	Reference 1
V, 5.3	Boiling point	180°C	Reference 2
V, 5.5	Vapour pressure	65 Pa at 30°C.	Reference 2
V, 5.7	Water solubility	4,000 mg/l.	Reference 2
V, 5.8	Partition coefficient n-octanol/water (log value)	1.13	Reference 2

### 2 MANUFACTURE AND USES

Not relevant for this dossier.

### **3 CLASSIFICATION AND LABELLING**

The substance is not currently classified in Annex I of Directive 67/548/EEC. No industry self-classification was proposed in the Chemical Safety Report for this substance for inclusion on the publicly available classification and labelling database.

### **4 ENVIRONMENTAL FATE PROPERTIES**

Not relevant for this example dossier.

### **5 HUMAN HEALTH HAZARD ASSESSMENT**

*[Note: the hazard information is presented in this example in text form. It will also be possible to extract information from the technical dossiers in IUCLID in table form to include in the Annex XV report.]*

#### **5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)**

No data available.

#### **5.2 Acute toxicity**

Not relevant for this example dossier.

#### **5.3 Irritation**

Not relevant for this example dossier.

#### **5.4 Corrosivity**

Not relevant for this type of dossier.

#### **5.5 Sensitisation**

Respiratory sensitisation has not been considered as part of this dossier.

*(Note: The unused subheadings have been deleted.)*

#### **5.6 Repeated dose toxicity**

Evidence of testicular toxicity has been seen in a 28-day repeated dose study in Wistar rats (Reference 7). The test was carried out according to the OECD 407 method, using oral doses of 0, 50, 250 and 1,000 mg/kg bw/day. Groups of five males and five females were exposed at each treatment level.

No treatment-related effects were noted in the 50 mg/kg bw/d treatment group. At 250 mg/kg bw/d, there was a decrease of the absolute and relative weight of the thymus that was statistically significant in females.

At the highest dose level (1,000 mg/kg bw/day) there was a significant decrease of the body weight gain and of water consumption in males. For haematology, a decrease of the number of platelets was noted for both sexes and a decrease of the leukocytes count was found in males only. Biochemistry analysis showed a decrease of ALP and bilirubine concurrent with an increase in creatin. For the organs, there was a decrease of the absolute and relative weight of the thymus with histological signs of involvement. There was also a decrease of the absolute and relative weight of the testes, with an important decrease in size. Histologically, azoospermia was seen and spermatogenesis was depressed at the spermatocyte I stage. There were also isolated foci of necrosis of the germinal epithelium. Histological evidence of oligospermia and sometimes azoospermia was seen in seminal vessels of all animals at this dose.

These results were not available at the time the original registration dossier was completed and so were not taken into account in the self-classification proposed by industry. This study provides supporting evidence for the proposed classification.

## **5.7 Mutagenicity**

Mutagenicity has not been considered as part of this dossier, and the data have not been reviewed.

## **5.8 Carcinogenicity**

Carcinogenicity has not been considered as part of this dossier, and the data have not been reviewed.

## **5.9 Toxicity for reproduction**

### **5.9.1 Effects on fertility**

A continuous breeding study with cross-over mating trial has been carried out with Swiss CD-1 mice (Reference 2 and Reference 3). Groups of mice (20 pairs per treatment group and 40 control pairs) were exposed to doses of 0.25, 0.5 and 1% in drinking water (equivalent to doses of 400, 800 and 1,400 mg/kg bw/day).

In the continuous breeding study, there was evidence of decreases of fertility and reproductive parameters that were dose-related and statistically significant at the 1% dose. At this dose level the number of litters/pair was reduced ( $4.2 \pm 0.2$  versus  $4.8 \pm 0.1$  in the control group), the number of live pups/litter was reduced ( $6.0 \pm 0.8$  versus  $12.2 \pm 0.3$  in the control group), and the proportion of pups born alive was reduced ( $0.8 \pm 0.4$  versus  $0.9 \pm 0.00$  in the control group).

There was also a trend to a dose-related decrease (significant at the highest tested dose) in the number of live pups per litter.

In the cross-mating study, the fertility of the females exposed to the 1% dose was decreased (the number fertile/number cohabited was 9/19 (47%) in the 1% treatment group compared with 16/20 (80%) in the control group) whereas there was no change in male fertility at any dose tested.

Effects noted in adults in the 1% treatment group included an increase of the relative and absolute liver weight of both males and females, and a decrease of the pituitary weight in females. There were no macro or histological changes in male sexual organs and no changes were noted in the quality of the sperm.

This information was considered in the registration dossier but was thought not to provide strong enough evidence for a classification based on effects on fertility as the effects seen in this study occurred only at doses that were also toxic to adults. However, we considered that the effects seen in the adults at the highest dose were minor in nature, and the effects seen on many of the fertility and reproductive parameters showed a clear dose-related response, and so, in our view, the study does provide positive evidence for effects on fertility.

### **5.9.2 Developmental toxicity**

The results of four developmental toxicity studies with two species (mice and rabbits) are available.

A screening study using CD1 mice has been carried out (Reference 4). In the study females were orally exposed to a dose of 3,500 mg/kg bw/d from gestation day 7 to gestation day 14. Maternal toxicity (mortality) was observed in 2 out the 50 exposed animals, and 100% resorption of implantation was seen in the surviving animals.

In the second fertility study using CD1 mice, groups of 26-28 mice were exposed to oral doses of 0, 250, 500 and 1,000 mg/kg bw/d from gestation day 6 to gestation day 15 (Reference 5). Minor maternal toxicity was noted (increase of the relative liver weight) at 500 mg/kg bw/d and higher. For the offspring, there was a clear increase in the adverse affected conceptus/litter (post implantation loss plus malformation) at 500 mg/kg and higher with a dose-related increase of the percentage in the live fetus malformed (11.09% at 1,000 mg/kg versus 0.27% in controls), a dose-related increase in the percentage of litters with one or more malformed fetus (50% in the 1,000 mg/kg group versus 3.85% in controls) and a non statistically significant dose-related increase in the percentage of resorption and in the percentage of late fetal death at 500 mg/kg and higher. Malformations observed were anomalies of development of the neural tube, cranio-facial structures and anomalies of development of the axial skeleton.

A third, poorly reported, study using mice has been carried out using a single oral dose of 713 mg/kg bw/d on gestation day 11 (Reference 6). The exposed fetuses were examined for paw defects only and not for visceral effects. In the conditions of this study, the substance did not induce any malformations on fetuses and no maternal toxicity was evidenced.

The results of a fertility study with rabbits are also available (Reference 7). In this study groups of 15-25 animals were exposed to oral doses of 0, 75, 125, 175 or 250 mg/kg bw/d on gestation day 6 to 19. The only maternal effect was a slight increase in the relative liver weight at 250 mg/kg bw/d. In the fetuses there was an increase of the prenatal mortality/litter at 175 mg/kg bw/d ( $24.8 \pm 6.1$  versus  $13.3 \pm 4.3$  in controls) and 250 mg/kg bw/d ( $53.9 \pm 8.1$ ) without effects on the fetal weight. There was also an increase of the percentage of malformed fetuses/litter (missing toenails, small spleen, hydronephrosis and a trend to an increase of cardiac malformations) at 175 mg/kg bw/d ( $51.3 \pm 7.1$  versus  $7.3 \pm 2.6$  in controls) and 250 mg/kg bw/d ( $75.2 \pm 5.1$ ).

The results from the three mice studies were considered in the registration dossier but were not considered to provide sufficient evidence for classification for reprotoxic effects as the effects seen generally occurred only at maternally toxic doses. However, we consider that the maternal toxicity seen was generally mild in nature. In addition, a further study with rabbits has become available since the registration dossier was originally submitted, and this provides clear evidence for

developmental toxicity at doses levels below the maternally toxic dose. Therefore, in our opinion, there is sufficient evidence for developmental toxicity in both mice and rabbits.

### 5.9.3 Human data

No data are available.

### 5.9.4 Other relevant information

No data are available for the kinetic properties of this substance but a comparison is possible with some other structurally-related substances (Substance X and Substance Y) that have been shown to cause toxicity to reproduction (Reference 8). Metabolism of Substance X and Substance Y lead to the formation of a common metabolite that is thought to be the active metabolite for reproductive toxicity. The same metabolite could almost certainly be formed from the metabolism of this substance. Moreover this is supported by the results of the tests performed in animals which give quite similar results (testicular atrophy and teratology at about the same level of dosing) for both this substance and Substance X and Substance Y. This information was not considered in the registration dossier.

### 5.9.5 Summary and discussion of toxicity for reproduction

No data from humans are available on the reprotoxicity of the substance.

In the continuous breeding fertility study (with cross-over mating trial) performed in mice, there were evidences of decreases in fertility parameters, dose-related and statistically significant at the highest dose tested in the presence of a slight maternal toxicity. There was also a dose-related decrease in the number of live pups per litter (statistically significant at the highest tested dose). In the cross-mating study, the fertility of the females exposed to the 1% dose was decreased whereas there was no change in male fertility at any dose tested. There were no macro or histological changes in male sexual organs and no changes were noted in the quality of the sperm.

In addition to this, evidence of testicular toxicity was seen at 1,000 mg/kg bw/d in a 28 day toxicity study with rats. The toxic signs were decreases of the testes size (moderate to severe) decreases of the absolute and relative weight of the testes. For histological signs, severe oligospermia to azoospermia was seen for all the animals of this group. No effects were seen for animals tested with 250 mg/kg bw/d.

The substance has also been studied for developmental toxicity (teratogenicity studies) in mice (3 studies) and in rabbits (1 study). Oral exposure to the substance leads to embryo lethality and malformations of the foetuses in both species at doses where no or very little maternal toxicity was seen.

It should be noted that no classification for toxicity to reproduction was proposed by industry in their registration dossier, based on the effects being seen mainly at doses that were also toxic to the adults. However, we believe that the toxic effects on adults were mild in nature, and further information has become available since the original registration dossier was submitted. Overall the results of the available fertility and developmental toxicity studies, together with consideration of the effects seen with structurally-related substances, lead to a proposal for classification as **Repr. Cat. 2; R61** for developmental effects and **Repr. Cat. 3; R62** for effects on fertility.

**5.10 Other effects**

Not relevant for this example dossier.

**6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICOCHEMICAL PROPERTIES**

Not relevant for this example dossier.

**7 ENVIRONMENTAL HAZARD ASSESSMENT**

Not relevant for this example dossier.

**8 PBT, vPvB AND EQUIVALENT CONCERN ASSESSMENT**

Not relevant for this type of dossier.

## **JUSTIFICATION FOR ACTION AT COMMUNITY LEVEL**

It is proposed that the substance is classified as Repro. Cat 2, R61 and Repro. Cat. 3, R62. Harmonised classification and labelling for reprotoxicants is considered a Community-wide action under Article 115 and it is recommended that the classification proposal is considered for inclusion on Annex I of Directive 67/548/EEC.

## OTHER INFORMATION

This substance has been registered under REACH. The producer company has been contacted during the production of this dossier and they provided the available industry reports for the substance. In addition, two significant new papers have been published in the literature since the original registration dossier was completed, and these have also been considered.

The information used in this dossier was taken from the following published sources reported in the registration dossier produced by Company X.

Reference 1. Authors. (Year). Title. Journal.

Reference 2. Authors. (Year). Title. Journal.

Reference 3. Authors. (Year). Title. Journal.

Reference 4. Authors. (Year). Title. Journal.

Reference 5. Authors. (Year). Title. Journal.

Reference 6. Authors. (Year). Title. Journal.

In addition the following two recent additional data sources were also taken into account.

Reference 7. Authors. (Year). Title. Journal.

Reference 8. Authors. (Year). Title. Journal.

During the development of this proposal there was some disagreement with Industry over the interpretation of several studies where reprotoxic effects were only seen at high doses that caused toxic effects in adults. As outlined in the registration dossier for Company X, Industry maintains that the results from such tests should lead to no classification for reproductive effects.

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## **APPENDIX 4 COMMUNITY LEGISLATION REFERRING TO THE CLASSIFICATION OF SUBSTANCES MADE UNDER DIRECTIVE 67/548/EEC**

### **Substances dangerous to health and environment**

Directive 1999/45/EC of the European Parliament and of the Council concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations, and relevant amendments.

Council Directive 91/414/EEC concerning the placing of plant protection products on the market, and relevant amendments.

Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, and relevant amendments.

Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations, and relevant amendments.

Regulation (EC) No 304/2003 of the European Parliament and of the Council concerning the export and import of dangerous chemicals, and relevant amendments.

Regulation (EC) No 850/2004 of the European Parliament and of the Council on persistent organic pollutants and amending Directive 79/117/EEC.

### **Worker health and safety**

Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC), and relevant amendments.

Council Directive 92/85/EEC on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding.

Directive 2004/37/EC of the European Parliament and of the Council on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC) [KH: Why give the reference to Directive 89/391 here but not for 92/85 (it is the 10<sup>th</sup> individual Directive) or 98/24 (it is the 14<sup>th</sup> individual Directive?]

Council Directive 94/33/EC on the protection of young people at work, and relevant amendments.

Council Directive 92/58/EEC on the minimum requirements for the provision of safety and/or health signs at work (ninth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC), and relevant amendments.

### **Major industrial accidents**

Council Directive 96/82/EC on the control of major-accident hazards involving dangerous substances (Seveso II), and relevant amendments.

### **Consumer products**

Council Regulation (EEC) No 880/92 on a Community eco-label award scheme, and relevant amendments.

Council Directive 88/378/EEC on the approximation of the laws of the Member States concerning the safety of toys, and relevant amendments.

Council Directive 75/324/EEC on the approximation of the laws of the Member States relating to aerosol dispensers, and relevant amendments.

Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, and relevant amendments.

### **Waste**

Council Directive 91/689/EEC on hazardous waste, and relevant amendments.

Directive 2002/96/EC on waste electrical and electronic equipment (WEEE).

Council Directive 96/62/EC on ambient air quality assessment and management, and relevant amendments.

### **Transport**

Council Directive 94/55/EC of 21 November 1994 on the approximation of the laws of the Member States with regard to the transport of dangerous goods, and relevant amendments.